Patient-Centered Opioid Tapering

- Opioid tapering is NOT for everyone. Patients with Moderate to Severe Opioid Use Disorder require different care pathways.
- Caution against forced opioid tapering. Work to partner with patients on voluntary opioid tapering.
- Recognize that most patients are fearful.
- Become aware of your reactions; managing frustration is critical.
- Explain the health benefits of reducing medications. Patients need to know why reducing opioids is good vs. likely to leave then suffering.
- Highlight why reducing medications may specifically help *them.* Tailor a personalized, conversation for each individual patient.
- Anxiety about reducing medications undermines patient engagement and patient response to the taper. Helping allay patient concerns is paramount to success.
- Forced tapers yield suboptimal results. Focus on building partnership.
- Avoid talking about ZERO opioids. Help them be willing to try a gentle reduction toward less opioids.
- Connect. Validate patients' concerns. Feeling heard is the foundation for patients to trust you.
- Share the data on opioid tapering results: pain does not typically increase when done the right way; for many, pain improves.
- Explain how you will partner with them (follow-up schedule, dose decrements)
- Explain that the goal is to *prevent withdrawals*.
- Help them feel in control (consider micro dose decrements to start, ability to pause)
- Give them support (pain psychology resources, clinic staff support)
- Provide a patient resource reading list for opioid tapering.
- If pain increases or otherwise deteriorate during a taper, consider increasing opioids.

Addressing Opioids

When opioid reduction is the goal:

- **Assess motivation** and readiness to reduce opioids.
- **Assess any/all negative impacts** from opioid use (e.g., cognitive effects, fatigue, poor sleep, effort to obtain scripts, stigma, etc).
- **Shift paternalistic dialog**. Help patients understand the long term risks of opioids and why using less medication is in their best interests. Doing so will minimize perceptions of injustice and blame.
- **Ask**: What are your concerns about reducing your opioids?
- **Set positive expectations**. The biggest patient fear is greater pain. Review the data that when opioids are reduced slowly and sensibly, pain intensity tends to remain constant or improve. Sleep improves with opioid reduction and that facilitates reduced pain.
- **Assess and provide education** for how psychosocial factors can maintain greater use of opioids

poor pacing → greater pain → opioids

anxiety → greater pain → opioids

- **Provide specific resources** (e.g., books on opioid reduction).
- **Declare your philosophy:** Opioids may be *one part* of an overall care plan-- not the whole story. For many, long term opioids may be contraindicated. And for others, opioids may be appropriate pain management.
- **Emphasize self-management**. Partner with patients in reducing their opioids risks by emphasizing behavioral medicine. Doing so yields the best outcomes.

Provide ongoing support. Classes, self-management groups, support groups.

Tips for Physicians / Prescribers

Remind Your Patients About the Benefits of Opioid Tapering: Studies suggest that on average patients get better with a VERY SLOW opioid taper. Many people report having less pain and feeling better overall. On top of that, they will enjoy fewer side effects and greatly reduced health risks.

Reassure your patients. Your patients are scared because they tried and failed before. Most patients have failed because they went too fast with their taper and had withdrawals. Remind them that the VERY SLOW taper will prevent withdrawals and keep them comfortable. Everyone can wean down on opioids but the trick is to go very slowly and use skills to keep yourself calm as your body adjusts. If you use adjuvants, tell them other medications may be used to help them reduce opioids more comfortably.

GO SLOW. Most taper guidelines suggest taper schedules that are too aggressive for the real-world chronic pain patient on multiple meds and high opioid doses. We do not recommend a specific taper schedule to you, but if a patient has been on opioids for years and decades, consider taking about 6 months for cessation or getting to the lowest possible dose. A good target is substantial reduction at 4 months, as low as possible at 10 months.

Not Everyone Will Taper Completely. The goal is to get patients as low as possible in 10 months.

Tapers Should Not Be Unidirectional. Patient-centered care recognizes that tapering is not right for everyone. Everyone should be offered a gentle taper. Based on their response, opioid stabilization may be appropriate.

Check in With Your Patients. At each follow-up, ask how they are doing. Assess mood, distress, pain, suicidality. If stable, ask if they are ready to go down on *one* of their doses.

Engage Them in Their Pain Care. Ask if they have read the book that was mailed to them. Ask them what they are learning about how to best keep their pain low so they naturally need less medication.

Narrative For Pitching Opioid Tapering to Your Patients

I was reviewing your chart and noticing that you've been on opioids for 5 years now without major improvement. New federal guidelines are asking doctors to reduce opioids for chronic pain because the data suggest they don't work well in the long term, and they cause a lot of problems and health risks. For instance, you have back pain, and data show that opioids don't help back pain and may make things worse. Interestingly, research also shows that when people like you who have been on opioids for years get off them, they do better. In general pain actually reduces. Mood improves. Side effects go away, and health risks decline. For all of these reasons, I think the best plan for your pain is to get you on a very, very slow opioid taper program. So slow your body will not even notice the medicine is being reduced, and you will have no side effects. We would take 6-10 months to get you down as low as possible. We will focus on treating your pain differently, getting you connected with self-management resources, and maybe using some lower risk non-opioid medications. I would like to partner with you on this. I will follow you closely and we will go very slowly to help you succeed.

More Tips & Scripts for Communicating with Patients

- "It's not about taking something away from you. It's about treating your pain better, with lower risks."
- Understand their concerns. Ask them if they are interested in reducing opioids. If not, why.
- Assess history of withdrawal symptoms. Patients often believe that they will experience withdrawals and increased pain if medications are reduced. "Have you ever missed a dose of medication, or had withdrawal symptoms before?"
- Educate patients about the distinction between withdrawal symptoms, "baseline pain", and what they can expect from a very slow opioid taper.
- "We can partner together and reduce your medications so slowly your body doesn't notice it. This keeps you comfortable and prevents withdrawal symptoms."
- "When done right, most people who reduce opioids do not have increased pain. In fact, pain actually improves for many people."
- Patient videos can be a valuable tool.
- Offer flexibilities: "We can pause the taper if we need to."
- Patient-centered care means flexing to the individual patient. While most patients will taper, some will not. Allow for individual differences in pain and pain treatment response.
- Assure patients they will still have access to acute pain care as needed, but the long-term goal may be to resume the opioid taper afterward.

Communication Examples:

- **PATIENT: "I tried stopping once and my pain was terrible."**

  YOU: "That's a common experience that usually happens when medications are reduced too quickly and it triggers withdrawals. Our goal will be to prevent you from having negative symptoms. To address this, we begin with such a slow reduction that your body will not notice the difference and will not react to it. This sets you up for success."

- **PATIENT: "I don't want to reduce my opioids because if my pain is worse I will want them back and you won't give them to me."**

  YOU: "When done very, very slowly most people do not have more pain – and studies show that many find their pain actually gets *better*. Reducing opioids can be an effective way to actually reduce your pain; it's just got to be done the right way.

  Would you be willing to partner on a very, very slow reduction to see if we can get you reductions in your pain? For instance, we might try reducing (by 5%) over the course of a month or more. Meanwhile, we will focus on giving you other tools that will help all areas of your life that are impacted by pain."

- **PATIENT: "What if I find my pain gets worse. Then what?"**

  YOU: "Our goal is to prevent this scenario. We can prevent it by going super slow. But, chronic pain does flare from time to time, even with opioids. We will stay in close communication so in the unlikely event your pain increases we can learn from it and understand why it's happening. We can also pause the taper and work with your body."

- **PATIENT: "I'm really scared about this."**

  YOU: "You are not alone. It is common for patients to fear opioid reduction, even though most say that they would like to take less opioid medication. Our plan will set you up for success. We will go slow, communicate with each other, and I will help address your needs. Your job will be to help yourself be calm because that will help our plan work better. Let me connect you with some resources and tools to help you feel less anxious about this."

When to Refer to a Pain Psychology Specialist

The use of pain psychology is often helpful when the **patient seems stuck in a passive role**, relying on doctors to "fix" or cure their pain, without fully appreciating the factors that impact pain and what they can do to improve their own experience.

Refer to your behavioral medicine colleagues when one or more of the following is noted in the patient's presentation:

- **Focus on medications and procedures, often to the exclusion of partnering in self-management**
- **Imbalanced activity levels** (e.g., doing too little, too much, having difficulty prioritizing self-care within the context of pain and competing life demands)
- **Unsure how to move forward and improve quality of life**
- **Lack of pain education and understanding about the relationship between mind and body**
- **Fear of pain** or injury preventing movement/activity
- **Lack of pain and stress management skills**
- **Feelings of helplessness and despair about pain**
- **Observation of psychological distress and/or anger**
- **Social isolation**
- **Pain-related anxiety and/or depression**
- **Excessive health care utilization without obvious benefit (red flags may include "doctor shopping" or frequent visits to the emergency department**
- **Chronic use of opioids or other habituating medications without corresponding functional benefits**
- **Suicidal ideation or other high risk behaviors in the context of chronic pain**
- **An interest in self-management approaches to pain is expressed**

Letters

RESEARCH LETTER

Patient-Centered Prescription Opioid Tapering in Community Outpatients With Chronic Pain

The risks associated with prescription opioids are well described.[1,2] Although reducing opioid use is a national priority, existing opioid tapering models use costly interdisciplinary teams that are largely inaccessible to patients and their physicians.[3,4] Patients and physicians need solutions to successfully reduce long-term prescription opioid dosages in settings without behavioral services. We conducted a study of voluntary, patient-centered opioid tapering in outpatients with chronic pain without behavioral treatment.

Methods | Patients with non–cancer-related chronic pain prescribed long-term opioids at a community pain clinic were provided education about the benefits of opioid reduction (reduced health risks without increased pain) by their prescribing physician. Physicians offered to partner with patients to slowly reduce their opioid dosages over 4 months. The only exclusion was current treatment for substance use disorder. The study was approved by the Stanford University institutional review board; participants provided written or electronic informed consent, and no compensation was provided to participants.

Of the 110 eligible patients, 82 (75%) agreed to taper their opioid dosages; of those, 68 provided baseline demographics, information on opioid use, pain, marijuana use and psychosocial measures. Patients received a self-help book on reducing opioid use, and a slow, individually designed taper. Opioid dosages were reduced up to 5% for up to 2 dose reductions in month 1 to minimize negative physical and emotional response, withdrawal symptoms, and to facilitate patient confidence in the process. In months 2 to 4, patients were asked to further reduce use by as much as 10% per week; dose decrements were tailored to the patient. Patient responses were monitored with close clinical follow-up (at least monthly) and doses adjusted accordingly. Follow-up surveys were administered at 4 months; patients who provided data at 4 months were considered study completers. We confirmed patient-reported opioid prescription with medical record review. We documented patient compliance and accuracy of reported medication use with periodic urine drug testing and continuous monitoring of the state Prescription Drug Monitoring Program (PDMP). No compliance issues or aberrant prescriptions were noted. We converted opioid doses to morphine equivalent daily dose (MEDD). Change in MEDD from baseline was the primary outcome and pain intensity was a secondary outcome. Kruskal-Wallis rank sum test was used for continuous variables and χ^2 test for polychotomous variables.

