Managing Patient Pain through Fentanyl Withdrawal

Jim Walsh, MD
Addiction Recovery Service
Swedish Medical Center
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Morris

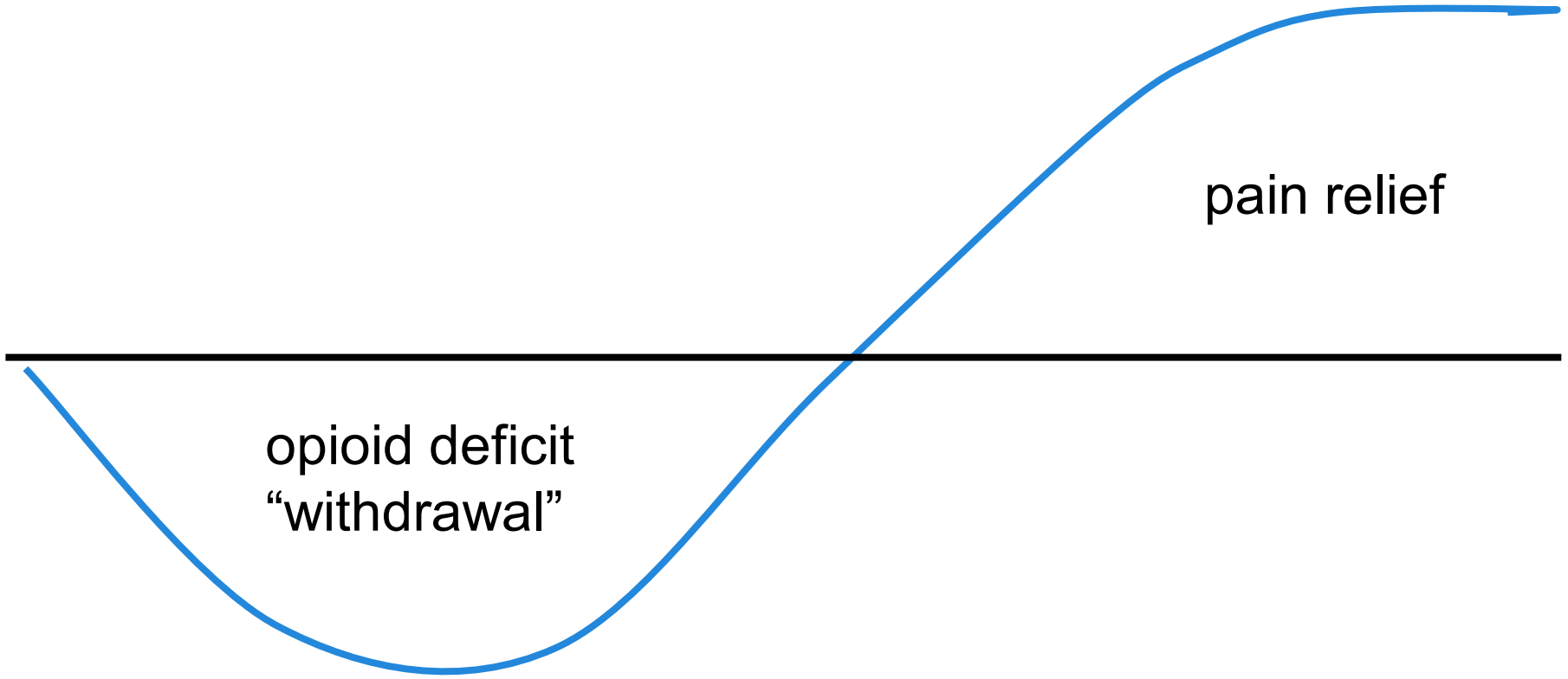
37-year-old man, smoking 1 gram fentanyl & methamphetamine daily

Cellulitis, large open wound with eschar on lower leg, possible osteomyelitis. Will need surgical debridement

Left AMA from another hospital twice last month

Tried buprenorphine several times “it never worked for me”

Giving Opioids



How much opioid is 1 gram smoked fentanyl ??

Fentanyl purity ~ 4% => 40 mg
Bioavailability of smoked opioid (heroin) around 40% => 16 mg

16 mg fentanyl / day = 16,000 mcg ~=

- 1600 mg IV Morphine Equivalent
- 3200 mg po oxycodone / day ~= 500 mg po oxycodone q4
- 240 mg IV hydromorphone / day = 30 mg IV q3
- 1200 po hydromorphone / day = 150 mg po q3
- 480 mg po methadone / day

Rapid changes in illegally manufactured fentanyl products and prices in the United States
Kilmer et al, Addiction 2022 Oct;117(10):2745-2749
Heroin self-administration by means of 'chasing the dragon': pharmacodynamics and bioavailability of inhaled heroin
Hendriks et al, Eur Neuropsychopharmacol 2001 Jun;11(3):241-52

Ancillary non-opioid medications to reduce withdrawal symptoms

Tizanidine 2-4 mg q4 (or clonidine 0.1 q2 prn)
Hydroxyzine 25-50 mg q4
Gabapentin 300 mg q4
Mirtazapine or Trazodone for sleep
Imodium 2 mg q3 prn diarrhea
Dicyclomine 10-20 mg q4 prn stomach cramps

These meds help with jerking, sweating, cramping, vomiting, diarrhea and insomnia.

