Buprenorphine for patients with serious illness

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Lake Geneva, WI
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Some slides created in collaboration with my colleague Dr Annette Nijjar

Disclosures

- I have no relevant financial disclosures
- Buprenorphine is approved as MOUD (Suboxone, Subutex, Zubsolv) and for chronic pain (Butrans, Belbuca). I will discuss using Subxxx buprenorphine **off-label** for chronic and cancer pain.

- Buprenorphine drug formulations are CONFUSING, and we will use trade names for better clarity (eg there are at least 4 transmucosal buprenorphine drug products out there and the only way to easily differentiate them are the trade names).

Overview of today

- 45 min: overview of buprenorphine + lower dose bup for pain
- 30 min: cases + discussion
- BREAK
- 45 min: higher dose bup for pain and OUD
- 30 mins: cases + discussion.

- Focus is on the practical use of buprenorphine for patients with serious illness

Fundamentally, buprenorphine is another opioid analgesic, just a significantly safer one

All the bad things you've heard about buprenorphine are WRONG

(Except for the precipitated withdrawal thing)

Ok, it really is confusing…

- Synthesized in 1966: a thebaine opioid
- FDA approved in US in 1981—injectable buprenorphine for pain (Buprenex)
- 2002 SL approved for **OUD**, schedule III (Suboxone, Subutex, Subsolv)
- 2010 TD bup approved for **chronic pain** (Butrans)
- 2015 buccal bup (“Belbuca”) approved for **chronic pain**
- 2017 subcut depot monthly injection (Sublocade) approved for OUD

- TD bup for pain 30-70 mcg/hr (Transtec) long available in much of Europe + 200 mcg SL tabs

Buprenorphine is Special!

- Buprenorphine appears to be as good an opioid analgesic as anything!
- Buprenorphine is far, far safer than other MOA w/r/t respiratory depression!
- Buprenorphine is far, far safer than other MOA w/r/t its addiction risk/'behavioral reinforcement'/inducing cravings in patients
- ONLY AT HIGH DOSES, buprenorphine can precipitate opioid withdrawal in opioid tolerant patients if initiated too quickly

But there are a couple key things which are poorly understood about buprenorphine

- When transitioning someone off other opioids to buprenorphine—at what dose of the baseline opioid do you simply ‘stop & start’ vs do you do a ‘buprenorphine induction’

- What are the best strategies for transitioning a patient off buprenorphine to another opioid?

Bup & Receptors - Simplified

Receptor Type	Effect of Activation (Agonism)
Mu via **G-Protein**	Analgesia
Mu via **ß-Arrestin**	Respiratory Depression, Tolerance, Physical Dependence, Hyperaglesia
Kappa	Craving, Depression, Hyperkatifeia (increased sensitivity/distress to negative emotions/cues), hyperalgesia
ORL-1 (opioid receptor like)	Analgesia

Receptors

Receptor Type	Effect of Activation (Agonism)	Effect of Bup
Mu via **G-Protein**	Analgesia	Strong Activation
Mu via **ß-Arrestin**	Respiratory Depression, Tolerance, Physical Dependence, hyperalgesia	Minimal Activation
Kappa	Craving, Depression, Hyperkatifeia	Inverse Agonist (actively *antagonizes*)
ORL-1	Analgesia	Agonist

This all adds up to…

Receptor Type	Effect of Activation (Agonism)	Effect of Bup at R	Clinical Effect of Buprenorphine
Mu via **G-Protein**	Analgesia	Strong Activation	**Strong Analgesia. No clear ceiling effect!**
Mu via **ß-Arrestin**	Respiratory Depression, Tolerance, Dependence	Minimal Activation	**Low risk of Respiratory Depression, Tolerance, or Dependence. Distinct ceiling effect on respiratory depression!**
Kappa	Craving, Depression, Hyperkatifeia	Inverse Agonist (actively antagonizes)	**Improved Mood, Less vulnerable to emotional distress, Less craving**
ORL-1	Analgesia	Agonist	**Likely enhances analgesia via MOR**
Via a chaperone effect, **bup increases availability of MOR on cell membrane** (most other opioids down-regulate MOR availability)--?less analgesic tolerance			

Pharmacology

- Bup has very strong opioid receptor binding→ it can displace other opioids!!