Table. Characteristics and Outcomes[a]

	Completers (n = 51)					Dropouts[b]		
	Baseline		4 mo			Baseline		
Variable	Median (IQR)	NA	Median (IQR)	NA	*P* Value[c]	Median (IQR)	NA	*P* Value[d]
Age	52 (43-50)	1				57 (50-63)	0	.12
Opioid duration[e]	6 (3-11)	10				6 (5-8)	4	.57
Opioid dose[f]	288 (153-587)	0	150 (54-248)	0	.002	244 (147-311)	1	.45
Pain Intensity	5.0 (3.0-7.0)	0	4.5 (3.0-7.0)	3	.29	3.5 (3.0-6)	1	.10
PCS	22 (10-30)	1	15 (7-23)	5	.04	22 (20-30)	0	.39
Fatigue[g]	60 (54-65)	4	59 (51-65)	3	.64	63 (59-66)	2	.45
Anxiety[g]	60 (53-64)	1	54 (46-62)	3	.06	62 (59-63)	1	.35
Depression[g]	56 (49-64)	1	55 (48-61)	2	.31	62 (57-65)	1	.05
Sleep disturbance[g]	59 (54-70)	2	56 (50-64)	2	.13	62 (53-67)	1	.66
Pain Interference[g]	63 (58-67)	1	63 (57-67)	2	.44	66 (61-68)	1	.13
Pain behavior[g]	60 (57-63)	2	59 (56-64)	2	.47	62 (60-64)	1	.14
Physical function[g,h]	39 (34-41)	1	39 (34-43)	2	.78	36 (34-41)	1	.07

Abbreviations: IQR, interquartile range; NA, not applicable; PCS, Pain Catastrophizing Scale.

[a] Completers provided 4-month data, dropouts enrolled but did not provide month 4 data.

[b] Thirty-one enrolled; 17 provided the baseline data.

[c] Probability of difference between week baseline and 4 months for completers where null hypothesis is true.

[d] Probability of baseline difference between completers and dropouts where null hypothesis is true.

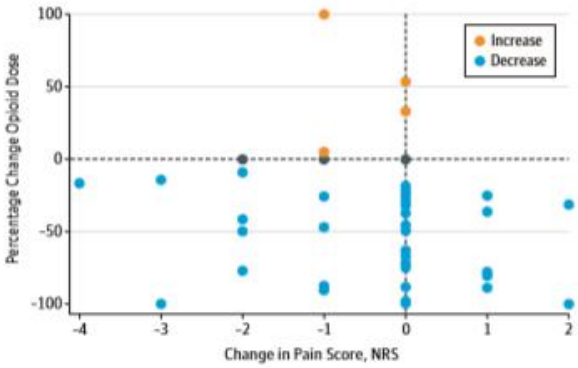
[e] Opioid duration (years taking opioids).

[f] Opioid dose (morphine equivalent daily dose).

[g] Patient Reported Outcomes Information System (PROMIS) measure.

[h] Lower scores reflect worse function, pain (numeric rating scale).

Figure. Change in Opioid Morphine Equivalent Daily Dose and Absolute Change in Pain Intensity Score From Baseline to Month 4 for Study Completers



NRS indicates numeric rating scale.

Results | The patients' mean (SD) age was 51 (12) years, and 41 (60%) were female. Thirty-one of 82 enrolled patients (38%) did not complete a 4-month follow-up survey and therefore were considered to have dropped out of the study. Depression negatively correlated (P = .05) and baseline marijuana use positively correlated (P = .04) with study completion. The **Table** provides characteristics and results for the sample; we found no sex association with study completion or opioid reduction.

Among study completers (n = 51) baseline median MEDD (interquartile range [IQR]) was 288 (153-587) mg, with a median 6-year duration (IQR, 3-9) duration of opioid use. Median pain intensity was moderate (5 out of 10 on a numeric pain rating). After 4 months, the median MEDD was reduced to 150 (IQR, 54-248) mg (P = .002). The likelihood of a greater than 50% opioid dose reduction was not predicted by starting dose, baseline pain intensity, years prescribed opioids, or any psychosocial variable. Neither pain intensity (P = .29) nor pain interference (P = .44) increased with opioid reduction. The **Figure** shows the relationship between percentage change in MEDD and pain intensity in study completers.

Discussion | Our findings suggest that a substantial fraction of patients at a pain clinic may wish to engage in voluntary opioid tapering. Our data challenge common notions that patients taking high-dose opioids will fail outpatient opioid tapers or that duration of opioid use predicts taper success. Combining patient education about the benefits of opioid reduction with a plan that reduces opioids more slowly than current tapering algorithms[5] with close clinician follow-up may help patients engage and succeed in voluntary outpatient tapering. Because our data are generated from a single pain clinic, studies are needed to assess how well our protocol would generalize to other types of patients and settings.

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Print Opioid Tapering Resources for Patients

Books (Beth Darnall, PhD):

- *The Opioid-Free Pain Relief Kit* ©2016 (Bull Publishing)
- *Less Pain, Fewer Pills: Avoid the dangers of prescription opioids and gain control over chronic pain* ©2014 (Bull Publishing)

Professional Coaching for Healthcare Clinicians

Enhancing patient engagement and clinician satisfaction with opioid-tapering

Dr. Claire Ashton-James is a social psychologist who works with clinicians around the world to enhance both patient and clinician satisfaction with opioid-tapering conversations. Dr Ashton-James draws on decades of research into emotions, interpersonal communication, and trust to equip clinicians with evidence-based tools for enhancing patient engagement with and adherence to opioid tapering advice. Individualized clinician coaching and customized group workshops are offered in-person or online with video conferencing.

Website: drashtonjames.com

Contact: info@drashtonjames.com

HHS Prescription Opioid Tapering Guidance

HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics

https://www.hhs.gov/opioids/sites/default/files/2019-10/Dosage_Reduction_Discontinuation.pdf

Pain Management
Opioid Taper Decision Tool

A VA Clinician's Guide

VA | U.S. Department of Veterans Affairs

https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/52_Pain_Opioid_Taper_Tool_IB_10_939_P96820.pdf

VA | U.S. Department of Veterans Affairs

OPIOID USE DISORDER

A VA Clinician's Guide to Identification and Management of Opioid Use Disorder (2016)

https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Academic_Detailing_Educational_Material_Catalog/45_OUD_Provider_AD_Educational_Guide_IB_933_P96813.pdf

Checklist for prescribing opioids for chronic pain

For primary care providers treating adults (18+) with chronic pain ≥3 months, excluding cancer, palliative, and end-of-life care

CHECKLIST

When CONSIDERING long-term opioid therapy

- ☐ Set realistic goals for pain and function based on diagnosis (eg, walk around the block).
- ☐ Check that non-opioid therapies tried and optimized.
- ☐ Discuss benefits and risks (eg, addiction, overdose) with patient.
- ☐ Evaluate risk of harm or misuse.
  - Discuss risk factors with patient.
  - Check prescription drug monitoring program (PDMP) data.
  - Check urine drug screen.
- ☐ Set criteria for stopping or continuing opioids.
- ☐ Assess baseline pain and function (eg, PEG scale).
- ☐ Schedule initial reassessment within 1–4 weeks.
- ☐ Prescribe short-acting opioids using lowest dosage on product labeling; match duration to scheduled reassessment.

If RENEWING without patient visit

- ☐ Check that return visit is scheduled ≤3 months from last visit.

When REASSESSING at return visit

Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm.

- ☐ Assess pain and function (eg, PEG); compare results to baseline.
- ☐ Evaluate risk of harm or misuse:
  - Observe patient for signs of over-sedation or overdose risk.
    - If yes: Taper dose.
  - Check PDMP.
  - Check for opioid use disorder if indicated (eg, difficulty controlling use).
    - If yes: Refer for treatment.
- ☐ Check that non-opioid therapies optimized.
- ☐ Determine whether to continue, adjust, taper, or stop opioids.
- ☐ Calculate opioid dosage morphine milligram equivalent (MME).
  - If ≥50 MME/day total (≥50 mg hydrocodone; ≥33 mg oxycodone), increase frequency of follow-up; consider offering naloxone.
  - Avoid ≥90 MME/day total (≥90 mg hydrocodone; ≥60 mg oxycodone), or carefully justify; consider specialist referral.
- ☐ Schedule reassessment at regular intervals (≤3 months).

REFERENCE

EVIDENCE ABOUT OPIOID THERAPY

- *Benefits of long-term opioid therapy for chronic pain not well supported by evidence.*
- *Short-term benefits small to moderate for pain; inconsistent for function.*
- *Insufficient evidence for long-term benefits in low back pain, headache, and fibromyalgia.*

NON-OPIOID THERAPIES

Use alone or combined with opioids, as indicated:

- Non-opioid medications (eg, NSAIDs, TCAs, SNRIs, anti-convulsants).
- Physical treatments (eg, exercise therapy, weight loss).
- Behavioral treatment (eg, CBT).
- Procedures (eg, intra-articular corticosteroids).

EVALUATING RISK OF HARM OR MISUSE

Known risk factors include:

- Illegal drug use; prescription drug use for nonmedical reasons.
- History of substance use disorder or overdose.
- Mental health conditions (eg, depression, anxiety).
- Sleep-disordered breathing.
- Concurrent benzodiazepine use.

Urine drug testing: Check to confirm presence of prescribed substances and for undisclosed prescription drug or illicit substance use.

Prescription drug monitoring program (PDMP): Check for opioids or benzodiazepines from other sources.

ASSESSING PAIN & FUNCTION USING PEG SCALE

PEG score = average 3 individual question scores
(30% improvement from baseline is clinically meaningful)

Q1: *What number from 0–10 best describes your **pain** in the past week?*
0="no pain", 10="worst you can imagine"

Q2: *What number from 0–10 describes how, during the past week, pain has interfered with your **enjoyment of life**?*
0="not at all", 10="complete interference"

Q3: *What number from 0–10 describes how, during the past week, pain has interfered with your **general activity**?*
0="not at all", 10="complete interference"

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS273808A

TO LEARN MORE | www.cdc.gov/drugoverdose/prescribing/guideline

PAIN MANAGEMENT RESOURCES

SINGLE-SESSION SKILLS-BASED PAIN CLASS (Healthcare Clinician Certification Workshop)

Visit: https://empoweredrelief.com

"Empowered Relief" is an evidence-based 2-hour skills-based pain psychology class that can be embedded into clinical care pathways. Provides rapid access to low-cost, low-burden behavioral medicine for chronic pain.

HEALTHCARE CLINICIAN BOOKS

Overview of Evidence-Based Behavioral Treatments for Chronic Pain

Psychological Treatment for Patients with Chronic Pain ©2018 (American Psychological Association). Includes clinician and patient free resources (By Beth Darnall, PhD)

FREE online book:
Kopf, A., & Patel, N. B. (Eds.) (2010). *Guide to pain management in low-resource settings.* Seattle, WA: International Association for the Treatment of Pain. Retrieved at https://s3.amazonaws.com/rdcms-iasp/files/production/public/Content/ContentFolders/Publications2/FreeBooks/Guide_to_Pain_Management_in_Low-Resource_Settings.pdf

PATIENT RESOURCES

WEBSITES

American Chronic Pain Association (ACPA)

http://theacpa.org

The ACPA is dedicated to peer support and education for individuals with chronic *pain* and their families so that these individuals may live more fully in spite of their *pain*. Their website includes free pain management tools (print and electronic), local support group information, and a resource guide for chronic pain treatments.