Patients will still have **fatigue, dysphoria, deep aching & hyperalgesia**.

Persistent impact of opioid withdrawal

Most immune parameters tested are suppressed following drug withdrawal. Recovery time to baseline response levels varies in the studies. In the single report of withdrawal in humans, immune function was suppressed for up to 3 years.

… immune system abnormalities in heroin addicted patients can be restored to almost normal values by controlled treatment with methadone and buprenorphine.

.

Effects of opioid tolerance and withdrawal on the immune system
Eisenstein et al, J Neuroimmune Pharmacol . 2006 Sep;1(3):237-49
Buprenorphine and methadone maintenance treatment of heroin addicts preserves immune function
Sacerdote et al, Brain Behav Immun 2008 May;22(4):606-13

Giving Opioids

You may need a lot.

But how much is too much?

For acute peri-operative pain:

if the patient is breathing, it isn't too much.

(respiratory rate >= 12)

Assess the person, not the numbers

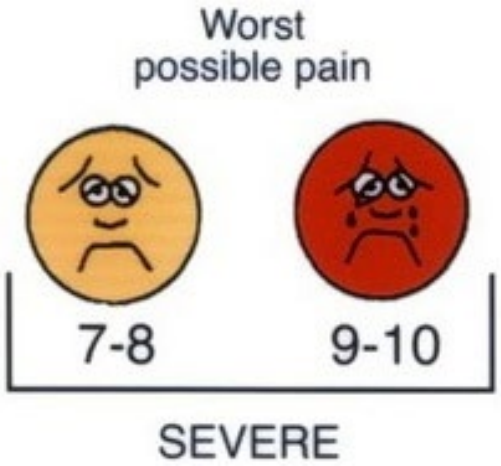
What about holding for sedation?

PRN Pain

Communication about pain can be complicated

When I tell you about my pain, I need…

- immediate relief
- prevention of anticipated suffering
- caring
- validation
- respect



Giving Opioids

You are treating both current misery
and the fear of future pain / withdrawal

Aggressive early dosing may increase the patient's confidence and decrease overall opioid medication needed.

Some patients won't believe it is working unless they can feel it 'kick in'.

Giving Opioids

It is helpful to stress that prevention of opioid withdrawal is something the patient deserves and is a goal of our care – although our efforts may still be imperfect.

Giving the patient a sense of control can decrease the anticipation of pain.

