Opioids in Pain Management

Andrew Friedman MD

Tri-Cities Pain Management Conference

April 27, 2024

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Impact of Chronic Pain

- 50% of Americans experience chronic or recurrent pain
- 62% of These Would Rate Pain Moderate or Severe
- Causes more disability than heart disease or cancer
- >$200 Billion/year in US in health care and disability

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Questions

1. **Do opioids work for chronic pain?**
2. **What are common adverse events?**
3. **What are best practices in opioid management?**
4. **How do we reduce the impact of opioid addiction?**

But first a little background…

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Opioid History

Opium poppies cultivated since 3500 BC
1806—Morphine isolated
1850s—1 in 400 Americans “addicted”
1914—Harrison Narcotics Act
1990s—Opioid prescribing accelerates in US

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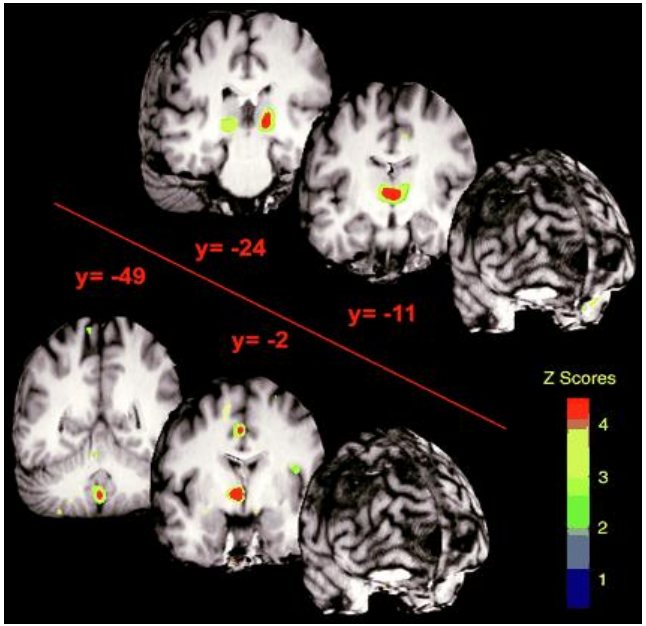
Opioid Effects:



Analgesia
Pleasure
Feelings of well-being
Neuroendocrine effect
Constipation
Respiratory Depression

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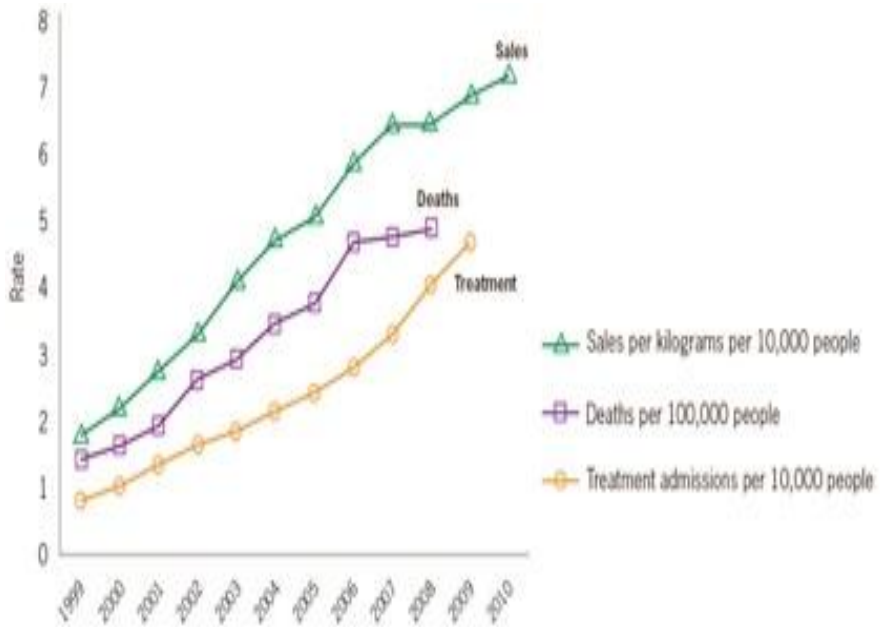
Opioid Crisis First Wave



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Prescription Opioid Analgesics

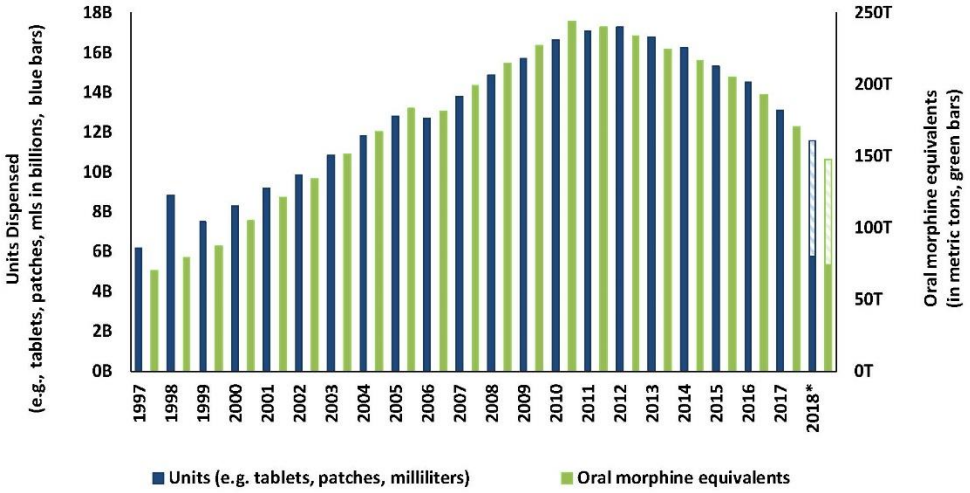

Figure 1: Estimated number of units (e.g., tablets, patches, milliliters) and calculated oral morphine equivalents (in metric tons) dispensed for opioid analgesic products from U.S. outpatient retail pharmacies, 1997 through projected year 2018*

Source: IQVIA, National Prescription Audit™. 1997-June 2018.

One billion MME is equivalent to 1 metric ton of oral morphine equivalents

*Projected year 2018 based on doubling the number of units and oral morphine equivalents dispensed during the first half of 2018 (Jan-June)