The Pain Toolkit

https://www.paintoolkit.org/

The Pain Toolkit website offers a wealth of FREE and LOW-COST pain self-management resources (e.g. $1-2). Website includes resources for patients and specific resources for medical clinicians.

RELAXATION / MINDFULNESS / MEDITATION

FREE Mobile Relaxation App: Breathe2Relax (from the Department of Defense)
http://t2health.dcoe.mil/mediakit/breath2relax-mobile-application

Mindfulness Meditation is evidence-based treatment for chronic pain. It involves helping calming mind and body, and learning to release the mental focus on pain that happens automatically. Research shows that mindfulness and meditation techniques work by changing how your brain responds to pain, thereby reducing pain intensity. Learning mindfulness and meditation can help you reduce your pain. Here are some resources to help you get started:

Free Online Mindfulness-Based Stress Reduction (MBSR)
8 week course http://palousemindfulness.com/

Free Mindfulness App and Guided Meditations: http://counselingcenter.utah.edu/services/mindfulness.php

Free Guided Meditations (English and Spanish)
http://marc.ucla.edu/body.cfm?id=22

HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics

This *HHS Guide for Clinicians on the Appropriate Dosage Reduction or Discontinuation of Long-Term Opioid Analgesics* provides advice to clinicians who are contemplating or initiating a reduction in opioid dosage or discontinuation of long-term opioid therapy for chronic pain. In each case the clinician should review the risks and benefits of the current therapy with the patient, and decide if tapering is appropriate based on individual circumstances.

After increasing every year for more than a decade, annual opioid prescriptions in the United States peaked at 255 million in 2012 and then decreased to 191 million in 2017.[i] More judicious opioid analgesic prescribing can benefit individual patients as well as public health when opioid analgesic use is limited to situations where benefits of opioids are likely to outweigh risks. At the same time opioid analgesic prescribing changes, such as dose escalation, dose reduction or discontinuation of long-term opioid analgesics, have potential to harm or put patients at risk if not made in a thoughtful, deliberative, collaborative, and measured manner.

Risks of rapid opioid taper

- Opioids should not be tapered rapidly or discontinued suddenly due to the risks of significant opioid withdrawal.
- Risks of rapid tapering or sudden discontinuation of opioids in physically dependent[ii] patients include acute withdrawal symptoms, exacerbation of pain, serious psychological distress, and thoughts of suicide.[1] Patients may seek other sources of opioids, potentially including illicit opioids, as a way to treat their pain or withdrawal symptoms.[1]
- Unless there are indications of a life-threatening issue, such as warning signs of impending overdose, HHS does not recommend abrupt opioid dose reduction or discontinuation.

Whether or not opioids are tapered, safe and effective nonopioid treatments should be integrated into patients' pain management plans based on an individualized assessment of benefits and risks considering the patient's diagnosis, circumstances, and unique needs.[2,3,4] Coordination across the health care team is critical. Clinicians have a responsibility to provide or arrange for coordinated management of patients' pain and opioid-related problems, and they should never abandon patients.[2] More specific guidance follows, compiled from published guidelines (the *CDC Guideline for Prescribing Opioids for Chronic Pain*[2] and the *VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain*[3]) and from practices endorsed in the peer-reviewed literature.

Consider[iii] tapering to a reduced opioid dosage, or tapering and discontinuing opioid therapy, when

- Pain improves[3]
- The patient requests dosage reduction or discontinuation[2,3,5]
- Pain and function are not meaningfully improved[2,3,5]
- The patient is receiving higher opioid doses without evidence of benefit from the higher dose[2,3]
- The patient has current evidence of opioid misuse[3,5]
- The patient experiences side effects[iv] that diminish quality of life or impair function[3]
- The patient experiences an overdose or other serious event (e.g., hospitalization, injury),[2,5] or has warning signs for an impending event such as confusion, sedation, or slurred speech[2,6]
- The patient is receiving medications (e.g., benzodiazepines) or has medical conditions (e.g., lung disease, sleep apnea, liver disease, kidney disease, fall risk, advanced age) that increase risk for adverse outcomes[3,5]
- The patient has been treated with opioids for a prolonged period (e.g., years), and current benefit-harm balance is unclear

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[i] https://www.cdc.gov/drugoverdose/maps/rxrate-maps.html

[ii] Physical dependence occurs with daily, around-the-clock use of opioids for more than a few days and means that the body has adapted to the drug, requiring more of it to achieve a certain effect (tolerance). Patients with physical dependence will experience physical and/or psychological symptoms if drug use is abruptly ceased (withdrawal).

[iii] Additional tools to help weigh decisions about continuing opioid therapy are available: Assessing Benefits and Harms of Opioid Therapy, Pain Management Opioid Taper Decision Tool, and Tapering Opioids for Chronic Pain.

[iv] e.g., drowsiness, constipation, depressed cognition

Important considerations prior to deciding to taper

Overall, following voluntary reduction of long-term opioid dosages, many patients report improvements in function, sleep, anxiety, and mood without worsening pain or even with decreased pain levels.[4,7,8,9,10,11] Other patients report increased pain, insomnia, anxiety, and depression.[4,7,9,12] The duration of increased pain related to hyperalgesia or opioid withdrawal is unpredictable and may be prolonged in some patients.[12] Decisions to continue or reduce opioids for pain should be based on individual patient needs.[2,13] Consider whether opioids continue to meet treatment goals, whether opioids are exposing the patient to an increased risk for serious adverse events or opioid use disorder, and whether benefits continue to outweigh risks of opioids.[2,13]

- Avoid insisting on opioid tapering or discontinuation when opioid use may be warranted (e.g., treatment of cancer pain, pain at the end of life, or other circumstances in which benefits outweigh risks of opioid therapy). ***The CDC Guideline for Prescribing Opioids for Chronic Pain does not recommend opioid discontinuation when benefits of opioids outweigh risks.***[2,4,13]
- Avoid misinterpreting cautionary dosage thresholds as mandates for dose reduction.[4] While, for example, the CDC Guideline recommends avoiding or carefully justifying *increasing* dosages above 90 MME/day, it does not recommend abruptly reducing opioids from higher dosages.[2,4] Consider individual patient situations.
- Some patients using both benzodiazepines and opioids may require tapering one or both medications to reduce risk for respiratory depression. Tapering decisions and plans need to be coordinated with prescribers of both medications.[2] If benzodiazepines are tapered, they should be tapered gradually[v] due to risks of benzodiazepine withdrawal (anxiety, hallucinations, seizures, delirium tremens, and, in rare cases, death).[2]
- Avoid dismissing patients from care. This practice puts patients at high risk and misses opportunities to provide life-saving interventions, such as medication-assisted treatment for opioid use disorder.[2,4,13] Ensure that patients continue to receive coordinated care.
- There are serious risks to noncollaborative tapering in physically dependent patients, including acute withdrawal, pain exacerbation, anxiety, depression, suicidal ideation, self-harm, ruptured trust, and patients seeking opioids from high-risk sources.[1,14]

Important steps prior to initiating a taper

- Commit to working with your patient to improve function and decrease pain.[2,7] Use accessible, affordable nonpharmacologic and nonopioid pharmacologic treatments.[2,3,7] Integrating behavioral and nonopioid pain therapies before and during a taper can help manage pain[10] and strengthen the therapeutic relationship.
- Depression, anxiety, and post-traumatic stress disorder (PTSD) can be common in patients with painful conditions, especially in patients receiving long-term opioid therapy.[15] Depressive symptoms predict taper dropout.[7,8] Treating comorbid mental disorders can improve the likelihood of opioid tapering success.
- If your patient has serious mental illness, is at high suicide risk, or has suicidal ideation, offer or arrange for consultation with a behavioral health provider before initiating a taper.[3,5]
- If a patient exhibits opioid misuse behavior or other signs of opioid use disorder, assess for opioid use disorder using DSM-5 criteria.[2,5] If criteria for opioid use disorder are met (especially if moderate or severe), offer or arrange for medication-assisted[vi] treatment.[2,3]
- Access appropriate expertise if considering opioid tapering or managing opioid use disorder during pregnancy. Opioid withdrawal risks include spontaneous abortion and premature labor. For pregnant women with opioid use disorder, medication-assisted treatment is preferred over detoxification.[2]
- ***Advise patients that there is an increased risk for overdose on abrupt return to a previously prescribed higher dose.***[2] Strongly caution that it takes as little as a week to lose tolerance and that there is a risk of overdose if they return to their original dose.[2,3,5,6] Provide opioid overdose education and consider offering naloxone.[2]

Share decision-making with patients

- Discuss with patients their perceptions of risks, benefits, and adverse effects of continued opioid therapy, and include patient concerns in taper planning. For patients at higher risk of overdose based on opioid dosages, review benefits and risks of continued high-dose opioid therapy.[2,5]
- If the current opioid regimen does not put the patient at imminent risk, tapering does not need to occur immediately.[4] Take time to obtain patient buy-in.[14]
- For patients who agree to reduce opioid dosages, collaborate with the patient on a tapering plan.[2] Tapering is more likely to be successful when patients collaborate in the taper.[vii] Include patients in decisions, such as which medication will be decreased first and how quickly tapering will occur.

[v] Example benzodiazepine tapers and clinician guidance are available at https://www.pbm.va.gov/PBM/AcademicDetailingService/Documents/Benzodiazepine_Provider_AD_%20Risk_Discussion_Guide.pdf