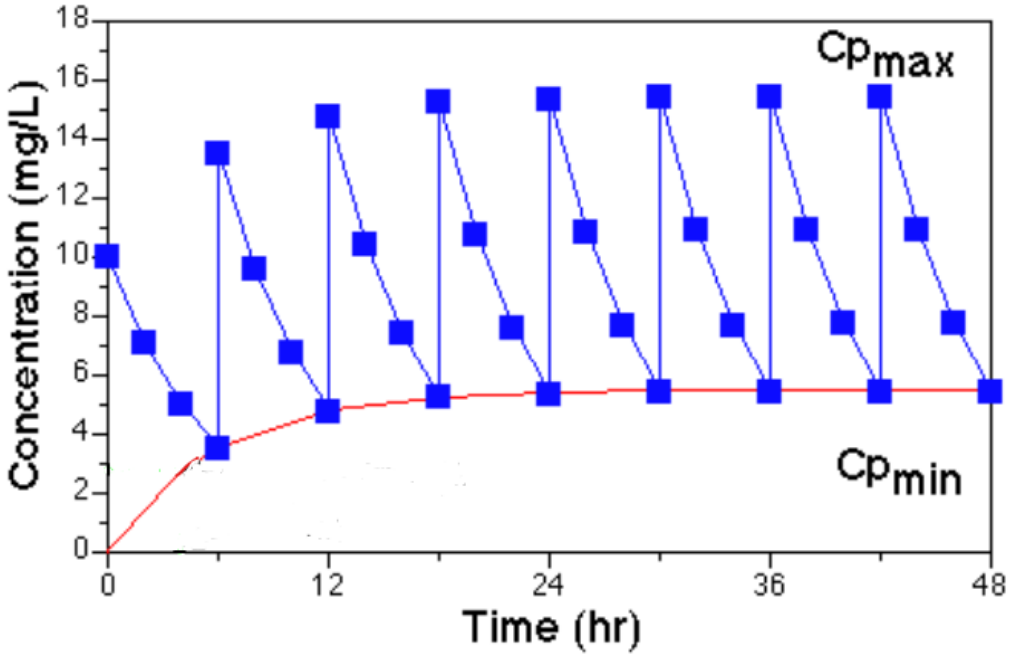
Reducing attachment

Pay attention to reinforcing events that promote salience of opioid doses

Speed of onset

Difference between nadir and peak

Relief of pain / withdrawal as reinforcers



https://www.boomer.org/c/p4/c14/c14.pdf

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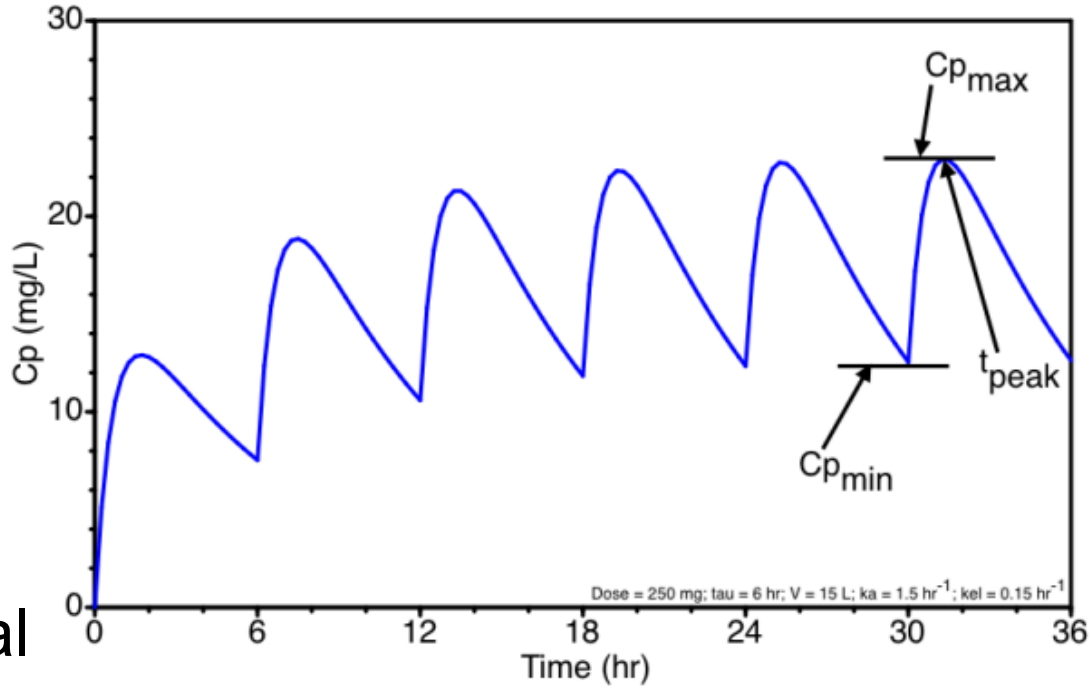
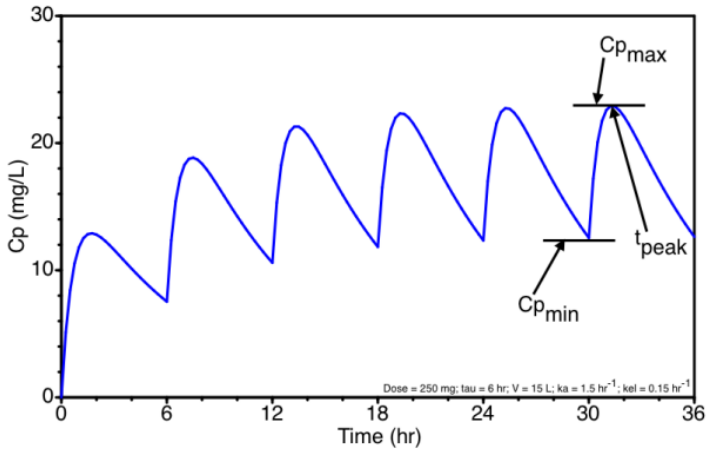


https://www.boomer.org/c/p4/c15/c15.pdf

Whenever possible …

Oral medications rather than IV medications
- slower onset

Frequent dosing
- avoid a lower nadir,
- and thus a smaller delta



Scheduled rather than prn dosing
- operant conditioning
- minimize conflict between patient and caregivers

https://www.boomer.org/c/p4/c15/c15.pdf

Short acting oral Opioids

Scheduled oral + prn oral, ***an example***

Oxycodone 15 mg q4h scheduled PLUS

Oxycodone 15 mg q4h prn for “pain or withdrawal not relieved by schedule doses”

Hydromorphone 4 mg q4h scheduled PLUS

Hydromorphone 4-8 mg q4h prn for “pain or withdrawal not relieved by scheduled doses”

PCA Opioids

More frequent dosing that RN given q1-2h prn allows lower nadir and smaller delta per dose

Higher doses than used for non tolerant patients, e.g.

- Instead of hydromorphone 0.2 - 0.6 mg bolus dose, use 0.5 - 1 mg bolus dose

Dose q 8 minutes

No maximum dose?

Starting methadone

Slow onset: 4 hours to peak effect

Long duration: t½ 18-36 hours

Accumulates over ~3 days

Highest initial dose that should be safe in all patients: 30 mg

Starting methadone

Slow onset: 4 hours to peak effect

Long duration: t½ 18-36 hours

Accumulates over ~3 days

Highest initial dose that should be safe in all patients: 30 mg

Divided dosing to improve safety

e.g. 20 mg q4h, rather than 120 mg qAM (hold if respiratory rate < 12)

What about sedation?