- Bup has a relatively long half-life (analgesic 6-12 h when used SL; elimination T12 over 24h)

This adds up to----

- **Good** analgesia
- **Far lower** respiratory depression risk
- **Lower risk** of developing OUD/addiction

- **Greatly attenuated** withdrawal symptoms

- But! Narrow circumstances where bup can **precipitate withdrawal**

Pro-tip

- Stop thinking about bup as a “partial agonist”!
  - It’s confusing and no one knows what it means!

- Never, EVER, talk about buprenorphine as being an opioid receptor blocker!
  - It’s incorrect and scary and confusing to patients on eg Suboxone who develop severe pain and HAVE BEEN TOLD buprenorphine will block the effectiveness of other opioid analgesics!

Pro Tip – Partial Agonist???

Think: some effects do occur, others don't

Don't think: partial effectiveness (i.e. not partial analgesia)

There are no data suggesting buprenorphine 'blocks' analgesic effects of 'full mu opioid agonists'. Analgesic effects of bup are ADDITIVE to morphine (etc) in animal models (EuJPain 2009).

Pro-Tip – Bup is MOR agonist, not a blocker!

Strong Binding to MOR:

→ It does not block at MOR—but it can displace other opioids!

→ Because **some** opioid effects are attenuated with buprenorphine (eg the B-arrestin ones) bup can precipitate withdrawal in narrow circumstances

= *Patient is highly opioid tolerant + you initiate a high dose of bup all at once!*

Receptor Affinity - Actually

Buprenorphine does not occupy *all* receptors

→ Full mu agonists can bind to open receptors

= opportunity for **additional analgesia** from other MORa

Dose dependent displacement

→ no WD symptoms at low doses (Initiating <1-2mg/day)

= **safely initiating it is easy!**

Note: Higher doses *can* precipitate WD in opioid tolerant patients

But!!! I heard Suboxone blocks other opioids and our patients will be in pain!!!

- *Patient on 8 mg tid Suboxone for OUD admitted with a femur fracture and gets poor relief from 50 mcg fentanyl in the ED*

Pro Tip – talk about buprenorphine as a opioid analgesic, not a ‘blocker’

This is a scary notion for our patients!

Think: appropriate prn dosing

(strong long-acting will need strong short-acting for additional effect)

Hmmmmm….

- For a patient on 30 mg tid methadone who had surgery & had poor pain relief from 2 Percocets afterwards…
- Would you call that ‘methadone is blocking the effectiveness of the oxycodone’?
- Or would you shrug and say ‘this is a highly opioid tolerant patient who needs far higher acute opioid doses’ as a routine matter?
- **A lot of what people ‘blame’ buprenorphine for is just normal stuff for all our patients on high dose opioid therapy!**

This all adds up to:

- **Good** analgesia
- **Far lower** respiratory depression risk
- **Lower risk** of developing OUD/addiction
- **Fewer** opioid toxicities **ESPECIALLY SUPRATENTORIAL ONES** including euphoria/mood alteration/craving
- Outcompetes most other MOR agonists so **reduces** euphoria + respiratory depression from other MOR agonists.
- **Other opioids** continue to work additively with buprenorphine

- But—it displaces other MOR agonists so effectively that it can **precipitate withdrawal** at higher doses (?>1-2 mg) for opioid tolerant patients

All the bad things you've heard about buprenorphine are WRONG

(Except for the precipitated withdrawal thing)

Pharmacokinetics

- High first-pass effect
  → no oral option
- Almost completely metabolized in liver
  → A preferred opioid in renal failure
- …via several independent pathways
  → Still ok in mild to moderate liver failure
- Metabolite norbuprenorphine active, but low concentrations in CNS, so less clinical effect

Pharmacokinetics

Medication	Route	Bioavailability	Onset	Half-Life
Buprenex	IV	100%	5-15 min	3h
Subutex, Suboxone	SL	30-50%	30-60 min	25-30h
Belbuca	Buccal	46-65%	30-60 min	27.6h
Butrans	TD	15%	18-24 h	26h

- <u>Sublingual Products:</u>
- Duration of analgesia: **6-12 hours**
- Suppress cravings/withdrawal **> 24h**

Buprenorphine PK made Easy

- Transmucosal buprenorphine: **~same PK as oral methadone!**
- Transdermal buprenorphine: **~same PK to TD fentanyl!**

Buprenorphine potency

- Buprenorphine is likely in range of 25-100x as potent as IV morphine
- DON’T SPEND ANY MORE TIME THINKING ABOUT THIS HOWEVER.
- With buprenorphine we only talk about SAFE, EFFECTIVE strategies for transitioning patients onto/off buprenorphine
- “Equianalgesia” is not a concern!