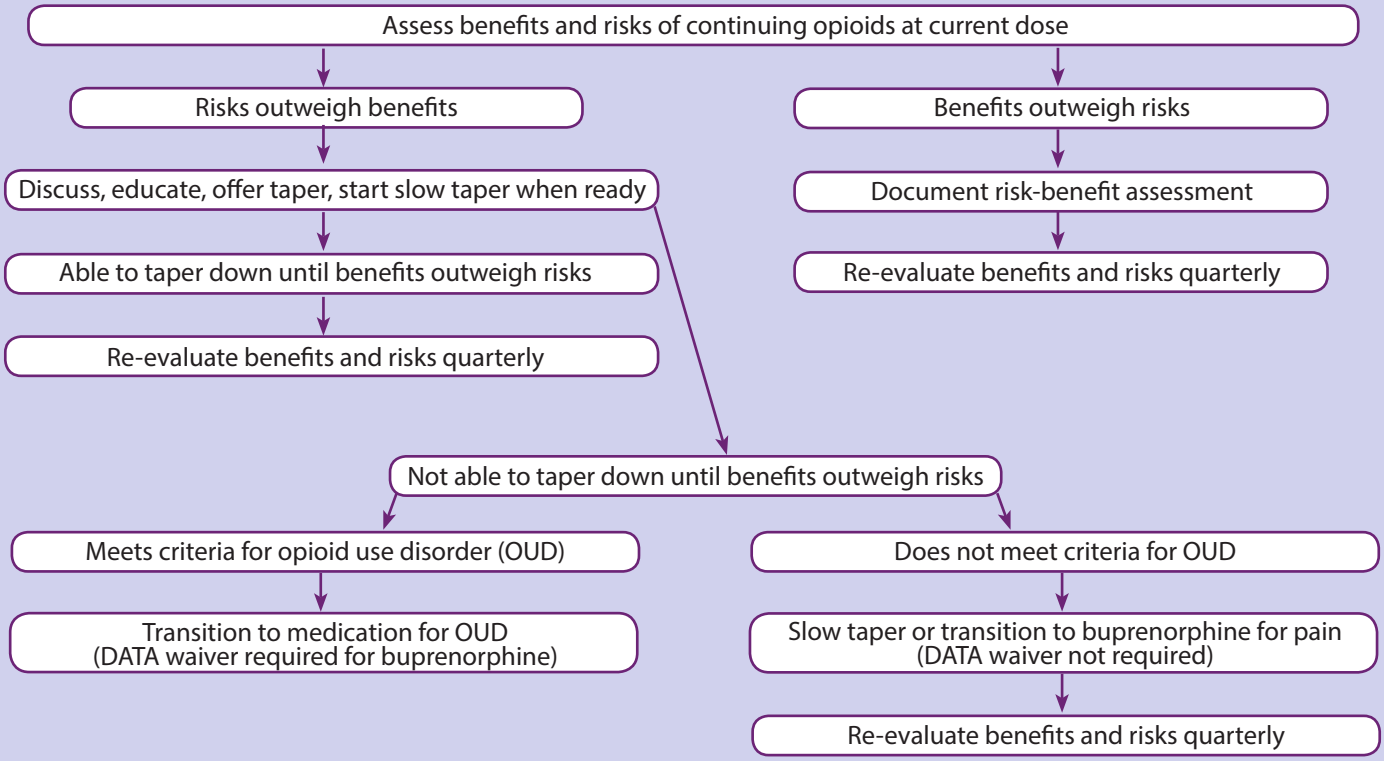
[vi] See SAMHSA's TIP 63: Medications for Opioid Use Disorder, SAMHSA's Buprenorphine Practitioner Locator, and SAMHSA's Opioid Treatment Program Directory

[vii] A recent systematic review found that when opioids were tapered with buy-in from patients who agreed to decrease dosage or discontinue therapy, pain, function, and quality of life improved after opioid dose reduction.[10]

Individualize the taper rate

- When opioid dosage is reduced, a taper slow enough to minimize opioid withdrawal symptoms and signs[viii] should be used.[2] Tapering plans should be individualized based on patient goals and concerns.[2,3,5,6]
- The longer the duration of previous opioid therapy, the longer the taper may take. Common tapers involve dose reduction of 5% to 20% every 4 weeks.[3,5]
  - **Slower tapers** (e.g., 10% per month or slower) are often better tolerated than more rapid tapers, especially following opioid use for more than a year.[2] Longer intervals between dose reductions allow patients to adjust to a new dose before the next reduction.[5] Tapers can be completed over several months to years depending on the opioid dose. See "slower taper" example here.
  - **Faster tapers** can be appropriate for some patients. A decrease of 10% of the original dose per week or slower (until 30% of the original dose is reached, followed by a weekly decrease of 10% of the remaining dose) is less likely to trigger withdrawal[7] and can be successful for some patients, particularly after opioid use for weeks to months rather than years. See "faster taper" example here.
- At times, tapers might have to be paused and restarted again when the patient is ready.[2] Pauses may allow the patient time to acquire new skills for management of pain and emotional distress, introduction of new medications, or initiation of other treatments, while allowing for physical adjustment to a new dosage.[3,5]
- Tapers may be considered successful as long as the patient is making progress, however slowly, towards a goal of reaching a safer dose,[2] or if the dose is reduced to the minimal dose needed.
- Once the smallest available dose is reached, the interval between doses can be extended.[2,5,7] Opioids may be stopped, if appropriate, when taken less often than once a day.[2,7] See "example tapers for opioids" here.
- More rapid tapers (e.g., over 2-3 weeks[16]) might be needed for patient safety when the risks of continuing the opioid outweigh the risks of a rapid taper (e.g., in the case of a severe adverse event such as overdose).
- Ultrarapid detoxification under anesthesia is associated with substantial risks and ***should not be used***.[2]

Opioid Tapering Flowchart



Adapted from Oregon Pain Guidance. Tapering – Guidance & Tools. Available at https://www.oregonpainguidance.org/guideline/tapering/.

DSM-5 Opioid Use Disorder

A problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain, use, or recover from the effects of opioids.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of opioids to achieve intoxication or desired effect, or
    b. Markedly diminished effect with continued use of the same amount of an opioid.

    Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic opioid withdrawal syndrome, or
    b. Opioids (or a closely related) substance is taken to relieve or avoid withdrawal symptoms.

    Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision.

Mild: Presence of 2-3 symptoms
Moderate: Presence of 4-5 symptoms
Severe: Presence of 6 or more symptoms

Treat symptoms of opioid withdrawal

- If tapering is done gradually, withdrawal symptoms should be minimized and manageable.
- Expectation management is an important aspect of counseling patients through withdrawal.
- Significant opioid withdrawal symptoms may indicate a need to pause or slow the taper rate.
- Onset of withdrawal symptoms depends on the duration of action of the opioid medication used by the patient. Symptoms can begin as early as a few hours after the last medication dose or as long as a few days, depending on the duration of action.[7] Early withdrawal symptoms (e.g., anxiety, restlessness, sweating, yawning, muscle aches, diarrhea and cramping[viii]) usually resolve after 5-10 days but can take longer.[5]
- Some symptoms (e.g., dysphoria, insomnia, irritability) can take weeks to months to resolve.[5]
- Short-term oral medications can help manage withdrawal symptoms, especially when prescribing faster tapers.[5] These include alpha-2 agonists[ix] for the management of autonomic signs and symptoms (sweating, tachycardia), and symptomatic medications[x] for muscle aches, insomnia, nausea, abdominal cramping, or diarrhea.[5]

Provide behavioral health support

- Make sure patients receive appropriate psychosocial support.[2,3,6,11] Ask how you can support the patient.[5]
- Acknowledge patient fears about tapering.[5] While motives for tapering vary widely, fear is a common theme. Many patients fear stigma, withdrawal symptoms, pain, and/or abandonment.[13,18]
- Tell patients "I know you can do this" or "I'll stick by you through this." Make yourself or a team member available to the patient to provide support, if needed.[3,6] Let patients know that while pain might get worse at first, many people have improved function without worse pain after tapering opioids.[7,8,9,10,11]
- Follow up frequently. Successful tapering studies have used at least weekly follow up.[10]
- Watch closely for signs of anxiety, depression, suicidal ideation, and opioid use disorder and offer support or referral as needed.[2,3,6] Collaborate with mental health providers and with other specialists as needed to optimize psychosocial support for anxiety related to the taper.[2]

[viii] Acute opioid withdrawal symptoms and signs include drug craving, anxiety, restlessness, insomnia, abdominal pain or cramps, nausea, vomiting, diarrhea, anorexia, sweating, dilated pupils, tremor, tachycardia, piloerection, hypertension, dizziness, hot flashes, shivering, muscle or joint aches, runny nose, sneezing, tearing, yawning, and dysphoria.[7] Worsening of pain is a frequent symptom of withdrawal that may be prolonged but tends to diminish over time for many patients.[7]

[ix] Alpha-2 agonists clonidine and lofexidine are more effective than placebo in ameliorating opioid withdrawal.[17] There is not similar research in patients tapering from long-term opioid treatment for pain.[7] Lofexidine has an FDA-approved indication for use up to 14 days for "mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults."

[x] NSAIDs, acetaminophen, or topical menthol/methylsalicilate for muscle aches; trazodone for sleep disturbance; prochlorperazine, promethazine, or ondansetron for nausea; dicyclomine for abdominal cramping; and loperamide or bismuth subsalicylate for diarrhea.[5]

Special populations

- If patients experience unanticipated challenges to tapering, such as inability to make progress despite intention to taper or opioid-related harm, assess for opioid use disorder using DSM-5 criteria.[2] If patients meet criteria for opioid use disorder (especially if moderate or severe), offer or arrange medication-assisted treatment.[2,3]
- If patients on high opioid dosages are unable to taper despite worsening pain and/or function with opioids, whether or not opioid use disorder criteria are met, consider transitioning to buprenorphine.[4,12] Buprenorphine is a partial opioid agonist that can treat pain as well as opioid use disorder,[19] and has other properties that may be helpful,[3] including less opioid-induced hyperalgesia[12] and easier withdrawal than full mu-agonist opioids,[3] and less respiratory depression than other long-acting opioids.[20] Buprenorphine can then be continued or tapered gradually.[12] Transitioning from full-agonist opioids requires attention to timing of the initial buprenorphine dose to avoid precipitating withdrawal.[xi]

  Consultation with a clinician experienced in use of buprenorphine is warranted if unfamiliar with its initiation. SAMHSA's Providers Clinical Support System offers training and technical assistance as well as mentors to assist those who need to taper opioids and may have additional questions.

- Closely monitor patients who are unable or unwilling to taper and who continue on high-dose or otherwise high-risk opioid regimens. Mitigate overdose risk (e.g., provide overdose education and naloxone). Use periodic and strategic motivational questions and statements to encourage movement toward appropriate therapeutic changes.[14]

[xi] To avoid precipitating protracted withdrawal from full agonist opioids when starting buprenorphine, patients need to be in mild to moderate withdrawal (including Clinical Opioid Withdrawal Score (COWS) objective signs) before the first buprenorphine dose.[12] To do this, wait at least 8 to 12 hours after the last dose of short-acting full agonist opioids before the first dose of buprenorphine.[12] Buprenorphine buccal film (Belbuca) and buprenorphine transdermal system (Butrans) have FDA-approved indications for "the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate." The full Belbuca prescribing information and the full Butrans prescribing information include instructions for conversion from full agonist opioids. More time should be allowed before starting buprenorphine following the last dose of long-acting full agonist opioids (e.g., at least 36 hours after last methadone dose); in addition, transition from methadone to buprenorphine is likely to be better tolerated after methadone is gradually tapered to 40mg per day or less.[12] Because the duration of action for analgesia is much shorter than the duration of action for suppression of opioid withdrawal,[21] "split dosing" (e.g., 8mg sublingual tablet twice a day) rather than once a day dosing is used when buprenorphine is provided for pain management.[3,12]

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CHAPTER SIX

Optimizing Placebo and Minimizing Nocebo to Reduce Pain, Catastrophizing, and Opioid Use: A Review of the Science and an Evidence-Informed Clinical Toolkit

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Abstract

Pain, a noxious psychosensory experience, motivates escape behavior to assure protection and survival. Psychological factors alter the experience and trajectory of pain, as well as behavior and treatment response. In the context of pain, the placebo effect (expectation for pain relief) releases endogenous opioids and facilitates analgesia from exogenously administered opioids. Nocebo hyperalgesia (expectation for persistent or worsening pain) opposes endogenous opioid analgesia and patient engagement in prescription opioid tapering. Reductions in nocebo hyperalgesia and pain catastrophizing may enhance descending modulation of pain, mediate adaptive structural brain changes and promote patient engagement in opioid tapering. Interventions that minimize nocebo and optimize placebo may adaptively shape the central nervous system toward pain relief and potentially opioid reduction. Here we provide a critical description of catastrophizing and its impact on pain, placebo and nocebo effects. We also consider the importance of minimizing nocebo and optimizing placebo effects during prescription opioid tapering, and offer a clinical toolkit of resources to accomplish these goals clinically.