Starting methadone

Slow onset: 4 hours to peak effect

Long duration: t½ 18-36 hours

Accumulates over ~3 days

Highest initial dose that should be safe in all patients: 30 mg

Divided dosing to improve safety (hold if respiratory rate < 12)

New OTP rules allow split BID dosing at methadone clinic

https://www.federalregister.gov/documents/2024/02/02/2024-01693/medications-for-the-treatment-of-opioid-use-disorder

Starting methadone

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Higher methadone doses seem to be more common during fentany era

https://www.statnews.com/2023/03/21/fentanyl-addiction-methadone-dose-new-rule

Starting methadone

Initial loading dose: 30 mg x 1

BID dosing: 20 or 30 mg BID
(hold for resp rate < 12)

Add'l 10 mg po q4h prn opioid withdrawal
prn COWS score or
"patient complaint of opioid withdrawal"
(hold for resp rate < 12)

Starting methadone

Initial loading dose: 30 mg x 1

If prn doses are not likely to work well,

scheduled dosing can be more frequent - e.g. 10 mg q6h or 20 mg TID (hold if resp rate < 12)

slower escalation of methadone, makes short acting opioids more important

Starting methadone

Initial loading dose: 30 mg x 1

BID dosing 20 or 30 mg BID
(hold for resp rate < 12)

Add'l 10 mg po q4h prn opioid withdrawal
prn COWS score or
"patient complaint of opioid withdrawal"
(hold for resp rate < 12)

Adjust scheduled dose each day, taking into account

~ Total methadone per day over last 2-3 days

~ Total short acting opioid needed

~ Severity of ongoing withdrawal symptoms

Starting methadone

Initial loading dose: 30 mg x 1

BID dosing 20 or 30 mg BID
(hold for resp rate < 12)

Add'l 10 mg po q4h prn opioid withdrawal
prn COWS score or
"patient complaint of opioid withdrawal"
(hold for resp rate < 12)

Continue ancillary medications
while withdrawal symptoms remain bothersome despite current amount of opioid

Starting methadone

Initial loading dose: 30 mg x 1

BID dosing 20 or 30 mg BID
(hold for resp rate < 12)

Add'l 10 mg po q4h prn opioid withdrawal
prn COWS score or
"patient complaint of opioid withdrawal"
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Taper down short acting opioid as methadone doses become adequate to resolve withdrawal symptoms

Starting methadone

Day	Methadone	Hydromorphone	Ancillary Meds
1	30 + 10 x 2 = 50 mg	4 mg q4 sched + 12 mg prn	yes
2	30 BID + 10 x 4 = 100 mg	4 mg q4 sched + 16 mg prn	yes
3	40 BID + 10 x 3 = 110	4 mg q4 sched + 4 mg prn	yes
4	45 BID + 10 x 3	4 mg q4 sched, no prn	no
5	50 BID + 10 x 2 = 120 mg	2 mg q4 sched	no
6	55 BID + 10 x 2 = 130 mg	2 mg q4 sched	no
7	60 BID + 10 x 2 = 140 mg	none	no
8	70 BID + 5 x 3 = 155 mg	none	no
9	80 BID + 5 x 2 = 170 mg	none	no

Starting buprenorphine

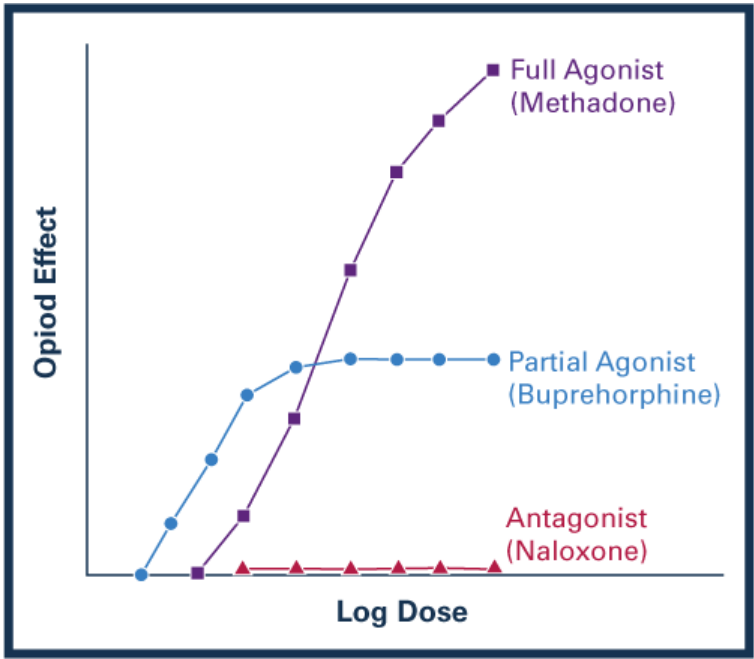
Partial agonist

Risk for precipitated withdrawal

concurrent low dose initiation vs rapid high dose initiation

Ceiling effect –

typically assumed to be equivalent to 30-40 mg methadone per day



Buprenorphine concurrent low dose initiation

How low to start? typically 0.5 mg SL or less

How frequent to dose? BID to q4h

How quickly to increase doses?

Typically doubled daily but sometimes faster

When to remove full agonists?

Usually after “full” buprenorphine doses

Stopping abruptly or gradually tapering

Ancillary medications may be needed.

