Common Threads: Session 5

Complex Persistent Opioid Dependence - THE GOOD AND THE BAD OF OPIOIDS

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30 Minutes

Disclosures

No disclosures.

Session Learning Objective

01 | Demonstrate knowledge in implementing diagnostic and treatment strategies for patients on long-term opioid therapy for chronic pain who do not meet the criteria for opioid use disorder.

1980s — LTOT: Hopeful Assumptions

Adapted to c/c pain care after roaring success with hospice!

- Analgesic model of LTOT
  - Analgesic therapy that ↓es pain and thus ↑es function
  - Effective and largely safe if used "properly"
  - Severe adverse effects like overdose and addiction are rare
  - Deprescribing is easy and safe if LTOT is ineffective/unsafe

2024: None of these assumptions are valid!

2010s — Opioid-Induced Chronic Pain Syndrome (OICP)

LTOT continuation:
Persistent worsening of pain, function, and medical stability
Whether dose ↑ed, ↓ed or discontinued, each dose provides relief while pain worsens
"It's working."

LTOT tapering:
Persistent clinical worsening, similar/worse than continuation
- Opioid dose reinstatement often reinstates prior level of dysfunction

"My pain is real, it's working."

- Indistinguishable from worsening chronic pain & medical/psychiatric conditions
  - Ineffective investigations and treatments that commonly worsen the situation
- Pts. insist ineffective LTOT is "working" and refuse change- cognitive dissonance!
- No OUD/Addiction

LTOT conundrum: Darned if you do, darned if you don't!

SOURCE: Manhapra, Arias, Ballantyne, *Substance Abuse* 2017; Manhapra *Curr. Treat. Options in Oncol.* 2022

2010—2020s Data clarifying OICP!

Complex Persistent Opioid Dependence—an Opioid-induced Chronic Pain Syndrome


Complex Persistent Opioid Dependence–an Opioid-induced Chronic Pain Syndrome

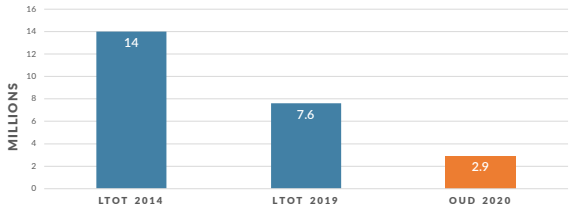
LTOT
Largely ineffective and harmful
- ↑ opioid availability → Opioid crisis
- Ineffective in longer trials[1]
- Pain/disability ↑ (NOT ↓) with two years of LTOT[2]
- 2/3rd - Poor pain control, function & health[3]
- ↑ OD mortality, a significant problem [4]
- ↑ all-cause mortality in addition[4]
- OUD not rare, in about 5% [5]

Deprescribing
Difficult, ineffective, and harmful for many
1. **Deprescribing is incredibly difficult**
   - Most continue even if ineffective [3]
   - 90% reinitiate even after an OD event[6]
2. ***Deprescribing* is NOT effective:**
   ↔ Pain: systematic reviews[7,8]
3. **Deprescribing ↑es LTOT risk, NOT ↓es risk**
   - ↑ed OD & all-cause mortality[4,9]
   - ↑ed psychiatric destabilization[10]
   - ↑ed overdoses even if tapering is slow[11]

SOURCES: [1]Chou R et. al 2020; [2]Shah et. al. Adv Ther 2020; [3]Motjabai et. al *Pharmacoepidemiol Drug Saf.* 2018, [4]Krebs et. al *PLoS One.* 2020 and *JAMA.* 2018 [5]Gordon, Manhapra et. al *Drug & alcohol dependence* 2020; [6]Hasin et. al. *AJP* 2022, [7]LaRochelle Ann Int Med 2016; [8]Frank et. al *Ann Int Med* 2017; [9]Mackey et. al *JGIM* 2020; [10]Oliva, Bowe, Manhapra et. al *BMJ* 2020. [11]Agnoli et. al *JAMA* 2021;, [11]DiPrete et. al. *JAMA Network Open* 2022

OICP - Unrecognized Opioid Crisis in Clinics!