1. INTRODUCTION

1.1 The Problem of Pain

Pain is a global health problem with broad negative impacts on physical (Sturgeon, Darnall, Kao, & Mackey, 2015; Sturgeon, Dixon, Darnall, & Mackey, 2015), mental (Bair, Robinson, Katon, & Kroenke, 2003; Feinstein et al., 2017; Ziadni, Sturgeon, & Darnall, 2018), spiritual (Halawa, Al-Diri, McLean, & Darnall, 2015), psychosocial (Karos, Meulders, Goubert, & Vlaeyen, 2018; Karos, Williams, Meulders, & Vlaeyen, 2018; Sturgeon et al., 2016; Ziadni, You, Wilson, & Darnall, 2018), and economic domains (Groenewald, Essner, Wright, Fesinmeyer, & Palermo, 2014; Gustavsson et al., 2012). The 2016 Institute of Medicine report on *Relieving Pain in America* estimated that roughly one-third of the world population is living with ongoing pain of some type (IOM Committee on Advancing Pain Research, 2011). Pain is more costly than diabetes, heart disease, and cancer combined, with combined estimates reaching up to $635 billion each year for medical costs and lost productivity in the United States alone (IOM Committee on Advancing Pain Research, 2011). Effective, scalable, and low-risk pain treatment strategies are urgently needed, particularly in light of calls to reduce opioid prescribing as a pathway to mitigate opioid-related morbidity and mortality in the United States·(CDC, 2016; Hoffman, 2018), Australia, Canada, and elsewhere. Indeed, opioid de-prescribing practices have

rapidly taken effect across the United States with scant attention given to the potential patient harms caused by aggressive tapering approaches, including clear nocebo effects (Hoffman, 2018; Langreth, 2017). Treating pain effectively and compassionately—and at lowest-risk—requires careful attention to the psychological dimensions of pain and, when relevant, opioid reduction (Darnall, 2014a, 2014b).

Pain is a psychosensory experience wherein the brain perceives and interprets pain signaling (Darnall, 2018b). Indeed, by definition pain comprises psychological elements (IASP, 1994), thereby suggesting that, in part, analgesia depends on them. The extant literature demonstrates that psychopathology is both an antecedent (Gerrits, van Marwijk, van Oppen, van der Horst, & Penninx, 2015) and a consequence of persistent pain (Archer et al., 2016). Extending the scope beyond formal psychopathology, psychological factors that are known to influence pain and analgesia include cognition (Burns, Glenn, Bruehl, Harden, & Lofland, 2003; Darnall et al., 2017; Salomons, Moayedi, Erpelding, & Davis, 2014; Seminowicz & Davis, 2006; Seminowicz et al., 2013; Ziadni, Sturgeon, et al., 2018), emotion (Burns et al., 2015; McCracken & Keogh, 2009; Vlaeyen, Crombez, & Linton, 2016), appraisal (Ziadni, Sturgeon, et al., 2018), expectations (Atlas et al., 2012; Colloca & Miller, 2011b; Palermo & Drotar, 1996; Wager, Atlas, Leotti, & Rilling, 2011), attention (Kucyi, Salomons, & Davis, 2013; Seminowicz & Davis, 2006), beliefs about pain and its treatment (Carriere, Martel, Kao, Sullivan, & Darnall, 2017; Carriere et al., 2018). Mechanisms of psychological effects on pain and analgesia include behavioral factors (Linton, Flink, & Vlaeyen, 2018; Vlaeyen et al., 2016), conditioning, and neurochemical pathways. Neurally, psychological factors can influence pain and analgesia through descending modulation of pain wherein pain is either facilitated or impeded depending on one's adaptive capacities. As such, low-risk analgesia may be achieved by targeting psychological factors known to amplify pain (Darnall, 2014a, 2014b). While adaptively engaging descending modulation confers in vivo analgesia, longitudinal clinical research in chronic pain has shown that a pattern of engaging descending modulation over a period of weeks is associated with structural changes in the brain that appear to prime the central nervous system for future analgesia, thereby altering the trajectory of pain (Seminowicz et al., 2013). We review the relevance of placebo and nocebo processing in shaping the central nervous system either toward relief or pain exacerbation, and provide an evidence-based clinical toolkit to enhance placebo and pain relief.

1.2 Placebo and Nocebo Are Integral to Pain Experience

Decades of mechanistic research on placebo and nocebo effects is serving to inform the development and integration of placebo optimization strategies into clinical care pathways to treat pain. To understand how placebo and nocebo science may be applied to address the current dual pain and opioid crises, we first review several elemental principles and relevant key research findings. Beginning with nomenclature, placebo and nocebo effects are psychoneurobiological responses that occur in the body as result of positive and negative expectations (Colloca, 2018a, 2018b; Wager & Atlas, 2015). Expectations result in brain events that trigger the release of endogenous neuropeptides and influence behaviors. Placebo effects due to positive expectations have been linked to the release of endogenous opioids for a review, see Eippert et al. (2009) and Pecina and Zubieta (2018) and cannabinoids (Benedetti, Amanzio, Rosato, & Blanchard, 2011). Studies using indirect pharmacological approaches have demonstrated that placebo analgesia is antagonized by the opioid antagonist naloxone, thus, indicating that endogenous opioids crucially involved in placebo analgesic effects. Moreover, pharmacological fMRI and PET studies using an in vivo receptor binding with opioidergic ligands have provided evidence of the anatomical localization of the neuropeptides in the brain (Eippert et al., 2009; Wager, Scott, & Zubieta, 2007; Zubieta et al., 2005). In another evoked pain paradigm, Tor Wager and colleagues illustrated engagement of mu-opioid activity during placebo analgesia (Wager et al., 2007). Participants in the study were told that pills they were given would relieve their pain. Results showed that reports of placebo analgesia following administration of an inert pill was correlated with endogenous release of opioids. As such, the release of endogenous opioids depended on the belief that treatment-related pain relief was imminent.

The cannabinoid receptor 1 (CB1) antagonist SR 141716A (rimonabant) blocks placebo analgesia elicited by placebo given after NSAID ketorolac indicating an involvement of to the release of endogenous cannabinoids (Benedetti et al., 2011). Recently, it has been shown that oxytocin and vasopressin agonists given intranasally enhance behavioral placebo analgesia in men (Kessner, Sprenger, Wrobel, Wiech, & Bingel, 2013) and women (Colloca, Pine, Ernst, Miller, & Grillon, 2016), suggesting that the oxytocinergic and vasopressinergic systems, typically involved in the modulation of social behaviors (Campbell, 2010; Heinrichs & Domes, 2008) can be used as enhancers of placebo analgesic effects. Further research is needed to determine how distinct doses of oxytocin and vasopressin influences outcomes and affect brain mechanisms underlying this potentiation.

On the contrary, nocebo effects have been linked to the release of cholecystokinins that are involved in the modulation of anxiety and hyperalgesia. The block of the CCK A and B receptors with the type A/B receptor antagonist proglumide antagonizes nocebo hyperalgesia (Benedetti, Amanzio, Vighetti, & Asteggiano, 2006).

A noxious stimulus, pain signals threat or harm to an individual, and motivates escape behavior to achieve protection and survival. Viewed in this light, acute or current pain may serve as a direct nocebo reaction. Context information that is derived from one's environment and habitus (i.e., pain itself) interact with an individual's psychological status—consciously or subconsciously—in dynamic fashion. Indeed, pain placebo and nocebo are opposing phenomena existing most likely on a continuum.

Accordingly, optimizing placebo in the clinical setting requires one identify and extinguish any existing nocebo effects. In later sections, we will address the importance and procedures for attempting to extinguish nocebo effects for pain and opioid reduction.

1.3 Conceptualizing Nocebo to Encompass Pain Proper

Expectation for pain elicits a nocebo effect: facilitation of pain, distress and disease. Given that pain triggers a latent appraisal of noxious experience of varying degrees and related components (e.g., sensory, physical, emotional), it could be argued that an individual's positive appraisal regarding their ability to reduce their pain constitutes a viable way to create placebo effects. Whereas, an appraisal that pain will only worsen and there is nothing that can reduce one's pain constitutes a nocebo effect, whether such appraisal is due to poor faith in current treatments or one's ability to effectively self-manage or self-modulate pain. The patient's prior negative experience (memory, learning, priming and conditioning), internal states, and external context cues may interact dynamically to influence her/his brain responses to either inhibit or facilitate pain (Benedetti, Mayberg, Wager, Stohler, & Zubieta, 2005; Di Blasi & Kleijnen, 2003; Mistiaen et al., 2016).

Research suggests that stronger belief in the treatment enhances its effects (Doering, Glombiewski, & Rief, 2018; Kong et al., 2006; Kube, Glombiewski, & Rief, 2018; Seminowicz, 2006). In this case, greater belief in one's ability to self-modulate pain in turns may facilitate the expected analgesic outcome. Whereas, strong belief in a deficiency to self-modulate pain in turn may result in amplified pain.

1.4 Nocebo and Pain Catastrophizing

Accordingly, pain catastrophizing, a psychological construct and potent index of descending modulation of pain, is a particularly useful model for studying placebo and nocebo effects. Pain catastrophizing is a persistent pattern of distressing cognitive and emotional responses to current or anticipated pain. First described by Rosenstiel and Keefe and measured with the catastrophizing subscale of the Coping Skills Questionnaire, pain catastrophizing is comprised of a pattern of rumination on pain and feelings of helplessness about pain (Rosenstiel & Keefe, 1983). This definition of pain catastrophizing was later expanded upon by Michael Sullivan and colleagues to also include a third component: magnification of pain. The expanded definition is assessed with the Pain Catastrophizing Scale (PCS), a lengthier 13-item measure that prompts respondents to reference painful incidents in their life and to rate the degree to which they tend to have various negative thoughts, expectations or emotions about pain when they are experiencing it (Sullivan, 1995). Example items from the PCS include: "I become afraid that the pain will get worse"; "there's nothing I can do to reduce the intensity pain"; and "[my pain] is terrible and I think it's never going to get any better." Each item is rated on a 0–4 scale wherein 0 = "not at all" and 4 = "all the time." The 13 items are summed to arrive at a total PCS score, which reflects an individual's trait disposition toward pain catastrophizing. Pain catastrophizing is a malleable construct that is responsive to both longer course (Cherkin et al., 2016; Seminowicz et al., 2013; Turner et al., 2016) and brief, targeted psychological treatment (Darnall, Sturgeon, Kao, Hah, & Mackey, 2014; Thorn et al., 2007).

Placebo effects have been linked to a distinct series of psychological factors such as dispositional optimism, hypnotic suggestibility, somatic focus, empathy, neuroticism, altruisms, and the locus of ego-reliance (for a review, see Colloca & Grillon, 2014). Conversely, anxiety (Staats, Staats, & Hekmat, 2001), harm avoidance and persistence (Corsi, Emadi Andani, Tinazzi, & Fiorio, 2016) and anxiety sensitivity and physiological suggestibility (Corsi & Colloca, 2017) have been associated with nocebo effects in healthy subjects. In particular, pain catastrophizing has also been associated to nocebo effects in experimental settings in which nocebo manipulations are performed (Corsi & Colloca, 2017; Swider & Babel, 2013; Vogtle, Barke, & Kroner-Herwig, 2013).