Buprenorphine concurrent low dose initiation

Swedish Protocol

0.075 mg q4 x 2 doses,
0.15 mg q4 x 2 doses,
0.3 mg q4h x 2 doses,
0.6 mg q4h x 2 doses,
1 mg q4h x 2 doses,
2 mg q4 x 2 doses,
4 mg q4 x 2 doses,
8 mg q4 x 2 doses, then
8 mg TID

Non opioid management of pain

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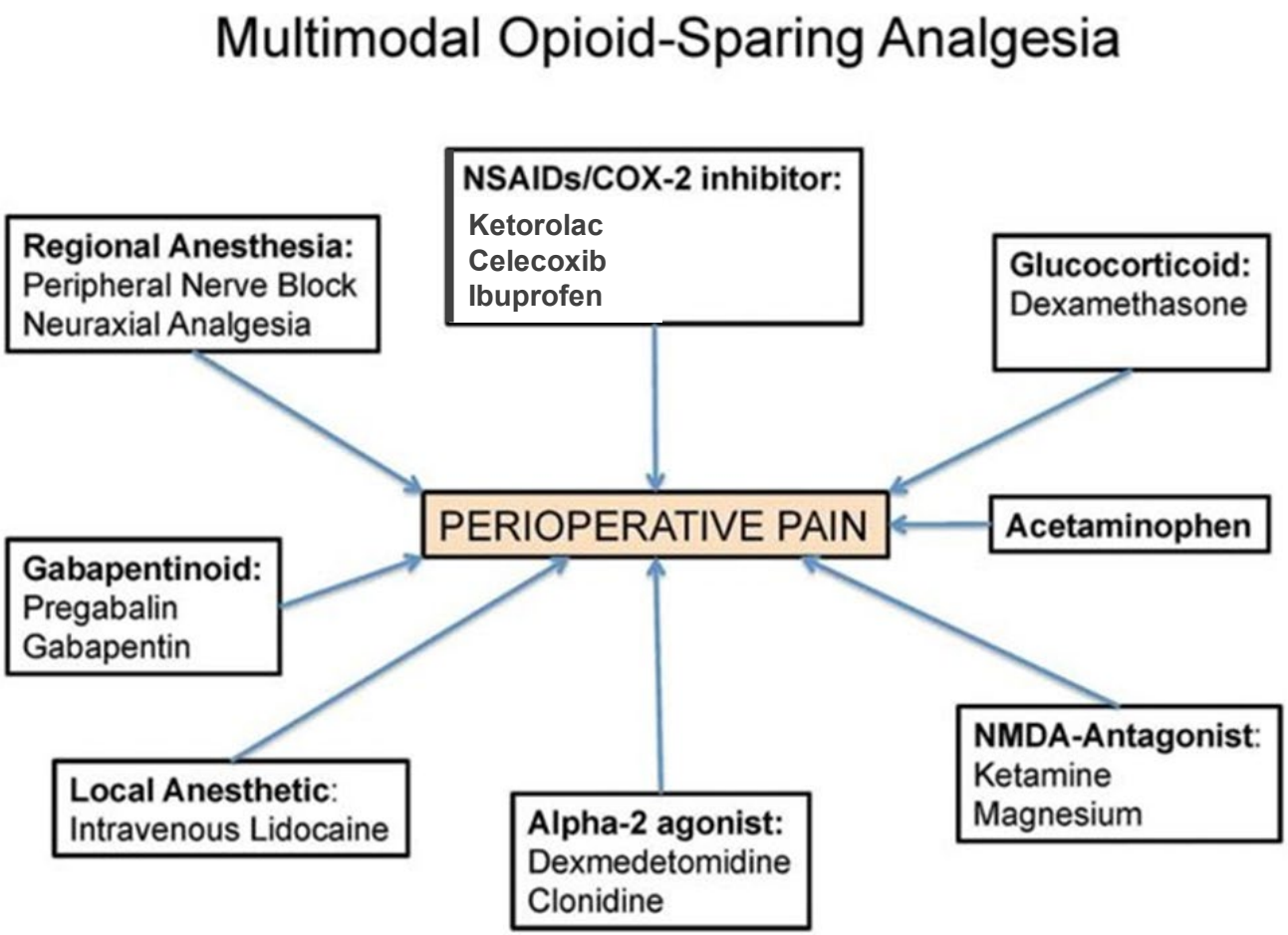


State of the art opioid-sparing strategies for post-operative pain in adult surgical patients, Gabriel et al, Expert Opin Pharmacother. 2019 Jun;20(8):949-961

Acetaminophen

Analgesic and opioid-sparing benefits
Some studies show benefit when started pre-operatively
No demonstrated benefit to IV formulation over oral

Don't exceed the recommended maximum daily dose
4 gram / day in adults.
Severe alcoholism, stable cirrhosis, body weight <50 kg
dose should be reduced to 2 grams per day

Order scheduled, not prn

State of the art opioid-sparing strategies for post-operative pain in adult surgical patients, Gabriel et al, Expert Opin Pharmacother. 2019 Jun;20(8):949-961
https://emcrit.org/ibcc/pain/

NSAID

Significant pain relief and reduced postoperative morphine consumption (about 50%).

Several studies demonstrated improvement in postoperative function, including earlier return to oral intake, time to ambulation, and decreased urinary retention

Contraindications

Renal dysfunction / AKI – esp with reduced renal perfusion
Increased leakage of bowel anastomosis?
Bone healing?
Bleeding?