ESTIMATED LTOT PREVALENCE AMONG US ADULTS



SOURCE: Motjabai et. al *Pharmacoepidemiol Drug Saf.* 2018; Groenewald et. al. *JAMA Network Open* 2021; SAMHSA

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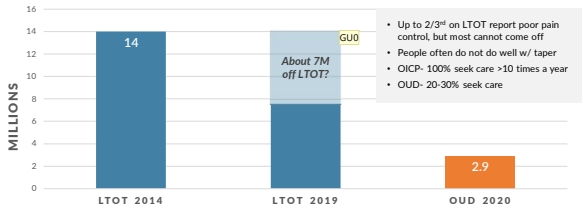


- Up to 2/3rd on LTOT report poor pain control, but most cannot come off
- People often do not do well w/ taper
- OICP- 100% seek care >10 times a year
- OUD- 20-30% seek care

SOURCE: Motjabai et. al *Pharmacoepidemiol Drug Saf.* 2018; Groenewald et. al. *JAMA Network Open* 2021; SAMHSA

OICP Among 2/3rd on LTOT - *Why?*

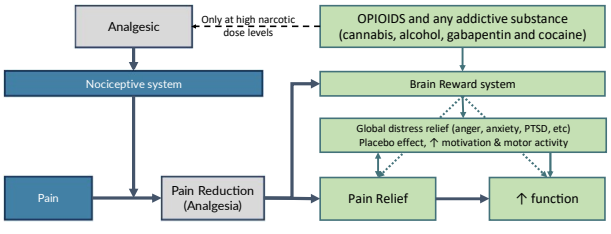
1. *Worsening of underlying pain condition?*
   - Appears a lot more complex than worsening of arthritis and disc disease!
   - Chronic pain rarely has a physical explanation
2. *OIH?*
   - Infrequent specific nociceptive problem in chronic pain (largely non-nociceptive)
3. *Addiction/prescription OUD?*
   - Ineffective among 2/3rd, but only < 5% have significant OUD- (Hasin et al., AJP 2022)
   - DSM-5 criteria is for illicit non-medical use, not for controlled medical use

Analgesic Model: Unsatisfactory Answers

- Why some do well on LTOT and tapers while others do not?
- Why do people develop worse pain on LTOT?
- Why pain and risk ↑ and not ↓ with LTOT tapering?

- *Time to revise the current analgesic model of LTOT?*
- *Are opioids effective analgesics?*
- *Is physiological opioid dependence benign?*

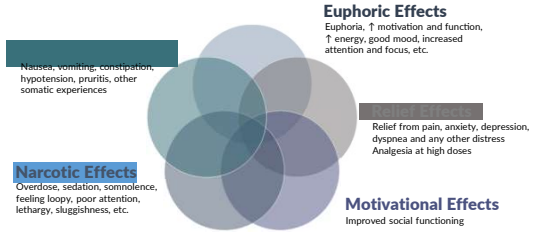
Rethinking Opioid Pain Relief Mechanisms



Source: Manhapra, Arias, Ballantyne, *Substance Abuse* 2017

Opioids: Not Just a 'Pain Killer:'

Sum of Multiple Effects: Environment and context of use, individual vulnerabilities



SOURCE: Manhapra, Arias, Ballantyne, *Substance Abuse* 2017

Opioids: Relief and ↑ function without much ↓ in pain intensity

- Not really a "pain medication"
- Individual variability and intolerance are not bugs, but features of opioid effect

Relief coded by brain as highly valued life sustaining "reward"

- Repeated use of substances with high reward value modifies primary experiences

SOURCE: Manhapra, Arias, Ballantyne, *Substance Abuse* 2017; Manhapra *Curr. Treat. Options in Oncol.* 2022; Porcera and Navratilova *PAIN* 2017

Allostatic Opponent Process

Opponent process:

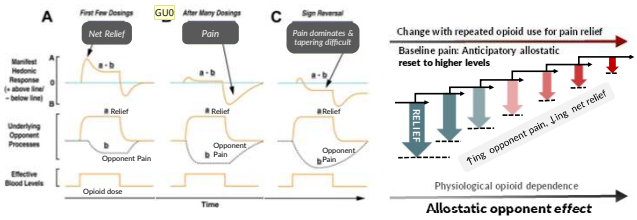
- With repetitive exposure to a salient experience, the body will generate a simultaneous contrasting experience (opponent effect)
- Pain and relief are opponent effects

Allostasis - physiological stability through change:

- When exposed to cycles of distress and relief, body adapts by resetting the baseline distress to higher levels in anticipation to maintain physiological stability
- Pain-relief cycles can automatically reset baseline pain to higher levels

SOURCE: Manhapra et. al. *Substance Abuse* 2017; Manhapra *Curr. Treat. Options in Oncol.* 2022; Solomon HL *Am. Psych.* 1980 ; Ballantyne & Koob *PAIN* 2021

Allostatic Opponent Effect - Opioid Tolerance and Pain Through Opioid-Induced Opponent Process