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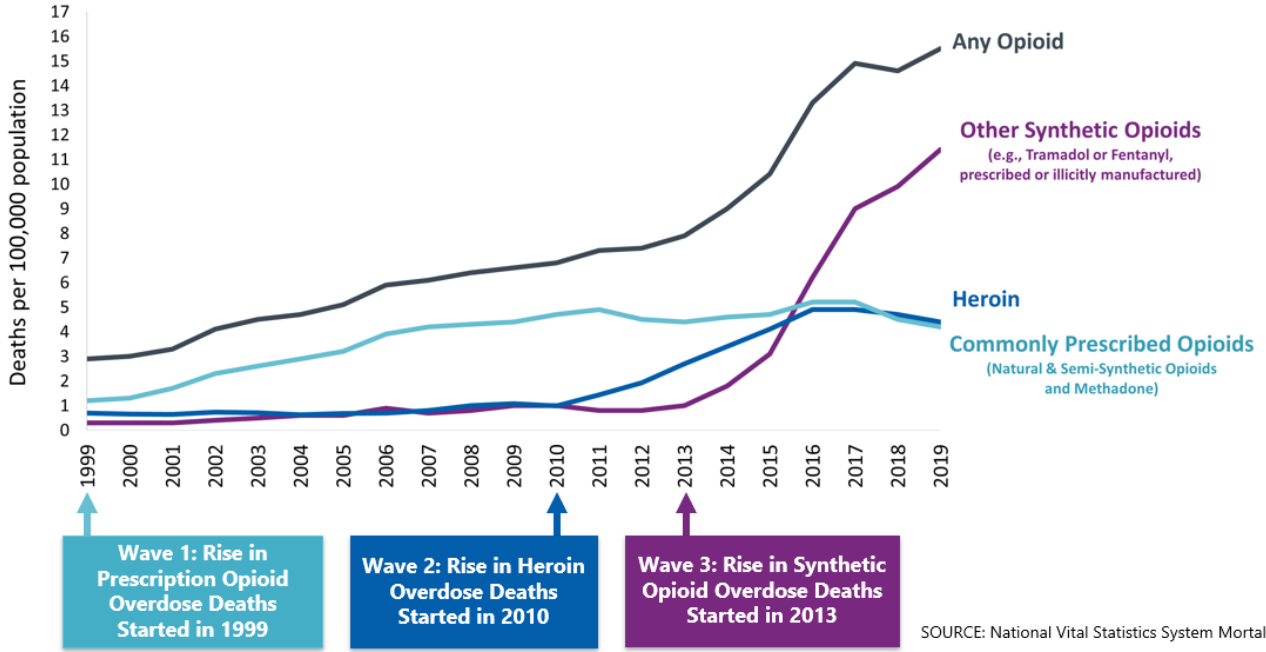
Three Waves of the Rise in Opioid Overdose Deaths



SOURCE: National Vital Statistics System Mortality File.

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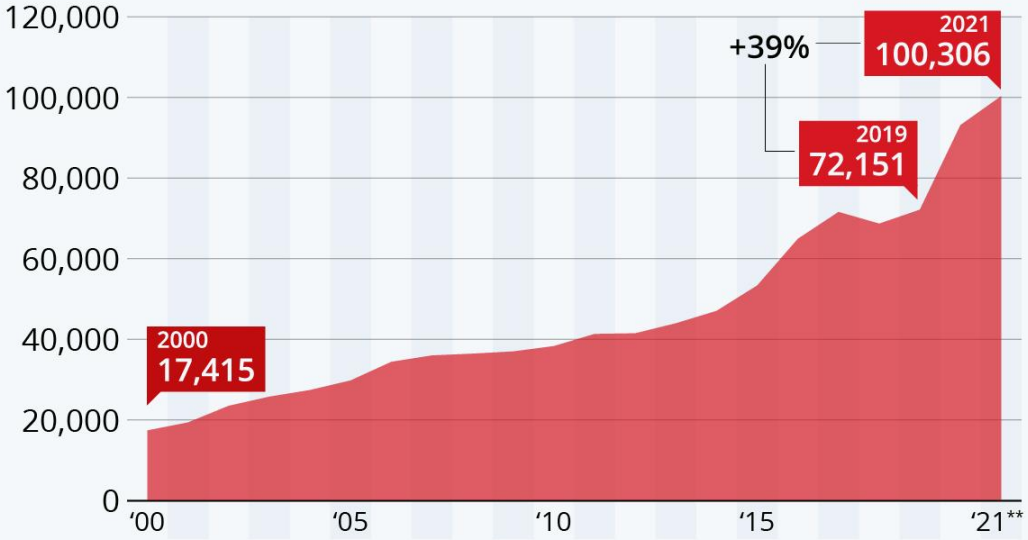
U.S. Drug Overdose Deaths Spike Amid the Pandemic

Number of drug overdose deaths in the United States*



* Estimates for 2020 and 2021 are based on provisional data.
** 2021 estimate refers to 12-month period ending April 2021
Source: Centers for Disease Control and Prevention

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statista

Efficacy of Opioids for Chronic Pain

Are Opioids Effective for Chronic Pain? Audience?

Perplexity AI's Answer

"Opioids have been shown in RCTs to provide some benefit in chronic pain with statistically significant but small reduction in pain averaging 0.7 points on a zero to 10 scale"

"Opioids therapy is associated with similar or decreased effectiveness compared to other pain medicines such as NSAIDs"

"Additionally, opioids carry significant risks including the risk of vomiting, opioid use disorder and overdose. The risks may outweigh the modest benefits for many patients with chronic pain"

References

1. Nadeau SE. Opioids For Chronic Noncancer Pain: To Prescribe Or Not To Prescribe-what Is The Question? Neurology. 2015 Aug 18;85(7):646-51. Doi: 10.1212/Wnl.0000000000001766. Epub 2015 Jul 2. Pmid: 26138946; Pmcid: Pmc4548284.
2. Busse Jw, Wang L, Kamaleldin M, Et Al. Opioids For Chronic Noncancer Pain: A Systematic Review And Meta-analysis. *Jama.* 2018;320(23):2448–2460. Doi:10.1001/Jama.2018.18472
3. Website: Royal College Of Anaesthetists: Fpm.Ac.Eu
4. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline For Prescribing Opioids For Pain — United States, 2022. MMWR Recomm Rep 2022;71(no. Rr-3):1–95. DOI: Http://Dx.Doi.Org/10.15585/Mmwr.Rr7103a1

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COT--Efficacy

Ballantyne and Mao—NEJM 2003

- --review of 16 lower quality studies
- --Doses up to 180 MED morpine
- --No studies >32 Weeks

Concluded that opioid treatment did reduce pain Scores. No clear effect on function.

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Efficacy

Ballantyne and Shin Clin J Pain 2008

- 26 RCT ~1200 patients
  - Significant improvement in pain scores
  - Both arthritides and neuropathic pain
  - No trial >32 weeks
  - Most <8 weeks
  - None >180 MED

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Opioid Efficacy 2011

- **Short-term efficacy**
  - 62 RCT's in one recent meta-analysis, duration <16 weeks in 61[a]
  - Opioids more effective than placebo for nociceptive and neuropathic pain (effects moderate; effect sizes 0.55-0.60)
  - Maximum dose ≤180 MME/day in all trials except for 3
- **Long-term effectiveness**
  - Cochrane review included 26 studies >6 months[b]
    - No placebo-controlled trials
    - 25 studies were case series or uncontrolled long-term trial •continuations
    - Many discontinuations due to adverse effects (23%) or insufficient pain relief (10%), but some patients who continued on opioids experienced long-term pain relief

Furlan 2011. Credit Roger Chou

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AHRQ Opioids for Chronic Pain

February 10, 2022

Key Messages

- Opioids are associated with small improvements versus placebo in pain and function, and increased risk of harms at short-term (1 to <6 months) followup; evidence on long-term effectiveness is very limited, and there is evidence of increased risk of serious harms that appear to be dose dependent.
- At short-term followup, evidence showed no differences between opioids versus nonopioid medications in improvement in pain, function, mental health status, sleep, or depression.
- Evidence on the effectiveness and harms of alternative opioid dosing strategies and the effects of risk mitigation strategies is lacking, although provision of naloxone to patients might reduce the likelihood of opioid-related emergency department visits, a taper support intervention might improve functional outcomes compared to no taper support, and co-prescription of benzodiazepines and gabapentinoids might increase risk of overdose.
- No instrument has been shown to be associated with high accuracy for predicting opioid overdose, addiction, abuse, or misuse.