Order scheduled, not prn

The Use of NSAIDs in the Postoperative period: Advantage and Disadvantages, Cosmo et al J Anesth Crit Care Open Access. 2015;3(4) : 1 4 ؤ 1 2 .
Perioperative Use of NSAIDs: Safety and Guidelines
https://www.cadth.ca/sites/default/files/pdf/htis/2018/RB1205%20Perioperative%20use%20of%20NSAIDS%20Final.pdf

Regional

Epidural can be left in several days, but may increase risk of infection

Peripheral Nerve Blocks

Local infiltration

Lidocaine patch

Significant reduction in post-sternotomy pain and total dose of rescue opioids used for 48 hours

Infection rates associated with epidural indwelling catheters for seven days or longer: systematic review and meta-analysis. Ruppen et al, BMC Palliat Care 6, 3 (2007)
Folino TB, Mahboobi SK. Regional Anesthetic Blocks. [Updated 2021 Oct 14]. In: StatPearls [Internet]. Treasure Island (FL)
Analgesic effects of a 5% lidocaine patch after cesarean section: A randomized placebo-controlled double-blind clinical trial. de Queiroz et al, J Clin Anesth. 2021 May 8;73:110328
The 5% lidocaine patch for decreasing postoperative pain and rescue opiod use in sternotomy: A prospective, randomized, double-blind trial. Parker, et al Clin Ther. 42(12):2311-2320

Gabapentinoids

bind to the alpha-2-delta subunit of voltage gated calcium channels, which decreases the release of glutamate, noradrenaline (norepinephrine), and substance P. This is believed to contribute to their anticonvulsant, analgesic, and anxiolytic actions.

Dizziness (19%), somnolence (14%), and gait disturbance (14%) are commonly reported with gabapentin

Mechanisms of the gabapentinoids and alpha 2 delta-1 calcium channel subunit in neuropathic pain. Patel, et al Pharmacol Res Perspect. 2016;4(2)
Gabapentin for chronic neuropathic pain in adults. Wiffen et al, Cochrane Database Syst Rev 2017;6:CD007938

Pregabalin

Absorption of gabapentin is saturable, leading to a non-linear pharmacokinetic profile. Bioavailability is 80% at lower doses such as 100 mg q8, but only 27% at 1600 mg q8

Unlike gabapentin, absorption of pregabalin is not saturable, and the drug has a linear pharmacokinetic profile.

Gabapentin is slowly and variably absorbed, with peak plasma concentrations around 3h. Pregabalin is quickly absorbed, peak blood concentrations within an hour

Pregabalin binding to delta subunit is greater than that of the Ü gabapentin.

https://www.pharmacytimes.com/view/how-gabapentin-differs-from-pregabalin

Ketamine

NMDA antagonist => Analgesia, sedation, anesthesia
May oppose development of tolerance / hyperalgesia

Low-dose i.v. ketamine reduces opioid consumption by 40%
Opioid-sparing effect of ketamine only while actively administered

The dose ranged from
0.15 mg/kg bolus + 0.12 mg/kg/h to 0.5 mg/kg bolus + 0.6 mg/kg/h

At around 0.2-0.3 mg/kg/hr ketamine may cause somnolence, agitation, euphoria, or hallucinations. Some patients may experience disturbing hallucinations.

Psychomimetic side effects will abate rapidly after pausing the ketamine infusion

The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. Jouguelet-Lacoste et al, Pain Med. 2015 Feb;16(2):383-40
What Is the Role of Ketamine in Postoperative Pain Management? Bruno Maranhao, Stephen H. Gregory, Journal of Cardiothoracic and Vascular Anesthesia, Volume 34, Issue 3, 2020, Pages 592-593
https://emcrit.org/ibcc/pain/#ketamine

Ketamine

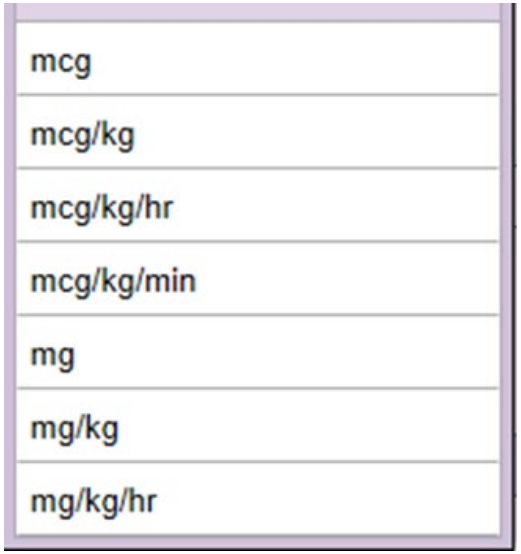
Too many units!

Very low risk dose of 0.12 mg/kg/hr

At Swedish Hospital, order defaults to units of ***mcg/kg/min***, but can also be ordered in a confusing array of measurements.