SOURCE: Manhapra et. al. *Substance Abuse* 2017; Manhapra *Curr. Treat. Options in Oncol.* 2022; Solomon HL *Am. Psych.* 1980 ; Ballantyne & Koob *PAIN* 2021

How Allostatic Opponent Effect Can Play Out in Pain Management

When starting off on opioids:

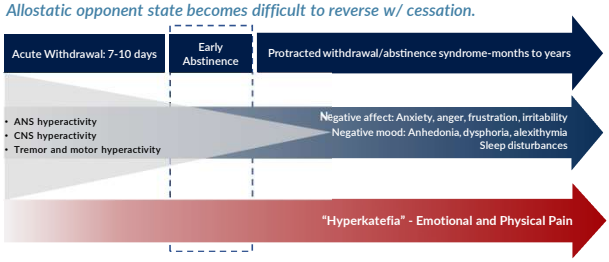
- Patient with 5/10 pain at baseline and can walk only 4 blocks
- Opioid reduces pain to 2/10 for 8 hours, and can walk a mile and a half
- Patient thinks it's working

After few years on LTOT:

- Patient with 7/10 pain at baseline and can barely walk 2 blocks
- Opioid reduces pain to 6/10 for 4 hours and can walk 3 blocks
- Patient still thinks it's working

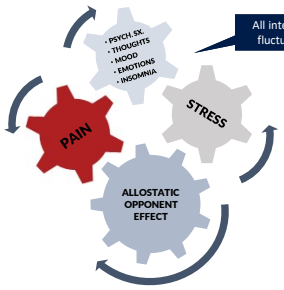
Protracted Withdrawals Beyond Acute Withdrawals

Allostatic opponent state becomes difficult to reverse w/ cessation.



Adapted from Heilig et al. 2010. Manhapra, Arias, Ballantyne, *Substance Abuse* 2017. Koob & LeMoal; *Nat Neuroscience* 2005. Sherman, Koob, Gutstein; *Pain Med* 2010.

Allostatic Opponent Effect & Affective Dynamism

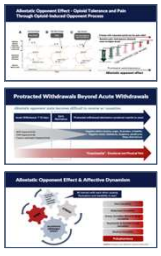


All interact with each other causing fluctuation and instability in each

- Pain Instability
- Behavioral Instability
- Stress, Emotion, Mood & Sleep Instability
- Psychiatric & Substance use Instability
- Medical Instability
- Polypharmacy

SOURCE: Manhapra, Arias, Ballantyne, *Substance Abuse* 2017

Opioid Induced Chronic Pain Syndrome: Making Sense



Why do pain, other symptoms and debility worsen on LTOT?
- Allostatic opponent effect

Why do pain, other symptoms and debility worsen after taper?
- Protracted withdrawal syndrome - persistent allostatic opponent effect

Why so much clinical instability when on or off opioids?
- Affective dynamism or cycling between opioid relief and distress effects associated with allostatic opponent effect

SOURCE: Manhapra et. al. *Substance Abuse* 2017; Manhapra *Curr. Treat. Options in Oncol.* 2022; Solomon HL *Am. Psych.* 1980 ; Ballantyne & Koob *PAIN* 2021

Reimagining LTOT With New Understanding

LTOT: Therapeutic induction of adaptive opioid dependence for functional improvement irrespective of pain reduction.

LTOT Initiation	Maintain adaptive dependence to achieve sufficient functional recovery and then deprescribe it while maintaining functional recovery
LTOT Reevaluation	Evaluating if the dependence adaptive or maladaptive
Treatment of Ineffective LTOT	Transform maladaptive dependence to adaptive dependence with improved function and then train to maintain function w/o dependence

The only way to sustainably reduce pain is to improve function with existing pain!

Basic Principle of LTOT Initiation

If opioids improve function:

- Debility is not due to physical deficits.
- There is room for functional improvement.
- Body is putting brakes on its ability to realize full functionality.
- Opioids just release the brakes.
- Patient should work to release the brakes further while on LTOT.
- After maximum functionality is achieved on opioids, patient should slowly train themselves to keep the brakes off without opioids.

SOURCE: Manhapra et. al *BJCP* 2024

LTOT Initiation in LTOT Naïve Patients

Frame appropriately with patients & providers

- Induction of LTOT dependence for functional improvement, not for "pain management"
- An option in severe disability unresponsive to other Txs
- May make pain and other symptoms worse, risky
- Patient must do their part to recover (function does not automatically improve)

Initiate. See if function ↑es sufficiently in the first 3 months. Discontinue if not!

- ↑ function- continue, monitor maladaptive dependence
- ↑ function means disability is not driven by physical impairment. Patient can train to ↑ function further
- Function will not ↑ w/o patient working on it

Only if function improves in the first few months!