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Risks and Harms

Harms

- Adverse Events—Falls and OD
- Tolerance
- Hyperalgesia
- Impaired function
- Addiction
- Endocrine, immune effects
- Death

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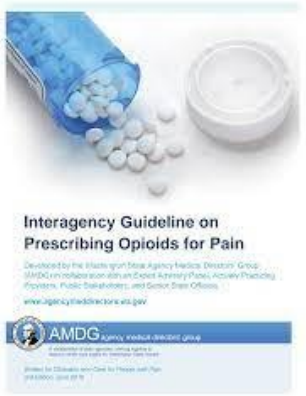

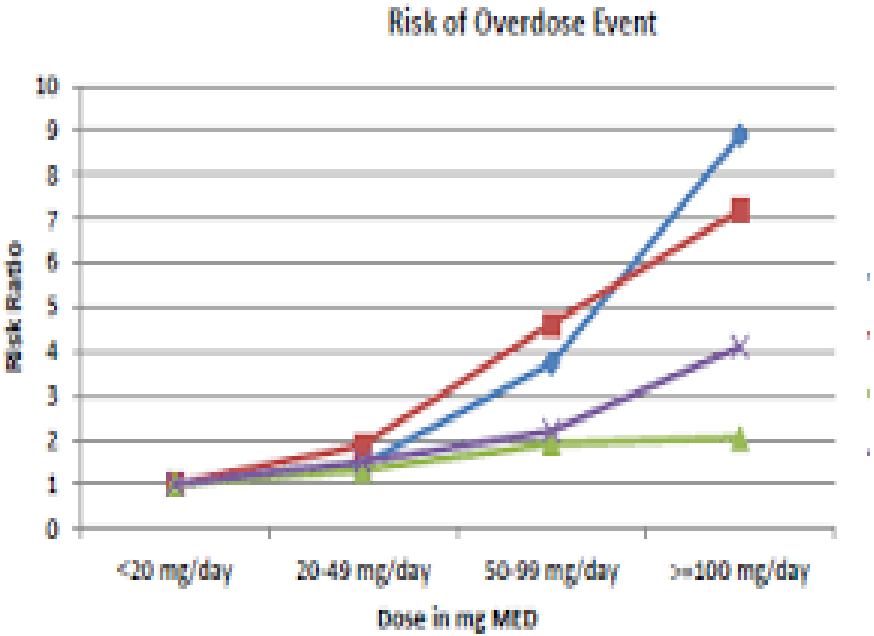

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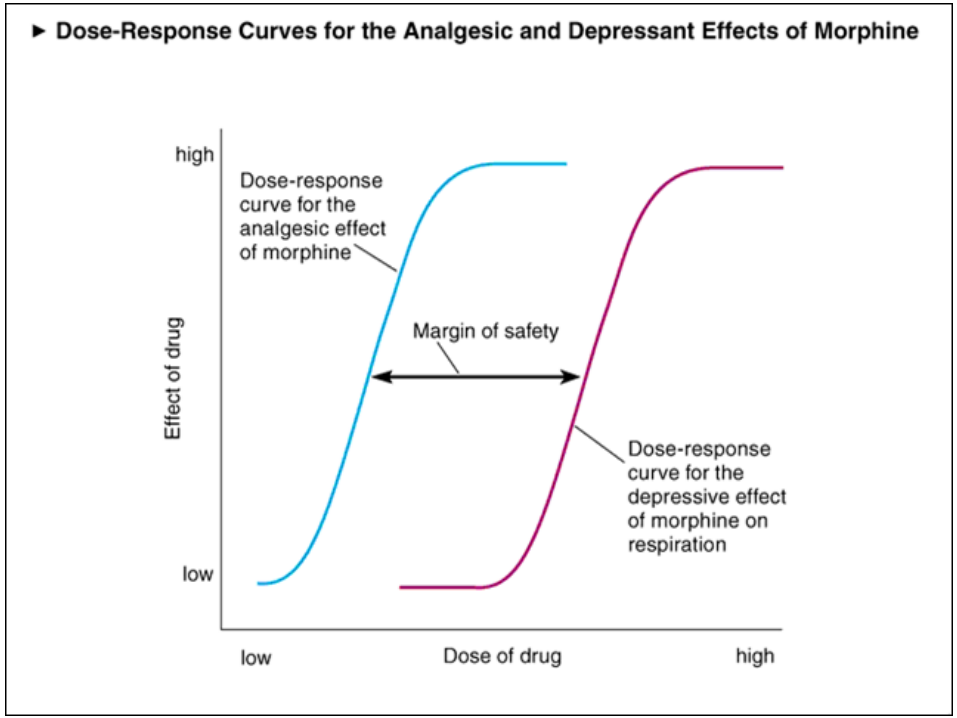
Tolerance



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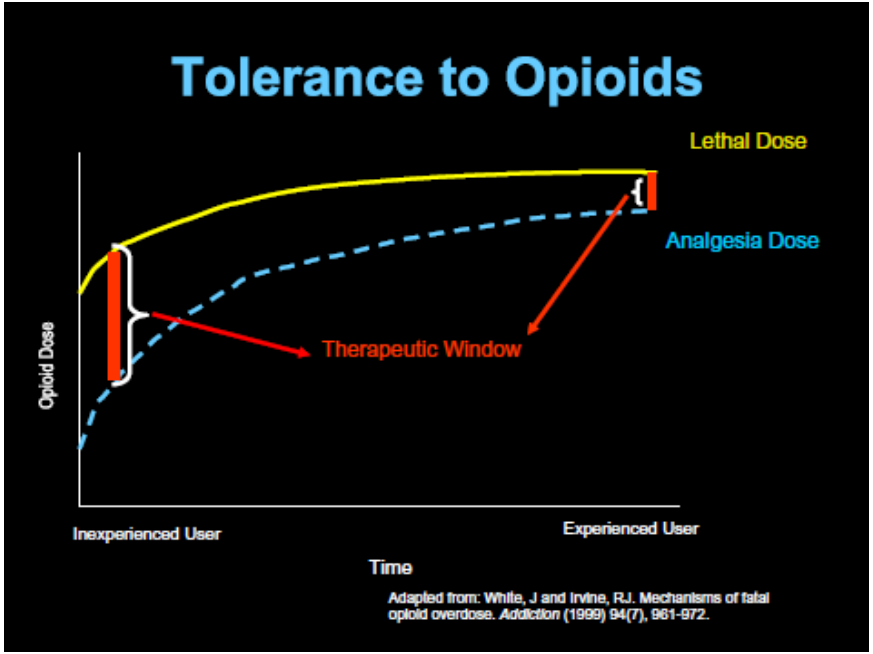
Therapeutic Window



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TOLERANCE

TOLERANCE

- Simply understood, tolerance is the need for a higher dose to achieve the same effect
- Often thought of as desensitization, which is reversible
- More importantly, opponent process which counteracts the drug effects – persistent, enigmatic, and pervasive