On the medical floor the maximum allowed rate is 10 mg/hr (not weight based)

For a 70 kg person , 0.12 mg/kg/hr => 8.4 mg/hr
For a 100 mg person, 0.12 mg/kg/hr => 12 mg/hr



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Central Ŭ2 agon

Clonidine, Tizanidine, Dexmedetomidine, Guanfacine

Reduce adrenergic outputs from the locus coeruleus,
a decrease in sympathetic tone

Analgesia & sedation

Hypotension and bradycardia

Dexmedetomidine

Studies assessing its benefit for postoperative analgesia when used during the perioperative period with mixed results.

Many studies have demonstrated reduce postoperative opioid use when given intraoperatively.

State of the art opioid-sparing strategies for post-operative pain in adult surgical patients, Gabriel et al, Expert Opin Pharmacother. 2019 Jun;20(8):949-961

Clonidine

clonidine decreased pain scores and time to first request of opioid

intraoperative clonidine reduced opioid consumption while not exacerbating sedation or side effects

3 mcg/kg bolus dose followed by a continuous infusion of 0.3 mcg/kg/hour was considered the optimal intravenous dose

Alpha-2 adrenergic receptor agonists: a review of current clinical applications. Giovannitti et al, Anesth Prog. Spring 2015;62(1):31-9

	Dexmedetomidine	Clonidine	Tizanidine	Guanfacine
Clinical Effects				
Sedative	+++	++	+	++
Analgesic	+++	+++	+++	?
Anti-shivering	++	++	++	?
Muscle relaxant			++	
Hypotension/Bradycardia	++	+++	+	++
Pharmacology				
Bioavailability	Only IV	85%	20-34%	
Onset	Infusion takes ~30-60 minutes to reach equilibrium levels	~2 hours	~1.5 hours	~4 hours
Half-life		12 hours	2.5 hours	16 hours
Metabolism/excretion	Mostly renal	50/50 renal/hepatic	Hepatic CYP450 1A2 into inactive metabolites.	
In ICU used for...	Sedation Multimodal analgesia	Sedation, Insomnia Hypertension Multimodal analgesia	Muscle spasm Multimodal analgesia	Sedation, Insomnia
Dose	Do not bolus. 0-1.4 mcg/kg/min. Start infusion at the high end (e.g. 1-1.4 mcg/kg/min) without a bolus. Observe carefully & down-titrate over 30-90 min, as it takes effect.	Sedation, opioid withdrawal Start: 0.2-0.3 mg q6hr Increase to 0.5 mg q6hr Insomnia Start ~0.2 mg QHS Increase to 0.4 mg QHS Multimodal analgesia Start 0.1-0.2 mg q12hr Increase to 0.3-0.4 mg q8hr	Multimodal analgesia Start: ~4 mg q8hr. May up-titrate to ~8 mg q8hr. Using an increased dose in the evening may enhance sleep. (Max dose is 12 mg q8hr)	Sedation, opioid withdrawal Start: 1 mg q12 Increase: to 3-4 mg/d total Insomnia 1-2 mg PO ~4 hrs before sleep
Contraindication	Bradycardia/hypotension	Bradycardia/hypotension	Hepatic injury CYP 2A1 inhibitor medication	Bradycardia/hypotension

The Internet Book of Critical Care

https://emcrit.org/ibcc/pain/#ketamine

Intravenous Lidocaine

analgesic and anti-hyperalgesic effect is obtained through inhibition of the voltage-gated sodium channels, voltage-gated calcium channels, various potassium channels, NMDA receptors, glycine system, and G protein pathways

Lidocaine has been associated with reduced opioid consumption, earlier return of bowel function, faster rehabilitation, and shorter hospital stays.

There is evidence that intravenous lidocaine prevents hypersensitization and hyperalgesia.

Intravenous lidocaine was also shown to be associated with improved postoperative cognitive function.

Can have a beneficial effect as a prophylactic measure to prevent the development of chronic pain.

State of the art opioid-sparing strategies for post-operative pain in adult surgical patients, Gabriel et al, Expert Opin Pharmacother. 2019 Jun;20(8):949-961
Non-opioid analgesics: Novel approaches to perioperative analgesia for major spine surgery. Dunn et al Best Pract Res Clin Anaesthesiol 2016 Mar;30(1):79-89

Possible approach to using a lidocaine infusion for analgesia

Good candidate for IV lidocaine infusion

- Either one of the following:
  - i) Practitioner is able to check lidocaine levels occasionally
  - ii) Patient is non-intubated, so symptoms can be used to monitor for lidocaine toxicity
- No heart block, severe heart failure, shock, or multi-organ failure
- Renal function adequate (e.g., GFR >30 ml/min)
- Liver function adequate (e.g., Bilirubin <1.5 mg/dL)
- Not at unusually high risk of seizure
- No interacting medications (check on Medscape or other program)

Lidocaine loading dose ("test dose")
~1.5 mg/kg
Administer over roughly 10-30 minutes

No improvement 😞 → **Try a different analgesic agent / strategy**

Improvement in pain 😃

Lidocaine infusion

- Infuse at ~1 mg/kg/hour ideal body weight.