Side effects = Just like any other opioid!

- (With improved safety as mentioned above in some parameters)
- There is a belief it has overall less severe side effects than ‘full opioid agonists’ = ***this is hypothetical and not currently evidence based.***
- QTc prolongation is minimal and FDA just ‘backed off’ on QT warnings for buprenorphine!
- **<u>Unique Side Effect:</u> prolonged use of transmucosal products can accelerate tooth decay!**
  - Common sense recs to mitigate; no evidence-based recs currently

Jun 27, 2022

Denise Myshko

Labels now warn that buprenorphine products that dissolve in the mouth can cause dental problems. Buprenorphine is used to treat opioid use disorder and pain.

The FDA has updated the safety labels of all products that contain buprenorphine to warn about the risks of dental disease and QT prolongation resulting from the use of these products. Buprenorphine is used to treat opioid use disorder and pain. These products are available as single-ingredient products and also in combination with naloxone.

The updates have been made to ensure all labels for buprenorphine products are consistent. This includes all generics as well as branded therapies, such as Belbuca, Buprenex, Suboxone, Zubsolv, and among others.

The QT interval is a measure made on an electrocardiogram and is used to assess the electrical properties of heart. Long QT can cause rapid heart rate and irregular rhythm and can be life-threatening.

The agency's action for ensuring all labels warn of QT prolongation is supported by several studies, including a November 2020 study published in PLoS ONE. Previous studies with buprenorphine products have demonstrated a small QT prolongation effect. The label addition indicates that buprenorphine alone is unlikely to cause serious issues in patients without risk factors, such as low potassium, low heart rate, congestive heart failure, digitalis therapy, baseline QT prolongation, or severe low magnesium.

This new subsection reads:

"Thorough QT studies with buprenorphine products have demonstrated QT prolongation less than or equal to 15 msec. This QTc prolongation effect does not appear to be mediated by hERG channels. Based on these two findings, buprenorphine is unlikely to be pro-arrhythmic when used alone in patients without risk factors. The risk of combining buprenorphine with other QT-prolonging agents is not known.

"Consider these observations in clinical decisions when prescribing … to patients with risk factors such as hypokalemia, bradycardia, recent conversion from atrial fibrillation, congestive heart failure, digitalis therapy, baseline QT prolongation, subclinical long-QT syndrome, or severe hypomagnesemia."

Buprenorphine clinical outcomes literature review

- OUD=saves lives, standard of care
- Cancer pain & chronic noncancer pain: in available H2H studies, seems just as effective as ‘full MOR agonists’
- Standard of care in 2023 is to continue higher dose buprenorphine for acute pain, and ‘add on’ full MOR agonists on top of it

Buprenorphine for OUD

- Preponderance of evidence = improves ~all relevant patient centered outcomes when it comes to OUD
  - Reduced fatal/nonfatal overdose (fatal OD is possible; biggest risk seems to be mixed with benzos + injected buprenorphine)
  - Reduce illicit drug use
  - Reduce comorbidities from injectable DU (eg infectious)
  - Improved retention in behavioral therapy/support for OUD
  - QOL improved!!
- Far easier to access than methadone – office based management
- Improves outcomes regardless if patients are in behavioral therapy or not
- First line standard of care treatment for OUD (vs methadone clinic for select patients---some belief methadone is better for fentanyl analog users?)