Slide credit Jane Ballantyne MD

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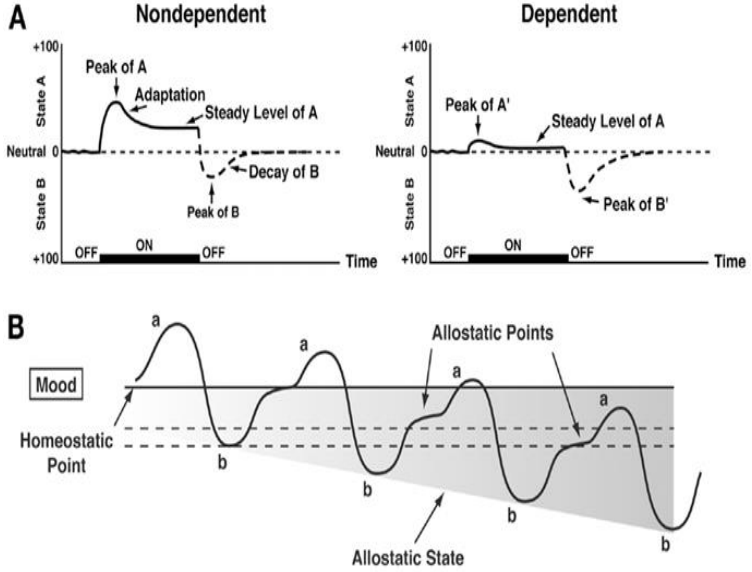
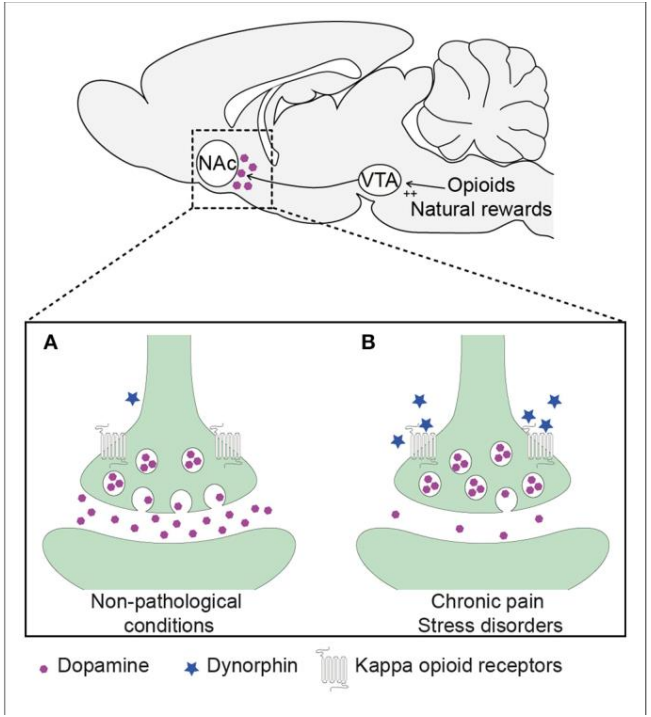
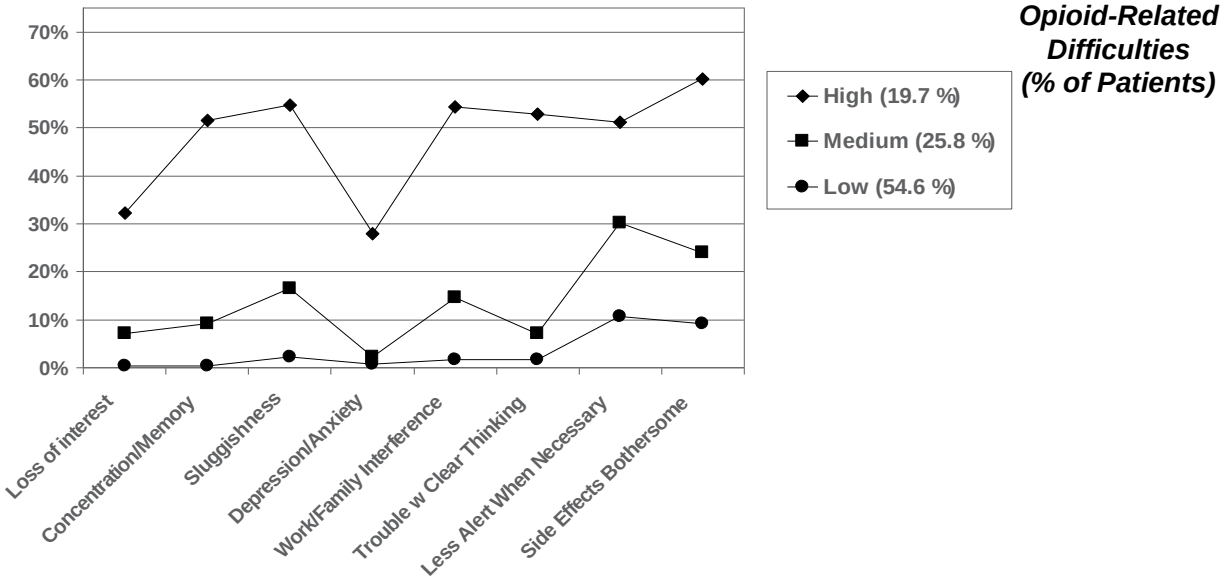
Reward Deficit Moderated by Dynorphin/Kappa Opioid Receptor





--Koob, Psychiatry 2013.

Profile of Psychosocial Problems
Among Patients Using Prescribed Opioids Long-Term



Problems Currently Attributed by Patients to Opioid Use

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Opioid-Induced Hyperalgesia

--Increased sensitivity to pain stimuli

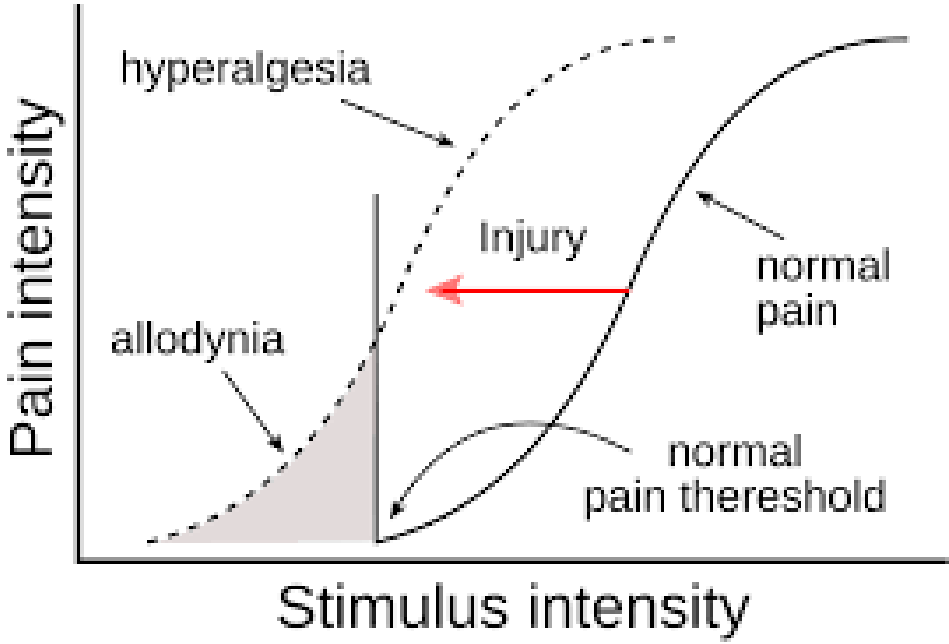
--May progress to generalized pain

--Improves with opioid dose reduction

--May be moderated by NMDA antagonists

--May be long-lasting/permanent

--Accompanied by hyperkatifia



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Endocrinopathies

Opioids inhibit HPA activity

Dose-related decrease in testosterone

High prevalence of osteoporosis in methadone maint. populations

Low testosterone associated with increased pain sensitivity, depression and anxiety

Opioids contribute to insulin resistance

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Addiction

Review > Pain. 2015 Apr;156(4):569-576. doi: 10.1097/01.j.pain.0000460357.01998.f1.

Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis

Kevin E Vowles [1], Mindy L McEntee, Peter Siyahhan Julnes, Tessa Frohe, John P Ney, David N van der Goes

- Literature quite variable
- Rates of misuse 21-29%
- Rates of addiction 8-12%

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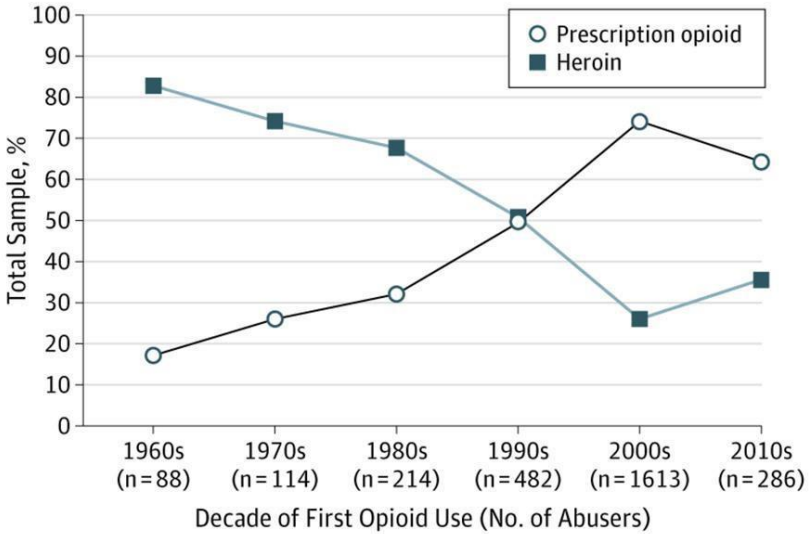
First Opioid of Abuse in Current Heroin Users



SAMSHA 2010 drug survey. Slide Accessed from Chou, PCSS

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Best Practices and Reducing Harm

Strategies

- Prevent acute to chronic transition
- Utilize best-practices when managing chronic opioid
- Recognize and treat opioid use disorder
- Educate patients about opioid disposal

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Preventing Acute to Chronic Transition

Brumett et. al JAMA Surgery April 2017

Minor
N=26,068

- Hemorrhoidectomy
- Varicose vein removal
- Lap Chole/Appy
- Thyroidectomy
- TURP
- CTR

Major
N=7109

- Ventral hernia repair
- Colectomy
- Hysterectomy
- Reflux surgery
- Bariatric surgery

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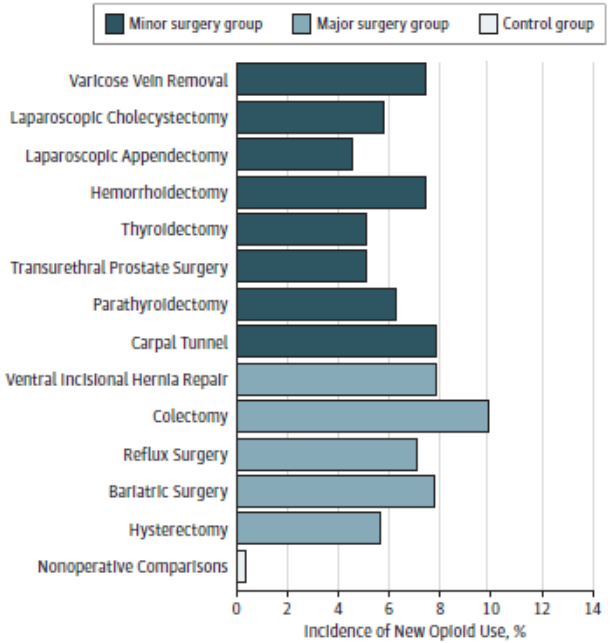
Persistent Opioid Prescriptions

90-180 Days:

- Major 6.5%
- Minor 5.9%
- Control 0.4%



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Brummett et. al (Cont)

Patient-related variables and not intensity of surgery is predictor of ongoing opioid use

Risk Factors

- Tobacco use RR 1.4
- SUD RR 1.3
- Mood d/o RR 1.2
- Anxiety RR 1.3
- Pain d/o 1.2-1.6

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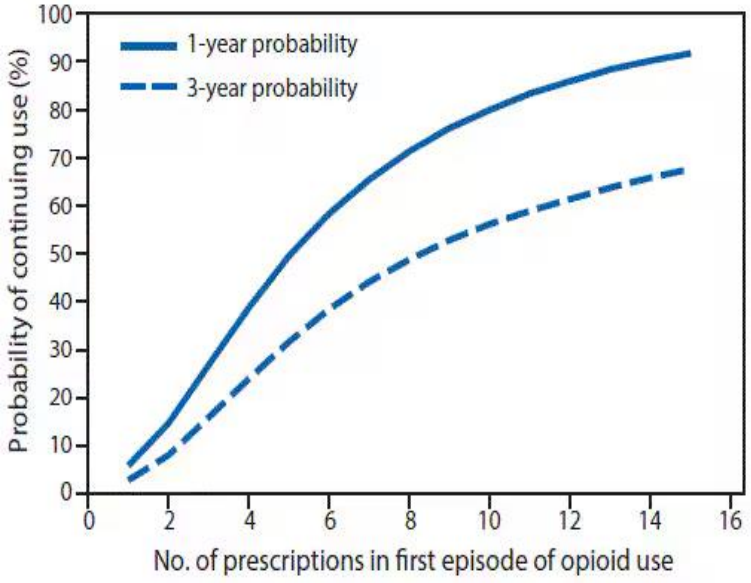

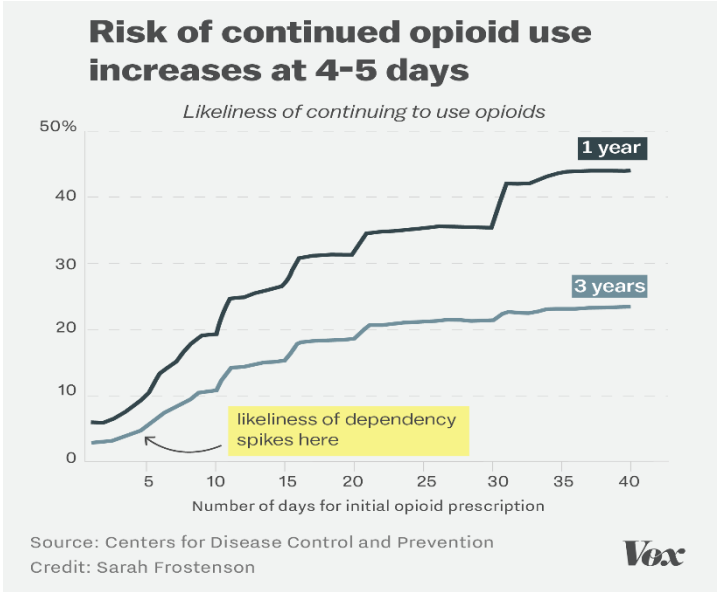

Shah A, Hayes CJ, Martin BC. Characteristics of Initial Prescription Episodes and Likelihood of Long-Term Opioid Use — United States, 2006–2015. MMWR Morb Mortal Wkly Rep 2017;66:265–269. DOI: http://dx.doi.org/10.15585/mmwr.mm6610a1external icon.

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Post-Surgical Guideline Bree 2018

Type I surgery-expected rapid recovery

- Dental extraction, lap chole, CTR,
    - <3 days

Type II-expected medium-term recovery

- ACL, laminectomy, open colectomy
    - <7 days=42 doses

Type III-expected longer recovery

- Lumbar fusion, thoracotomy, TKR
    - <14 days

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Additional Measures

Use non-opioid measures first and where possible

Think twice before second prescription

Recognize drivers of chronicity and address these

Use beyond normal healing is a critical concern. Reassess for clinically meaningful benefit in function.