LTOT Maintenance

- Achieve and maintain maximum function on LTOT
- Train to maintain same function with less opioids
- Maximum duration 1-2 years, not a lifelong Tx

Eventual goal is a functional life without opioids

SOURCE: Manhapra et. al *BJCP* 2024

Reevaluation of LTOT Effectiveness in Legacy* Patients

Is LTOT dependence adaptive or maladaptive?

1. Does the patient have OUD?
   Treat, if present!
2. Does LTOT dependence benefit overwhelm its risk?

**Patients on LTOT for several years*

SOURCE: Manhapra et. al *BJCP* 2024

How to estimate LTOT benefit?

Long-term treatment strategy w/ goal of functional improvement, not just pain control.

Is functional status similar to a healthy person of similar age and gender? **OR** *Is disability substantially better than before starting LTOT?*

LTOT is beneficial *if* the answer is ***yes*** to either of the two questions

- Longitudinal history is critical
- Effect of each opioid dose and opioid dose reduction/discontinuation cannot be used to estimate LTOT benefit

SOURCE: Manhapra et. al *BJCP* 2024

LTOT Benefit Assessment Pitfalls

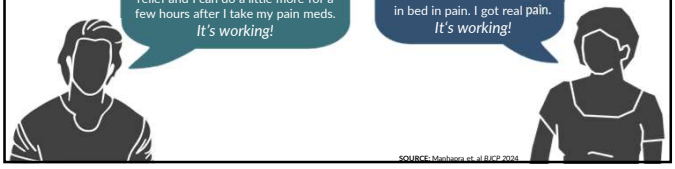
DO NOT use as indicators of benefit!

Brief improvement in pain and disability following each dose

I can't do much, but I get so much relief and I can do a little more for a few hours after I take my pain meds. *It's working!*

Worsening of pain and disability following opioid cessation

I tried stopping pain meds a few times and I would be in bed in pain. I got real pain. *It's working!*



SOURCE: Manhapra et. al *BJCP* 2024

LTOT Dependence: Risks

1. Have any high impact risks occurred already?

- Overdose, suicide events, resp. failure
- Compromised mental state, lethargy or confusion, excess sedation/sleep
- Misuse of opioids, meds/substances
- Opioid use disorder/Addiction
- Psychiatric and medical destabilization
- Constipation or other ADE requiring hospitalization/sustained medical Tx
- Recurrent falls

2. Is there a high risk of high impact adverse events in future?

- Dose and benzos play only a small role
- Indicators of overall health has a larger impact
- CNS polypharmacy need
- Medical, psychiatric and SUD comorbidities
- Acute healthcare utilization for above, especially SUD
- Tapering and cessation often increases risk instead of reducing it

SOURCE: Manhapra et. al *BJCP* 2024.
STORM Analysis: Oliva et. al. *Psych. Services* 2017.

LTOT Dependence Effectiveness Categories Based on Benefits, Past Adverse Effects, and Future Risks

GROUP 1 — LTOT dependence effective
1. Good functional benefits
2. No high impact adverse effects in past
3. Low future risk

- LTOT can be continued
- Risk mitigation and education
- Reevaluate 6-12 months
- Long term: Eliminate LTOT need

GROUP 2 — LTOT dep. ineffective
1. No functional benefits, or
2. High impact adverse effects in past, or
3. Unacceptably high future risk

- Modify LTOT to ↓ risk and/or ↑ benefit
- Risk mitigation and education
- Reevaluate every 3 months
- Long term: ***Eliminate LTOT need***

GROUP 3 — Effectiveness??!!
1. Good functional benefits
2. No high impact adverse effects in past
3. High future risk

- Individualize risk/benefit balance and decide if LTOT dependence effective/not.
- Treat based on individualized decision on effectiveness.

SOURCE: Manhapra et. al *BJCP* 2024

Transforming LTOT Dependence: Maladaptive to Adaptive

Pharmaco-Behavioral Treatment of CPOD/OICP (Not Pain)

Treatment goal is functional recovery, and not pain management

Behavioral change by patients (self-recovery) is the primary treatment:

1. Acceptance of the opioid problem (CPOD/OICP) and the need for self-recovery
2. Changes in opioid use and behavioral management of pain
3. Engagement in functional recovery with pain

With opioid agonist therapy for dependence
- Long-acting opioids with right expectations and goals *(not to ↓pain, but to ↑ function)*, without short-acting, as needed, opioids or other pain meds

Without opioid agonist therapy for dependence
- ***aka taper***

Buprenorphine
- Preferred
- High doses achievable with lower undesired effects
- Lower mortality risk