A recent study looked at low scores of pain catastrophizing along with expectation for pain relief, anxiety, depression and the personality trait neuroticism and high levels of positive emotions as predictors of placebo responses in randomized, double-blind, placebo-controlled, crossover study

with the anticonvulsant oxcarbazepine for treatment of peripheral neuropathic pain (Lund et al., 2017). Multiple regression analyses with pain reduction during placebo treatment as the dependent variable and baseline pain, age, sex, and pain duration revealed high significance ($P < 0.001$), while other psychological variables did not reach statistical significance. Further studies are needed exploring the link between placebo and nocebo effects in patients suffering from chronic and acute pain.

Before we discuss the possibility to target psychotherapy to treat catastrophizing thoughts and pain exacerbation = in extinguishing nocebo, we first review its impacts and importance as a therapeutic target.

1.4.1 Experimental Studies

The extent to which a persistent pattern of catastrophizing might sensitize the nervous system has been a recent topic of interest and investigation. Neuroimaging studies conducted on healthy volunteers have shown that pain catastrophizing is associated with amplified activity in areas of the brain associated with the experience of pain, and this directly correlates with report of increased pain (Seminowicz & Davis, 2006).

Our group conducted a controlled pilot study that tested the psychosensory effects of a pain catastrophizing induction in women with chronic pain (evoked pain catastrophizing), and specifically tested whether secondary hyperalgesia was associated with pain catastrophizing during evoked pain (Taub, Sturgeon, Johnson, Mackey, & Darnall, 2017). Study participants assigned to the catastrophizing condition were guided to imagine their pain worsening and to envision great negative consequence resulting from increased pain. The imagined scenario was designed to allow for a personally relevant construction of worsening pain, reduced function, and "worst case scenario" as it pertained to each individual. Quantitative sensory testing conducted before and after the induction was designed to reveal whether greater pain catastrophizing was associated with increased pain intensity (hyperalgesia) as well as spread of pain to non-painful areas (allodynia). Findings revealed that two quantitative sensory tests (weighted pin and mechanical allodynia) were associated with secondary hyperalgesia for women with greater levels of evoked pain catastrophizing. Replication of this work would confirm central sensitization as a mechanism of pain catastrophizing (Taub et al., 2017). Other research provides supporting evidence of catastrophizing having a mechanistic role in central sensitization, though viewed from the other direction. Salomons and colleagues conducted a randomized controlled experiment to test a brief cognitive behavioral

intervention designed to enhance descending modulation of experimental pain could mitigate catastrophizing and pain (Salomons et al., 2014). The intervention included 5-min instructional sessions on cognitive regulation of pain given prior to each of eight sessions of evoked heat pain. The researchers found that the brief cognitive training reduced pain unpleasantness—but not pain intensity—as well as secondary hyperalgesia and pain catastrophizing. The authors stated that their reported association between reduced secondary hyperalgesia and pain catastrophizing suggested that reductions in central sensitization are related to volitional alterations of pain-related cognitions (Salomons et al., 2014).

Longitudinal studies conducted in clinical samples are needed to extend beyond the proximal impacts of nocebo and characterize the mechanisms of pain catastrophizing and placebo and nocebo effects.

1.4.2 Clinical Research

Across different treatment settings spanning outpatient, inpatient, and perioperative environments, pain catastrophizing consistently emerges as one of the strongest predictors of pain treatment outcomes.

A systematic review of pain catastrophizing (total $N = 2269$) found that pain catastrophizing predicted pain intensity and disability, and pain catastrophizing mediated back pain treatment efficacy in outpatients seeking specialty pain care (Wertli et al., 2014). Independent of depression, pain catastrophizing has been associated with an array of negative phenomena including increased affective distress (Picavet, Vlaeyen, & Schouten, 2002; Spinhoven et al., 2004), muscle and joint tenderness (Severeijns, Vlaeyen, van den Hout, & Weber, 2001), muscular tension at rest (Smeets, van Geel, Kester, & Knottnerus, 2007), pain-related disability (Severeijns, Vlaeyen, & van den Hout, 2004; Severeijns et al., 2001), and poor response to various pain treatments including surgery (Abbott, Tyni-Lenne, & Hedlund, 2011; Helmerhorst, Vranceanu, Vrahas, Smith, & Ring, 2014; Jensen, Thomsen, & Hojsted, 2006; Kennedy, Vranceanu, Nunez, & Ring, 2010; Smeets et al., 2007; Spinhoven et al., 2004; Theunissen, Peters, Bruce, Gramke, & Marcus, 2012). Indeed, the perioperative setting is useful for investigating the clinical impacts of pain, nocebo-induced hyperalgesia, particularly with surgery often involving a clear pain stimulus and a defined recovery period. To investigate the impact of pain catastrophizing on post-surgical outcomes, researchers typically measure pain catastrophizing tendencies prior to surgery. Greater pain catastrophizing has been shown to be directly associated with greater use of opioids and pain

in the hospital after surgery (Papaioannou et al., 2009; Wright, Hoang, Sofine, Silva, & Schwarzkopf, 2017), longer hospital stay (Wright et al., 2017), delayed recovery from surgery (Roh et al., 2014), and persistent opioid use (Helmerhorst et al., 2014). Pain catastrophizing also harmful in the context of acute pain and even for individuals who are pain-free. For instance, pain catastrophizing is implicated in the persistence of back pain (Picavet et al., 2002) and researchers found that pain catastrophizing accounted for 47% of the variance in the *development* of chronic back pain following an episode of acute back pain (Burton, Tillotson, Main, & Hollis, 1995). Moreover, a cross-sectional observational population study revealed that among all factors investigated, pain catastrophizing best predicted the acquisition of chronic low back pain 1 year after a pain-free baseline (Linton, 2005). Taken together, these data illustrate the detrimental impacts of pain catastrophizing across settings and populations, and suggest that early treatment for pain catastrophizing may serve as prophylaxis for prevention of chronic pain phenotypes.

Given that pain catastrophizing appears to undermine response to medical pain treatments, it is perhaps unsurprising that *reductions in pain catastrophizing are associated with subsequent* improvements in pain and intervention effectiveness. In a prospective study, Burns et al. used cross-lagged analysis to show that early reductions in pain catastrophizing significantly improved later response to multidisciplinary treatment in terms of pain intensity and pain interference (Burns, Glenn, et al., 2003; Burns, Kubilus, Bruehl, Harden, & Lofland, 2003). Neuroimaging studies conducted on individuals with chronic pain reveal that greater pain catastrophizing is associated with volumetric deficits in key brain regions associated with descending modulation of pain (Seminowicz et al., 2013). While it is unknown whether structural deficits were antecedents or consequences of catastrophizing, their co-occurrence suggests a mutually-reinforcing biobehavioral cycle of pain and potential nocebo-induced hyperalgesia (Blasini, Corsi, Klinger, & Colloca, 2017). Indeed, pain catastrophizing in individuals with chronic pain has been shown to associate with altered neural functioning outside of the context of evoked pain or in vivo catastrophizing (Jiang et al., 2016). Greater pain catastrophizing is associated with altered brain functioning in the default mode network—an over-coupling between the central executive network and the amygdala—that attune the brain to pain (Jiang et al., 2016). These findings suggest that pain catastrophizing is associated with neural alterations in individuals with chronic pain that appear to prime their nervous pain signaling systems for future pain.

1.5 Reducing Pain Catastrophizing: Shaping Patient Expectations Toward Pain Relief

Cognitive behavioral therapy for chronic pain (pain-CBT) effectively reduces pain catastrophizing and increases pain self-efficacy; that is, the belief in one's ability to engage in various life activities despite living with ongoing pain (Cherkin et al., 2016; Stewart et al., 2015; Thorn et al., 2007; Williams, Eccleston, & Morley, 2012). Pain-CBT is typically delivered by a trained psychologist either individually or in group classes. Most often, group pain-CBT is a series of 2-h classes (often 8–11 classes) delivered weekly. Classes include social interaction, didactic content, and experiential exercises. Didactic content includes education about pain and the role of psychology in its treatment, thereby establishing the treatment rationale, as well as remoralization around the notion that personal control over pain may be cultivated. Participants learn about the role of cognition in pain perception, emotional experience, and physiological responses. Importantly, participants learn to identify their maladaptive thought patterns that maintain and amplify pain and distress. Often negative thoughts involve catastrophizing, and pain-related negative thoughts (e.g., "My pain is never going to go away," or "I am at the mercy of my pain."). Acquired skills specifically enhance descending modulation of pain. Cognitive restructuring, relaxation training, and positive distraction are adaptive modulatory skills that may effectively interrupt in vivo catastrophizing. Repeated application and thought interruption weakens the negative neural and behavioral patterns. Volitionally calming the nervous system allows for recoding of physiological responses that oppose pain and nocebo (e.g., relaxation, positive expectation for relief and belief in one's ability to self-soothe) and lead to lasting adaptive changes in the nervous system. Seminowicz and colleagues provided strong evidence in this direction. The research group conducted pre-post treatment neuroimaging on patients with chronic pain who underwent an 11-week course of group pain-CBT (Seminowicz et al., 2013). The authors reported that prior to pain-CBT, patients evidenced volumetric deficits in regions of the brain associated with pain control. However, the pre-treatment volumetric deficits were mitigated substantially in the post-treatment scans, and the pre-frontal gray matter brain volume increases were entirely mediated by reductions in pain catastrophizing. The adaptive structural brain changes and reductions in pain catastrophizing correlated directly with decreased pain intensity.

These findings underscore that descending modulation of pain may be applied to directly impact pain perception and cultivated to shape enduring

brain changes that confer relief. Placebo and patient engagement in pain-CBT may be optimized by sharing these specific neuroscientific findings for treatment research conducted on clinical samples. Indeed, a central goal of pain-CBT is to enhance descending modulation of pain. Colloca and colleagues' work reveals that a reinforced expectancy (e.g., via conditioning) strongly create large pain modulatory effects (Au Yeung, Colagiuri, Lovibond, & Colloca, 2014; Colloca, Jonas, Killen, Miller, & Shurtleff, 2014; Klinger, Colloca, Bingel, & Flor, 2014). The greater one's expectations for pain to improve (or worsen), the greater pain modulation occurs in the expected direction (Corsi & Colloca, 2017). Shaping placebo to enhance descending modulation and facilitate ongoing engagement with adaptive skills may optimize its clinical manifestation (Klinger, Blasini, Schmitz, & Colloca, 2017). A recent meta-analysis of 27 studies showed that how interventions are presented to patients impacts their pain. Basic information about a treatment can serve to reassure patients that they will have a good response to the treatment—they experience greater analgesia, including individuals with chronic pain (Peerdeman et al., 2016). Providing compelling positive results for scientific studies may boost placebo further, in part by enhancing patient preference and engagement in the treatment. Indeed, a common notion is that psychological treatment for pain is "palliative care," something to be administered when all real medical treatment fails. This common flawed perspective that relegates psychological treatment to "learning how to cope with pain" can severely limit engagement in pain-CBT and undermine placebo. Placebo optimization for pain-CBT includes providing patients with the scientific evidence that psychological treatment extends well beyond "pain coping"; rather, pain-CBT alters the pain experience itself, shapes the trajectory of pain, changes the functioning and the structure of the brain so that the nervous system becomes "primed" for relief.