Check PMP before prescribing

Transition phase and COT

Initiating or Continuing Treatment

Pause

- Alternative treatments have higher long-term efficacy
- Average person gets a small benefit over the long-term
- Is this the right diagnosis for COT? Is this the right person for COT?
- How do I examine my biases in this decision?

Patients who use opioids for at least 90 days have a greater than 60% chance of still being on chronic opioids in five years.

- Martin BC. J Gen Inern Med 2011

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Consider:

- Correct medical diagnosis?
- Comorbid psychological condition?
- Non-pharmacological treatment
- Risks vs. Benefits of long-term opioid plan
- Define CMIF for this patient
- Is this palliative care?

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Factors which may predict poorer outcome

Family history of addiction

Personal history of addiction

Smoking

Depression/anxiety

Excessive pain scores

Multiple pain sites

Multiple pain descriptors

Poor perception of coping effectiveness

Poor percieved social support

Unrealistic expectations

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Determining Risks

ORT—defines “low, moderate and high risk” individuals for COT—used in AMDG guides

- good prediction of ADRB in low v. high

SOAPP-R—24 question tool with validated variable cutoffs to adjust sensitivity for high vs. low risk

Further information at
www.agencymeddirectors.wa.gov

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DIRE SCORE

DIRE Score: Patient Selection for Chronic Opioid Analgesia

For each factor, rate the patient's score from 1-3 based on the explanations in the right-hand column

SCORE	FACTOR	EXPLANATION
	DIAGNOSIS	1 = Benign chronic condition with minimal objective findings or no definite medical diagnosis. Examples: fibromyalgia, migraine headaches, non-specific back pain. 2 = Slowly progressive condition concordant with moderate pain, or fixed condition with moderate objective findings. Examples: failed back surgery syndrome, back pain with moderate degenerative changes, neuropathic pain. 3 = Advanced condition concordant with severe pain with objective findings. Examples: severe ischemic vascular disease, advanced neuropathy, severe spinal stenosis.
	INTRACTABILITY	1 = Few therapies have been tried and the patient takes a passive role in his/her pain management process. 2 = Most customary treatments have been tried but the patient is not fully engaged in the pain management process, or barriers (severe insurance, transportation, medical illness) 3 = Patient fully engaged in a spectrum of appropriate treatments but with inadequate response.
0	RISK	(R = Total of P+C+R+S below)
	Psychological	1 = Serious personality dysfunction or mental illness interfering with care. Example: personality disorder, severe affective disorder, significant personality issues. 2 = Personality or mental health interferes moderately. Example: depression or anxiety disorder. 3 = Good communication with clinic. No significant personality dysfunction or mental illness.
	Chemical Health	1 = Active or very recent use of illicit drugs, excessive alcohol, or prescription drug abuse. 2 = Chemical coper (uses medications to cope with stress) or history of chemical dependence (CD) in remission. 3 = No CD history. Not drug focused or chemically reliant.
	Reliability	1 = History of numerous problems: medication misuse, missed appointments, rarely follows through. 2 = Occasional difficulties with compliance, but generally reliable. 3 = Highly reliable patient with meds, appointments & treatment.
	Social Support	1 = Life in chaos. Little family support and few close relationships. Loss of most normal life roles. 2 = Reduction in some relationships and life roles. 3 = Supportive family/close relationships. Involved in work or school and no social isolation.
	EFFICACY SCORE	1 = Poor function or minimal pain relief despite moderate to high doses. 2 = Moderate benefit with function improved in a number of ways (or insufficient info – hasn't tried opioid yet or very low doses or too short of a trial). 3 = Good improvement in pain and function and quality of life with stable doses over time.

0 **Total score = D + I + R + E**

Score 3-13: Not a suitable candidate for long-term opioid analgesia

Score 14-21: May be a good candidate for long-term opioid analgesia

NOTES

A DIRE Score of ≥13 indicates that the patient may not be suited to long-term opioid pain management.

Used with permission by Miles J. Belgrade, MD

Diagnosis
Intractibility
Risk

- Psychological
- Chemical coping
- Reliability
- Social Support

Efficacy

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Initiating Treatment:

Review non-opioid treatment
Consider medical context
Make a conscious decision to begin a trial of opioid
Screen for risk factors for poor outcome
? Urine toxicology

Set realistic expectations
Set functional goals
Tie continued treatment to health outcomes
? Opioid “contract”
Follow up within a few weeks to evaluate
Use a tool to assess functional attainment

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Chronic Opioid Analgesic Tx

What is “effective COAT”

- 30% reduction in pain and improvement in function
- Benefits are sustained over time needed
- Minimal opioid-related adverse effects
- No unintended drug-drug or drug-condition interactions
- No dose escalation over time
- No leakage of medicines into the community
- No provider risk related to regulatory or legal exposure

In other words clear evidence that the benefits outweigh the risks and that the process for prescribing conforms to best practices

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Chronic Opioid Therapy 2024

2022 Guideline

--Addresses concerns arising from 2015 Guideline

- --overly broad application
- --interpretation of dose concerns
- --prescriber fears of COT
- --patient abandonment

Three “pathways”

1. Maintain and monitor
2. Taper
   Recommends HHS 2019 guidance
3. Medications for OUD

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Informed Consent

Agreement about goals, avoidance of non-medical use, assessment

Describes risks of therapy and alternatives

Describes prescriber's responsibility

May include a signed agreement

Should be periodically revisited

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Monitoring

Intensity of monitoring should be based on individual:

- Medical stability
- Medical risk
- Medication profile
- Risk of non-medical use

Visit frequency, specialty consultation, UDT, prescription length, periodic review can all be adjusted to risk

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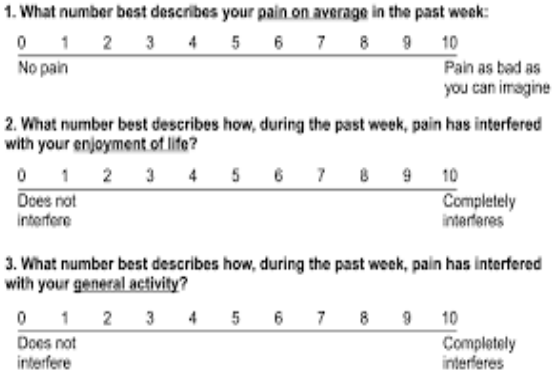
Monitoring Tools

- PEG
- COMM
- PMP
- PHQ
- Urine toxicology
- Aberrancy tracking



1. What number best describes your pain on average in the past week:

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

2. What number best describes how, during the past week, pain has interfered with your enjoyment of life?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

3. What number best describes how, during the past week, pain has interfered with your general activity?

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

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Monitoring

4 “A”s

- Analgesia
- Adverse effects
- Activity (Function)
- ADRB

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Urine Drug Testing

Elisa or GCMS assays

Quantitative testing not currently useful

20-30% Unexpected results:

- Illicit substance or adulterant
- Non-prescribed pain meds
- Absence of prescribed pain meds

- Make sure your urine screening tests detect fentanyl

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“Doctor, I need more pain medicine”-Ddx

- Progression of disease
- New disease
- Increased activity
- Emotional distress
- Drug-drug interaction
- Unrealistic expectation
- Addiction or diversion
- Hyperalgesia

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ADRB

Less suggestive of addiction:

Complaint of need for more drug
Unapproved use of drug for other symptoms
Unsanctioned escalation of dose on 1 or 2 occasions

More suggestive of addiction:

Selling prescriptions
Forgery
Multiple episodes of prescription loss
Repeatedly seeking prescriptions from ED
Concurrent use of alcohol or other illicit drugs

Behaviors Suggesting ADRB

Cigarette smoking
Absenteeism
Sudden job changes
Marital discord
Financial problems
Legal problems
Mental health problems

Suicide attempts
Accidents or trauma
Diabetes, BP, Depression not responding to treatment

What if problems arise?
Should you stop prescribing?