Methadone
- Induces significant dependence that can worsen pain over time
- Medical complications

Other long-acting opioids
- LA morphine & oxy
- No breakthrough doses
- Avoid fentanyl

Retraining body to function & stabilize on lower doses
- Patient controls, not providers!
- Requires high internal motivation
- High destabilization risk among those with comorbidities

COMORBIDITY MANAGEMENT AND RISK MITIGATION

SOURCE: Manhapra et. al BJCP 2024; *Curr. Treat. Options in Oncol.* 2022; PAIN 2023

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↓

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↓

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SOURCE: Manhapra et. al BJCP 2024; *Curr. Treat. Options in Oncol. 2022*; PAIN 2023

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***Without* opioid agonist therapy for dependence (*aka taper*)**

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COMORBIDITY MANAGEMENT AND RISK MITIGATION

SOURCE: Manhapra et. al BJCP 2024; *Curr. Treat. Options in Oncol. 2022*; PAIN 2023

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COMORBIDITY MANAGEMENT AND RISK MITIGATION

SOURCE: Manhapra et. al BJCP 2024; *Curr. Treat. Options in Oncol. 2022*; PAIN 2023

Shared Decision-Making with Appropriate Choices

"Based on the assessment, long-term opioid therapy appears to be ineffective for helping you get back to doing what you want to do.

Your risk for harmful effects are also unacceptably high.

So, continuation of the current ineffective opioid regimen is medically inappropriate and needs to be changed to be more beneficial and safer.

At this point, you have limited options to change your opioid regimen...."

SOURCE: Manhapra et. al BJCP 2024

Shared Decision-Making with Appropriate Choices

1

"Convert to long-acting opioids such as buprenorphine without any additional use of shorter-acting opioids for pain in between the doses.

This is to treat the adverse effects of opioid dependence and tolerance that can paradoxically cause more pain, and not for pain management."

2

"Train your body to function adequately with lower and lower doses of current opioids and eventually without any opioids.

This takes time, commitment and a lot of personal effort."

3

"Immediate stoppage of opioids with withdrawal management.

This is going to be the hardest option to do and can be ineffective and risky."

SOURCE: Manhapra et. al *BJCP* 2024

Shared Decision-Making with Appropriate Choices

Center the conversation on what is medically appropriate and not on what the provider wants to do.

Avoid statements such as:

"I won't (or cannot) prescribe opioids anymore."

Instead, consider:

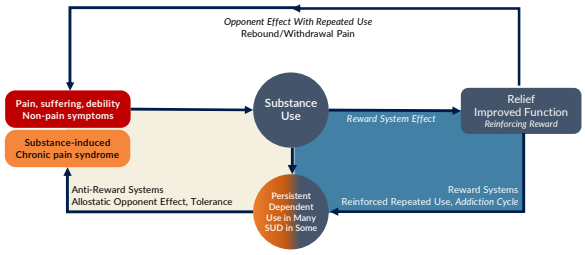
"Do you need some time to think about this? Let's fix an appointment in one month."

OR

"What do want to do? We can help with whichever choice you pick."

SOURCE: Manhapra et. al *BJCP* 2024

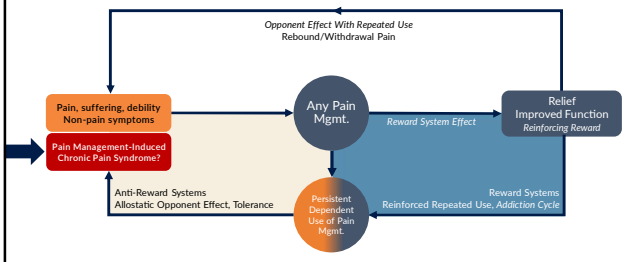
Substance Use & Pain: Reciprocal Reinforced Relationship



SOURCE: Ditre et. al. *Ann reviews* 2018; Manhapra et. al. MCNA 2018; Manhapra et. al., *Substance Abuse* 2017

A Provocative Thought Exercise:

Allostatic opponent effect is a general adaptation to repetitive exposure to relief by any means, not just by substance use!



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Knowledge Check

Which of the following is accurate regarding long-term opioid therapy (LTOT) for chronic pain?

A. LTOT is effective largely because of its analgesic/anti-nociceptive effect.

B. LTOT can improve function without lowering pain intensity.

C. LTOT dependence is always benign if there is no addiction.

D. LTOT cessation is associated with decreased overdose risk vs LTOT continuation.

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D. LTOT cessation is associated with decreased overdose risk vs LTOT continuation. ✗

References

SESSION FIVE

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