Monitor for toxicity

- Check levels daily if possible (but test unavailable in most hospitals).
- Monitor for early signs of toxicity (*discontinue* infusion if these occur)
  - Paresthesias or numbness (especially perioral)
  - Auditory or visual disturbance, light-headedness
  - Tinnitus
  - Metallic taste
  - Confusion, somnolence

The Internet Book of Critical Care

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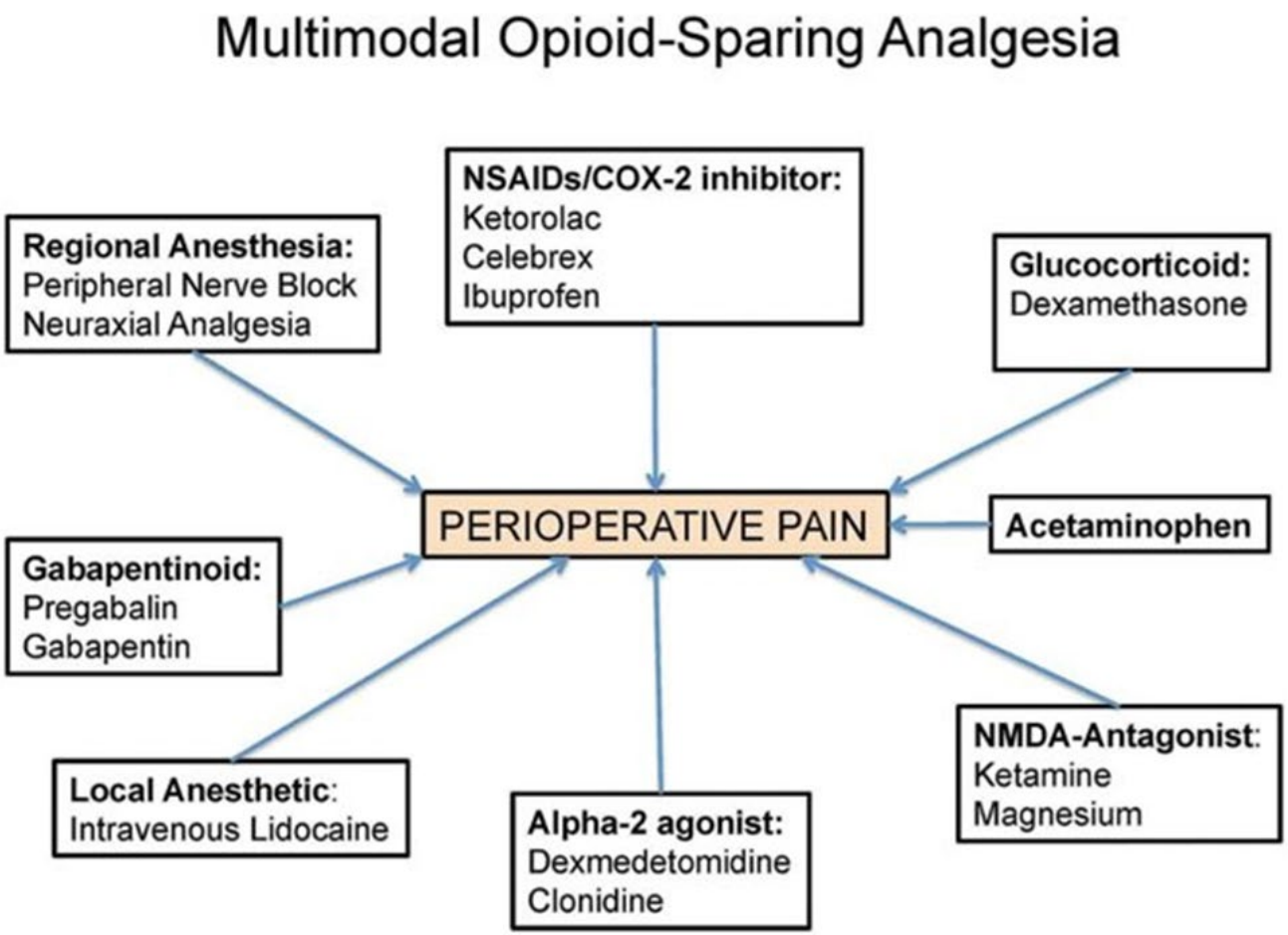
Non opioid management of pain



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Patients already on MOUD

Don’t stop or reduce methadone or buprenorphine

Divided dosing may offer some advantage

Maximize non opioid pain treatment

Full agonist opioids at 2, 3, 4 or 5 times normal dosing may be needed

but the duration that opioids are needed should not be longer than other patients with the same condition

Multi-society Working Group on Opioid Use Disorder

Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Kohan L, et al. Reg Anesth Pain Med 2021;46:840–859.

Respect Gets Respect

Sit down

Slow down

Eye position

"Not a whiff of judgement"

Notice opportunities for affirmation / validation

Don't let anxiety or defensiveness keep you from showing your genuine self

Nursing process

Be predictable.

Keep promises.

Manage expectations

White board

Treating PRN meds as scheduled: inquire at the ordered frequency about need for medication

Limit Setting is a Team Sport

Setting limits vs Seeking control

It's not about what the patient is going to do, it is about what *we* are going to do.

Inconsistency is agony for both patient and staff.

Creating consistency requires communication.

Don't hesitate to gather a care conference.
This may be necessary every day or every shift.

Getting Ready for Discharge

change to PO dosing... and hold!

Patients who came to the hospital actively using may return to active use after discharge.

"Detoxing" in the hospital is unlikely to have much impact on sobriety after leaving.