Diversion
OUD
Misuse
Overdose
Loss of benefit
Side effect

Don’t Abandon Your Patient

JAMA | Original Investigation

Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids

Alicia Agnoli, MD, MPH, MHS; Guibo Xing, PhD; Daniel J. Tancredi, PhD; Elizabeth Magnan, MD, PhD; Anthony Jerant, MD; Joshua J. Fenton, MD, MPH

IMPORTANCE Opioid-related mortality and national prescribing guidelines have led to tapering of doses among patients prescribed long-term opioid therapy for chronic pain. There is limited information about risks related to tapering, including overdose and mental health crisis.

OBJECTIVE To assess whether there are associations between opioid dose tapering and rates of overdose and mental health crisis among patients prescribed stable, long-term, higher-dose opioids.

DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study using deidentified medical

Editorial page 388
Supplemental content
CME Quiz at jamacmelookup.com

Original Investigation | Pharmacy and Clinical Pharmacology

June 13, 2022

Long-term Risk of Overdose or Mental Health Crisis After Opioid Dose Tapering

Joshua J. Fenton, MD, MPH[1,2]; Elizabeth Magnan, MD, PhD[1,2]; Iraklis Erik Tseregounis, PhD[2,3]; et al

» Author Affiliations | Article Information

JAMA Netw Open. 2022;5(6):e2216726. doi:10.1001/jamanetworkopen.2022.16726

Key Points

Question Is opioid dose tapering associated with reduced longer-term risks of overdose, withdrawal, or mental health crisis in patients prescribed long-term opioids?

Findings In this cohort study of 19 377 patients, in a posttaper period (beginning at least 12 months and extending up to 24 months after taper initiation) vs the pretaper period, the adjusted incidence rate ratios were 1.57 for overdose-withdrawal and 1.52 for a mental health crisis. Both were significant.

Meaning These findings suggest that opioid dose tapering was associated increased risks of overdose-withdrawal and mental health crisis that persisted up to 2 years after taper initiation.

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Opioid Renewal Clinic

335 patients

- 170 had ADRB
  - 45% adhered to OTA without further ADRB
  - 40% self-discharged
  - 15% referred for addiction treatment

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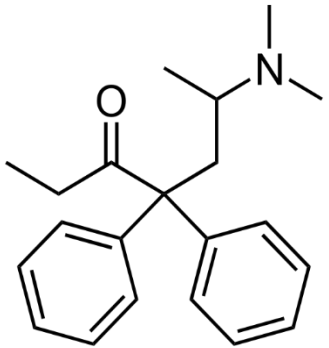
Pharmacologic Treatment Options for OUD and for failing COT—Methadone and Buprenorphine

Methadone



Developed in 1937
Patent sold for $1 in 1947
Long hx use in maintenance programs
Pain use rose dramatically over last 20 years
Can only be used in treatment of OUD by licensed treatment program

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Buprenorphine

- Partial mu agonist
- Very high binding affinity for mu receptor—difficult to reverse with naloxone. Full agonist at the delta opioid receptor (possible AD effects) and Kappa receptor (may mitigate hyperalgesia)
- Significant analgesic properties
- May precipitate withdrawal effects
- Buprenorphine/naloxone primary form of drug used in management of OUD
- New x waiver not required for tx of up to 30 patients *

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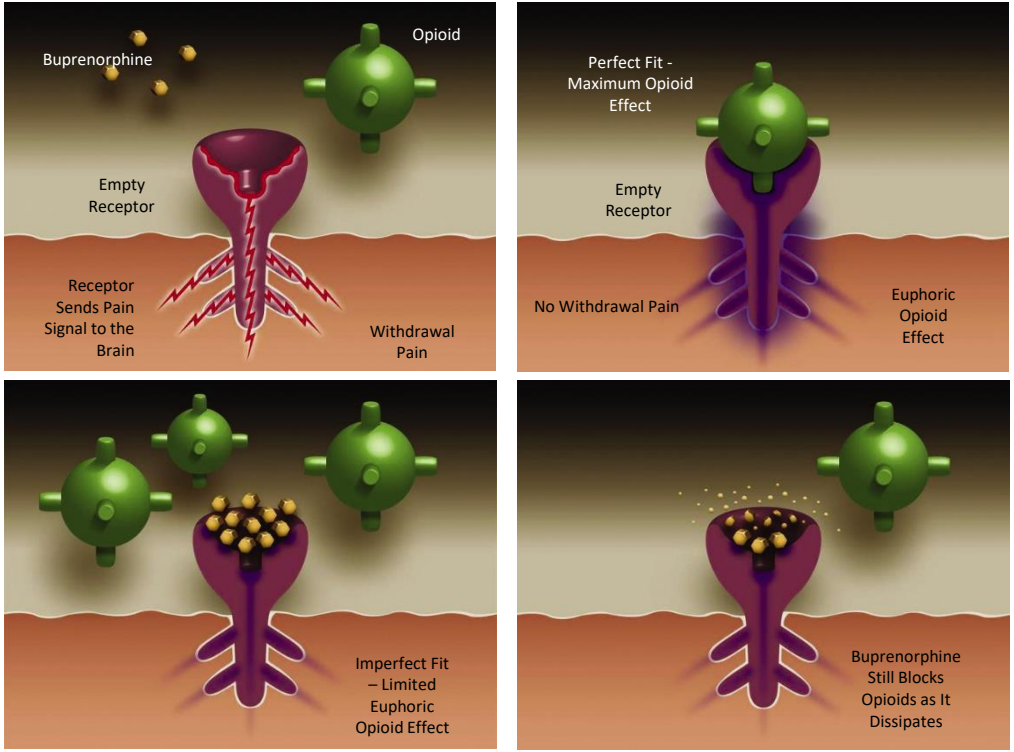

Courtesy of NAABT, Inc. (naabt.org)

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Pharmacodynamics of BUP

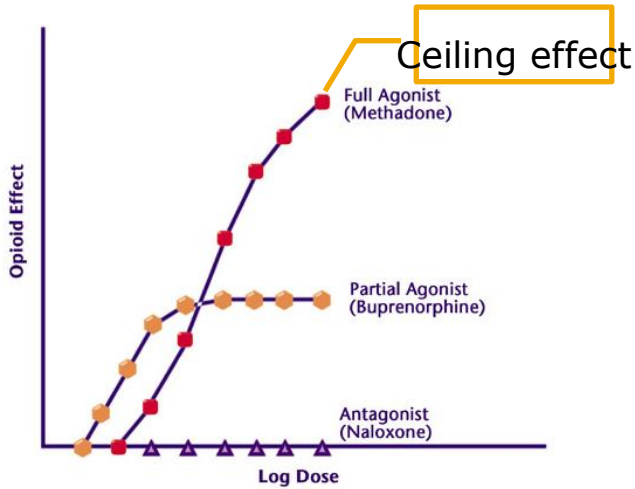
BUP = partial mu-opioid agonist, delta- and kappa-opioid antagonist

Activates mu-receptor and opioid receptor-like 1 (ORL1)

Analgesic duration 6-8hr

Blocks full agonist

Opiate	Ki (nM)
Hydrocodone	41.58
Oxycodone	25.87
Methadone	3.378
Fentanyl	1.346
Hydromorphone	0.365
Buprenorphine	0.215



The National Alliance of Advocates for Buprenorphine Treatment. Thorough technical explanation of buprenorphine. Volpe DA et al. *Regul Toxicol Pharmacol*. 2011;59(3):385-390.