1.6 The "Actual" Effect of a Treatment: A Mythical Pursuit in Chronic Pain?

To date, research has mainly focused on controlling for placebo effects and minimizing them for the purpose of elucidating the "actual" effect of a therapy in the context of clinical trials. However, the recent research suggests that it is challenging to isolate the so-called "actual" treatment effect in real-world clinical settings (emerging uncertainty principle, see Colloca & Benedetti, 2005) wherein treatments are applied to patients who bring their entire psychology with them—including their cognition, emotion, beliefs

and expectations about the treatment they are about to receive—the very factors that profoundly influence pain and treatment response. Furthermore, the success of behavioral treatment such as pain psychology treatment is dependent on patient engagement and a belief that the treatment will benefit them (placebo). As such, the notion of a static pain treatment effect existing in the absence of placebo/nocebo may have questionable value in everyday clinical settings. Pain is an individual experience, as is treatment response, and both interact dynamically with psychological factors. As such, perhaps the most useful clinical pathway is to phenotype patients prior to treatments, identify therapeutic targets for minimizing nocebo and optimizing placebo, and direct resources to enhance pain treatment outcomes (Darnall, 2018a). Owing to its impacts and relationship to nocebo and treatment outcomes, pain catastrophizing remains a primary, high-yield therapeutic target.

1.7 Patient Preference: A Fly in the Ointment

The potential mechanisms of placebo effects are manifold and in addition to neural and pharmacological pathways include behavioral factors that impact engagement and adherence to the treatment regimen, including patient preference for a particular treatment. Patient preference may partially index a belief that the treatment will be beneficial, although various other factors are known to influence patient preferences (Enck, Grundy, & Klosterhalfen, 2012), such as burdens related to actively engaging in a treatment, associated costs, and potential side effects.

Above we briefly touched on the importance of placebo optimization for pain-CBT as a pathway to enhance patient preference and engagement in this clinical treatment pathway. The goal is to provide compelling contextual information that makes the patient *want* the treatment, then boost their engagement in the treatment (behavior change). Combined, this creates a powerful cycle of cognitive, emotional, and behavioral reinforcement related to the treatment. Despite its strong influence on placebo and treatment response, patient preference for treatment type is often ignored in pain research, thereby confounding study findings. Indeed, similar to the placebo studies, in the "gold standard" of clinical trials designs, the randomized controlled clinical trial, patient participant treatment preference is often "subtracted out" as if real-world treatment response does not depend on it. Admittedly, controlling for patient preference in analytic models does

inform its predictive value. However, assigning a patient to a treatment group they do not believe will benefit them reduces the likelihood of positive treatment response. In the absence of patient choice, treatment research results likely underestimate true treatment effects (Bingel et al., 2011), particularly in psychological treatment studies that require a high degree of active engagement compared to relatively passive pharmacologic treatments. Recognizing that clinical care does not exist in blinded fashion, research that aims study treatment effects should consider allowing patient choice in the treatment (Enck et al., 2012) whenever possible (equipoise randomized stratification is one statistical method that can be applied for this purpose (Lavori et al., 2001)), as well as include strategies to further enhance preference. The rationale is that the true *available* treatment effect is:

Treatment applied in an engaged patient who chooses the treatment pathway based on a belief that the treatment will be of benefit:

- With treatment = x and placebo = y, the true available treatment effect is x + y.

While the treatment (x) is relatively static, (y) is malleable and dependent on a variety of contextual factors, including the patient-provider dynamics, careful education and patient comprehension about treatment benefits and why they are important to the patient. A new era of patient-centered care and precision medicine stands to improve the effectiveness of various treatments both because the treatment has greater precision and because patient receptivity is enhanced by clear understanding of the personal relevance and importance of the treatment. Placebo optimization strategies may also be applied within the context of any type of analgesic treatment, including psychological treatment, physical therapy, as well as strategies individuals use in their daily lives to self-manage their pain.

1.8 Minimizing Nocebo and Optimizing Placebo for Opioid Reduction

Klinger and colleagues discussed several approaches to optimize placebo response for prescribed analgesic medications (Klinger et al., 2017, 2014). Two examples of strategies designed to enhance positive patient expectations include emphasizing the drug's positive value while minimizing side effects, as well as carefully explaining the drug's mechanisms of actions to the patient (Klinger et al., 2017, 2014). Here, through the lens of prescription opioids, we extend the discussion of placebo optimization beyond the

medication to include medication prescribing procedures (e.g., patient engagement), medication titration procedures and specifically symptom management in regards to prescription opioid tapering.

1.9 Avoiding the Nocebo Pitfall of Opioid Tapering

Human physiology fairly rapidly adapts to daily administration of opioids. Over the course of weeks of daily opioid use, most people will develop a degree of physical dependence; that is, if the drug is suddenly withdrawn, noxious symptoms arise (e.g., withdrawal symptoms). Withdrawal symptoms may include increased pain, nausea, anxiety, restlessness, opioid craving, muscle aches, and stomach cramps. While not dangerous, the severity of withdrawal symptoms and related discomfort may range from mild to intolerable. Most patients taking long-term opioids understand withdrawal symptoms through prior experience: they may have accidentally missed a dose of medication, or may have tried to taper or stop opioids and experienced withdrawal symptoms. The experience of opioid withdrawal symptoms may lead patients to encode a false belief that they are unable to taper their opioids and must maintain their current dose. In fact, withdrawal symptoms do not index an individual's capacity to reduce prescription opioid dose; rather, withdrawal symptoms index a need for better tapering methods. Moreover, increased pain is a common opioid withdrawal symptom; however, many patients may encode the false belief that this amplified withdrawal-related pain is their "baseline pain level," thereby leading them to conclude that opioids are the only way to maintain a tolerable level of pain. These common false beliefs are may be powerfully anchored with negative reinforcement in that re-administration of opioids eliminates noxious symptoms, including amplified pain. Unfortunately, current guidelines may be in some clinical cases too aggressive for chronic pain patients who often have been taking opioids for years or decades (Berna, Kulich, & Rathmell, 2015). Aggressive tapers may trigger withdrawal symptoms and unintended nocebo effects, thereby perpetuating the false beliefs that can maintain patients on opioids when they otherwise would have been interested in reducing or stopping opioids if offered a successful pathway forward.

Even in the absence of prior experience with opioid withdrawal symptoms, it is intuitive for patients to assume that their pain will increase in the absence of their pain medication. However, data from opioid tapering studies demonstrate that opioid reduction is more often associated with *reduced* pain when they are tapered the right way (Baron & McDonald, 2006;

Crisostomo et al., 2008; Murphy, Clark, & Banou, 2013). While these studies involved resource-intense methods to achieve opioid cessation (e.g., inpatient interdisciplinary treatment delivered over the course of weeks), intensive and costly treatment may not be requisite. For instance, Darnall and colleagues' findings suggested that patient-centered opioid tapering methods may help community-based outpatients achieve opioid reduction without costly resources, and without increased pain (Darnall et al., 2018). A key aspect of patient-centered opioid tapering methods involves identifying and addressing opioid tapering negative expectations and related-nocebo effects as a pathway to patient engagement in the taper process. A second key aspect is reducing the pace of the taper to allow ample time for physiologic and psychologic adaptive to occur; this serves to obviate nocebo effects, as well as contextually cultivate placebo and a belief that successful tapering is possible.

To set the stage for placebo optimization and patient-centered opioid tapering, we administered an online survey to 1561 patients with chronic pain taking long term opioids to understand their opinions and concerns regarding potential opioid reduction. Surveys were completed by 248 patients (16% response rate). Results were perhaps unsurprising: patients reported that their primary concerns about opioid reduction were increased pain and withdrawal symptoms—negative thoughts and nocebo effects about opioid reduction. Results also revealed that respondents were unaware that opioid reduction could be associated with reduced pain. Seventy percent of patients reported that they would be interested in trying to reduce their opioids if they knew first about the positive results for prior opioid tapering studies (unpublished data). These findings dovetail with work conducted by Darnall, Colloca and others showing that patient concerns and fears about opioid tapering must be addressed first to minimize nocebo effects, empowering positive expectations by optimizing patients' education and patient–clinician communication (Colloca & Finniss, 2012) including amplified pain and poor taper result, and to best ensure patient engagement in the opioid tapering process and clinically-relevant outcomes (Benedetti, Lanotte, Lopiano, & Colloca, 2007; Colasanti, Rabiner, Lingford-Hughes, & Nutt, 2011; Colloca & Benedetti, 2007; Colloca, Klinger, Flor, & Bingel, 2013; Colloca & Miller, 2011a, 2011b; Darnall et al., 2018; Horin, Lee, & Colloca, 2014). Brief education from the prescribing physician can reassure, soften or eliminate negative expectations and enhance patient receptivity and actual analgesic response to the intervention (Benedetti et al., 2007; Colasanti et al., 2011; Colloca & Benedetti, 2007; Colloca & Finniss, 2012;

Colloca et al., 2013), a particularly crucial strategy when opioids are being reduced (Colloca & Miller, 2011b; Darnall et al., 2018; Horin et al., 2014). Indeed, positive patient expectations can enhance response to opioids, reduce pain, and help opioids work better at lower doses.

Assessment of patient expectations and readiness to taper opioids is vitally important for clinical outcomes as well as empirical study on the topic. Scant research exists on prescription opioid tapering, and few studies that have assessed patient expectations prior to the taper. To address this unmet need, our national clinical trial on patient-centered prescription opioid tapering will be carefully assessing patient expectations for opioid tapering (https://www.pcori.org/research-results/2017/comparative-effectiveness-pain-cognitive-behavioral-therapy-and-chronic-pain, 2017). Further, it includes methods to enhance placebo and patient readiness to engage in opioid tapering process. This pragmatic study will allow us to conduct a large scale test of placebo/nocebo on opioid tapering, as well as methods to optimize placebo effects and taper response.

An additional strategy can be employed to challenge patient expectation that they will experience withdrawal symptoms and pain as a consequence of prescription opioid tapering: micro-dose decrements. Anxiety regarding opioid reduction is likely to be highest at the outset of a taper. As such, making tiny reductions in dose can obviate withdrawal symptoms and allow patients to remain comfortable and gain confidence in their ability to reduce their opioids very slowly without experiencing noxious symptoms (Darnall et al., 2018). As such, preventing noxious symptoms at the outset of a taper—and providing sufficient time for physiologic and psychologic adaptation to opioid dose reductions—may minimize attrition and improve taper response (Darnall et al., 2018).

Finally, whenever possible, helping patients have choice and control in the process will best support successful outcomes. As discussed earlier, patient preference *for the intervention*—in this case choosing to reduce opioids because they are convinced of its benefits—enhances treatment outcomes. Going one step further, accounting for patient preferences *during the tapering process* may be equally important. Allowing patients to control over the pace of their taper—pausing their taper or go more slowly when desired—can provide added reassurance during critical time points that are likely to be laden with emotional distress. Continuing the taper process when the patient has confidence in their own readiness signals optimized placebo and increased likelihood for successful outcome.