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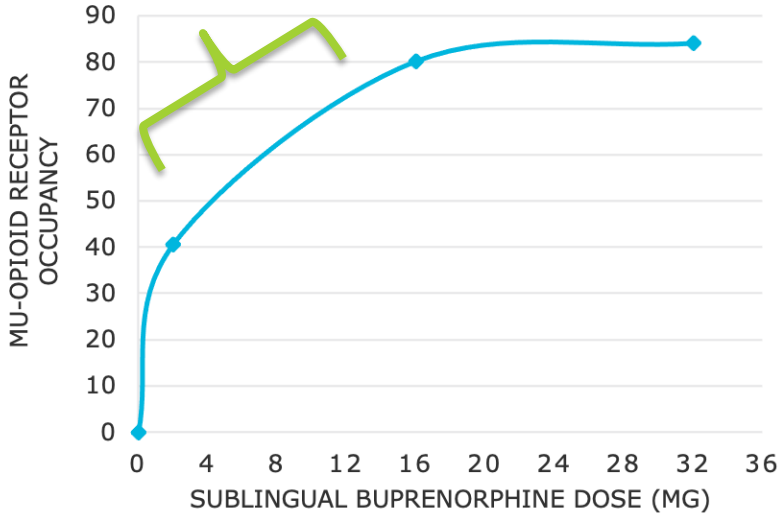
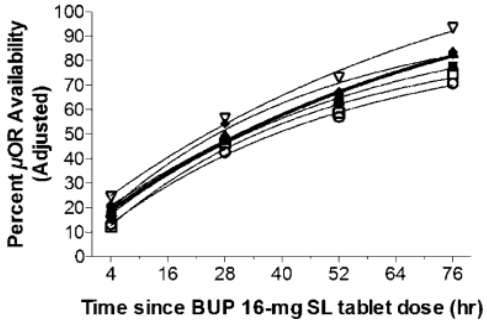
Receptor Occupancy





Greenwald MK et al. *Biol Psychiatry*. 2007;61:101–110.
Greenwald MK et al. *Neuropsychopharmacology*. 2003;28:2000–2009.

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Patients on High Dose Opioids

Daitch J et al. *Pain Physician*. 2012;15:ES59-ES66.

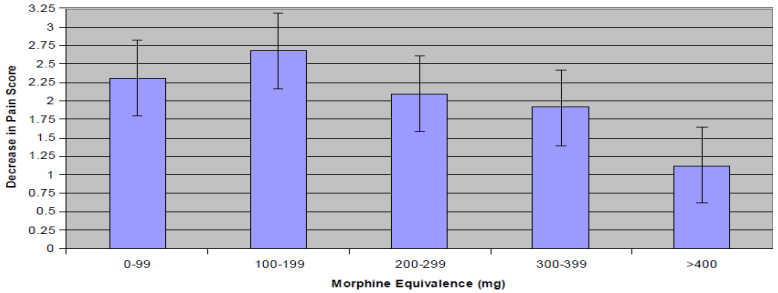
Patients: 104 patients from chronic pain clinic on full opioid agonists – high dose or ineffective use

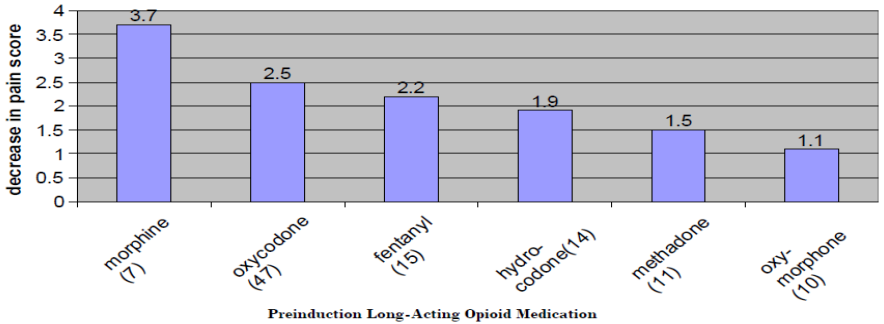
- Pre-induction MED: 180mg (range 10-840)
- 45% converted from oxycodone, 14% from fentanyl, 13% from hydrocodone, 11% from methadone, 7% from morphine

Intervention: Suboxone starting 24hr after last dose of full agonist

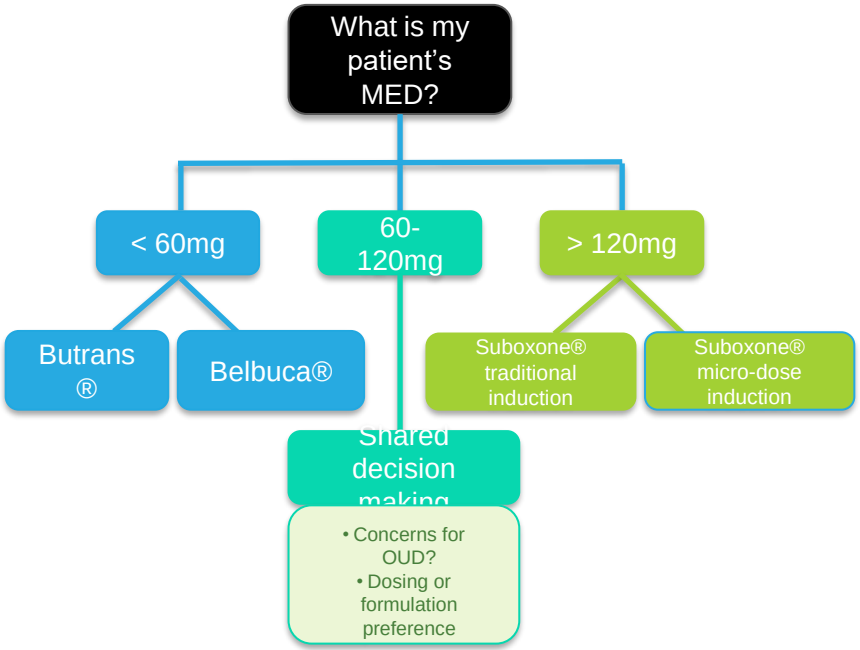
- Starting dose: 8mg, may repeat 8mg 1hr later if pain or withdrawal symptoms continued
- NTE 32mg/daily
- Duration of treatment: mean 10.3mo (range 2-42mo)

Outcome: Those that continued Suboxone for >60 days experienced 2.3 point reduction in pain score





Buprenorphine:Decision Tree



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Final Question:

Question:

58 y.o. woman on suboxone 8mg tid for OUD is admitted for surgery. Which is best way to handle incident pain?

a. Increase dose of suboxone
b. Discontinue suboxone and initiate full agonist
c. Continue buprenorphine and add full agonist

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Additional Resources

CDC Opioid Guideline cdc.gov

AMDG Guideline agencymeddirectors/wa.gov

Bree Collaborative breecollaborative.org

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Thank you!