1.10 Clinical Implications of Placebo and Nocebo Effects and Endogenous Mediated-Opioid Analgesia

As discussed earlier, evidence reveals that placebo/nocebo expectations influence the endogenous release of opioids, suggesting influence on analgesic response to exogenously administered opioids. Bingel et al. investigated the impacts of opioid analgesia on 22 healthy volunteers who were exposed to a heat pain stimulus while simultaneously being administered IV remifentanil in each of three conditions (Bingel et al., 2011). Pain intensity was individually determined to a self-reported moderate intensity, and was applied to participants during in all three conditions. In the first condition, participants were told they were receiving a powerful painkiller during the pain experiment. In the second condition, participants were told they were receiving only saline through the IV, and therefore they would experience the moderate amount of pain that had been individually determine. In the third condition, participants were told they would receive something that would amplify their experience of the heat pain. As such, the researchers only altered participant expectations for pain and relief thusly: (1) placebo, (2) neutral, (3) nocebo. Positive expectations for pain relief due to opioids (opioid placebo) were found to double the analgesic effect of remifentanil relative to the neutral condition. Conversely, nocebo expectations that were induced in the third condition effectively abolished the analgesic effect of remifentanil. Moreover, pain and analgesia findings correlated with functional neuroimaging data supporting modulation of pain processing in the brain based on the condition group. Finally, across the conditions, modulation of anxiety directly aligned with expectations for pain. The findings from this study suggest profound influence of placebo and nocebo effects on exogenously administered opioid analgesia with implications for real-world patients receiving prescription opioids for acute and chronic pain.

To summarize, findings for nocebo/placebo suggest that: (1) treatment beliefs (placebo) are sufficient to release endogenous opioids; (2) opioid analgesia was doubled when coupled with placebo relative to when opioids are administered without knowledge of receipt; (3) nocebo can block analgesia from exogenously administered opioids. Given that placebo/nocebo profoundly influence opioid analgesia it is somewhat surprising that there are no widely used interventions to that target placebo as a pathway to boost opioid analgesia. Moreso, it is clear that opioid reduction nocebo is a timely and urgent issue given its potential iatrogenic harms.

In the United States multiple government agencies and leaders, including the Centers for Disease Control, the U.S. surgeon general, the Institute of

Medicine, and the Department of Health and Human Services have called for reduced opioid prescribing. Such calls have led to local, state, and federal guidelines and policies that recommend or enforce prescribing limits, regardless of patient readiness or willingness, two indices of potential nocebo for opioid reduction (Hoffman, 2018; Langreth, 2017; McCoy, 2018). Overlooking these key patient factors may greatly undermine patient response to opioid tapering because (1) nocebo increases distress and amplifies pain; (2) nocebo opposes opioid analgesia; and (3) forced tapers may contaminate the doctor-patient bond and its positive influence on treatment outcomes; (4) the placebo context of the medical environment can quickly shift to a nocebo context with detrimental effects. Forced tapers have questionable clinical value, amplify patient suffering and may contribute to self-harm and suicide (Demidenko et al., 2017). Compassionate opioid tapering requires attention to patient preference and willingness to taper and applying placebo optimization to cultivate patient engagement, placebo effects, and enhanced outcomes. Outside the context of opioid tapering and considering new or existing opioid prescriptions, such findings underscore the importance of minimizing nocebo effects to potentially prevent risky dose escalation, and optimizing placebo as a pathway to either enhance opioid analgesia or obviate the need for opioids. The question then becomes how might we help patients cultivate placebo effects for improved outcomes?

As outlined in Table 1, we argue that it is possible to minimize nocebo effects and optimize placebo for pain relief and opioid reduction and summarize the clinical strategies as follows.

(1) *Set positive expectations*. Placebo effects and positive expectations for treatments are strengthened when patients are educated about the treatments and their analgesic effects. In the case of pain being the contextual cue, the discussion centers around the potential *placebo cultivation* by facilitating belief in one's ability to shape adaptive brain responses toward pain relief and wellbeing.

(2) *Identify and Extinguish Nocebo*. Assess cognition negative thoughts, expectations and beliefs about pain and opioid use/reduction, self-efficacy to self-manage pain, and treatments.

(3) *Equip individuals with skills to enhance descending modulation of pain and distress reduction*. Enhanced descending modulation of pain dually promotes awareness of pain control and therefore placebo proper. While the Clinical Toolkit (Table 1) is not exclusive to psychologists several of the skillsets are specific to trained pain psychologists, including cognitive behavioral therapy (CBT) for pain.

Table 1 Placebo Optimization Clinical Toolkit

	Placebo Optimization Toolkit	
Clinical Goal	**The Clinician Toolkit**[b]	**The Patient Toolkit**
Enhance positive expectation for the cultivation of pain relief skills[a]	• Establish the basic treatment rationale by explaining the role of psychology in the experience of pain • Establish psychological treatment and enhanced descending modulation of pain as *primary* pain treatment • Summarize results of psychology treatment research as evidence-informed medicine • Provide education on psychological treatment and self-treatment yielding some of the largest effects • Provide education regarding psychological treatment's ability to "boost" medical treatments for pain • To ensure comprehension, answer questions, ask patients to tell you their understanding of the information you provided	• Acquire a fundamental understanding of the importance of psychoneurobiological processes on pain experience Understand that there are many evidence-informed simple skills that can be learned, that, when used over time, shape brain changes toward the experience of pain relief
Extinguish pain nocebo. Part 1	• Assess nocebo/catastrophizing using the Pain Catastrophizing Scale or other relevant measure • Review the patient's findings with them. (e.g., "Your score tells me that we can help you learn to reduce your distress around pain, and even the pain itself.") • Validate their distress, and connect their distress to being a pain amplifier • Using patient-friendly language, such as "negative pain mindset" in lieu of the term pain catastrophizing may enhance receptivity to the concepts and the treatment plan • Use imagery and narrative: "Nobody want more pain, but having a negative pain mindset is like picking up the can of gasoline and pouring it on a fire. You can learn to put the can of gasoline down, and by doing so it changes your pain in the moment, and steers your nervous away from pain in the future"	• Acquire a personal understanding the relevance of psychoneurobiological processes (e.g., one's score on the measure) • Understand that negative thought patterns amplify pain processing and oppose relief • Receive reassurance that while it's not "all in your head," there is much you can do to impact brain-pain experience • Become re-moralized that while a "negative pain mindset" amplifies pain, mindset is under your control. "I can learn to put the can of gasoline down so that I am not unwittingly contributing to my pain and distress"

Continued

Table 1 Placebo Optimization Clinical Toolkit—cont'd

	Placebo Optimization Toolkit	
Clinical Goal	**The Clinician Toolkit**	**The Patient Toolkit**
Part 2. Entrain descending modulation with frequent application of acquired skills	• Cognitive restructuring (reframing negative/nocebo thoughts) • Positive self-talk; learning to "talk back" to the automatic negative thoughts • Demonstrate the relaxation response and discuss its utility for comfort and control over physiological processes and self-treatment of pain • Mindfulness observing • Learn to identify pain-related distress and apply self-soothing techniques (e.g., relaxation response, mindfulness meditation, diaphragmatic breathing) • Utilize distraction	• Acquire ability to identify negative thoughts and reactions (physical, emotional) and apply adaptive strategies to interrupt pain nocebo: ✓ Cognitive reframing ✓ Positive self-talk ✓ Relaxation response ✓ Mindfulness observing ✓ Distraction ✓ Self-soothing actions • Practice the relaxation response as a self-treatment tool to reduce pain, distress and adaptive conditioning. Positive biofeedback enhances placebo—a belief that one can modulate pain and distress
Enhancements: Behavioral engagement and reinforcements	• Provide visual material, handouts and video-clips • Provide clinical worksheets • Prescribe exercises that cultivate a pain-relief mindset • Review progress in follow-up; acknowledge any challenges that arise, provide supportive encouragement, and highlight small successes • Remind patients that structural brain changes are shown after 11 weeks of skills use • Encourage a focus on skills use and behavior change vs change in pain intensity—which typically follows later	• Review visual material, handouts and video-clips • Complete worksheets and apply information • Set goals • Review progress in follow-up • Adopt an approach to skills use that is not pain contingent but rather focuses on long-range adaptation with an eye to achieving adaptive structural changes of the nervous system

Extinguish opioid reduction nocebo	• "Tell me your concerns about reducing opioids." Listen and address their fears • Discuss the data for patient-centered opioid tapering • Review the physiology of opioid reduction and how very slow tapering will allow for comfortable adaptation • Prescribers may use adjuvant medications to address discomfort and optimize placebo with a non-opioid medication • Withdrawal symptoms are just a sign that the taper is going too fast. Remind them you have a plan to prevent withdrawals, and you will work with them to adjust the taper if any discomfort arises • Keep the process very simple, avoid making any other changes during an opioid taper to obviate confounding, patient anxiety, and negative effects • Maintain very small dose reduction for the first month (see Darnall et al., 2018) • Partner with your patient. As much as possible, allow them to feel and be in control (e.g., allow them to go slower or pause the taper) • Follow-ups every 3 weeks for the first few months for close monitoring, to address any discomfort or concerns quickly, and to solidify therapeutic trust and placebo • Provide access to descending modulatory skills	• Understand the science behind endogenous pain modulation and opioid tapering: most patients experience the same or less pain when opioids are tapering the right way—very slowly so that brain and body have time to adjust • Encode that withdrawals are not harmful; they are uncomfortable and mostly preventable. My doctor will help me stay comfortable and will track me closely to make sure I'm doing ok • My doctor and I created a plan that helps me be in control. I can pause my taper if I need to during a difficult time • Understand that there's much I can do during my taper to help manage my pain (see above Patient Toolkit for the clinical goal, "Entrain descending modulation with frequent application of acquired skills" • Additional targeted reading and skills application specific to opioid reduction may be useful (Darnall, 2014a, 2014b, 2016)

[a]Enhancing placebo may dually optimize patient preference for the treatment.
[b]To assure comprehension, use simple lay language to explain complex concepts. Ask patients to explain their understanding of the concepts you describe to (1) facilitate learning through verbal recall; and allow you to (2) positively reinforce their accurate comprehension, (3) correct any misunderstandings, and (4) identify and address any concerns they raise.

2. CONCLUSION

Historically, pain-related placebo and nocebo effects have been viewed as psychological responses to external contextual information, often involving aspects of treatment. Considering the role of the patient in self-modulating, self-managing, and self-treating chronic pain, we argue for an expanded therapeutic exploitation of placebo and nocebo effects to include strategies immediately feeding back to either amplify the analgesic experience or diminish the pain experience. Pain catastrophizing illustrates the concept of pain amplification and related nocebo effects, with supporting experimental and clinical data suggesting that it may contribute inhibiting descending pain modulation. Therefore, it is necessary to face the burden of pain and the epidemic of opioids with novel approaches including psychological interventions to manage catastrophizing thoughts and other psychological factors known to amplify pain and undermine pain treatment outcomes. Clinical toolkits are needed, and we have provided a resource that may facilitate these goals of patient-centered pain management and successful tapering of prescription opioids by minimizing and optimizing placebo effects and descending pain control.

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