- Taylor. Opioid Use Disorder. Ann IM 2022 https://doi.org/10.7326/AITC202201180

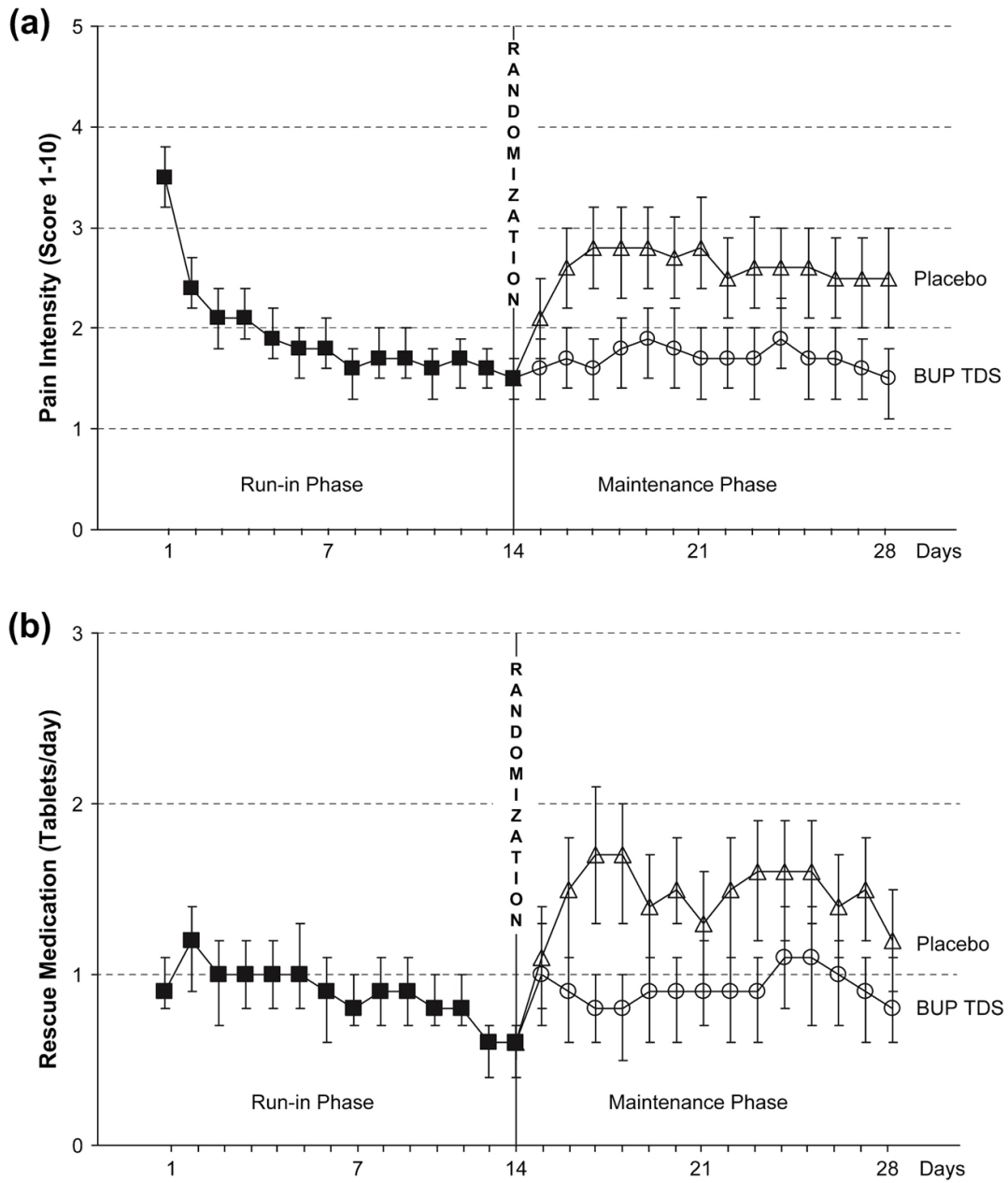
NO MORE X-WAIVER!!

YOU, TODAY, CAN RX BUPRENORPHINE FOR OUD!!

Bup for cancer pain—literature review

- Poulain JPSM 2008: WILD study design:
  - 289 European/advanced cancer pt; refractory pain despite opioids (eg 90-150 mg/d morphine)
  - All patients converted to 70 mcg/h TDS bup (1.68 mg/d) and other opioids stopped, for 2 weeks.
  - Those who ‘responded’ were randomized to bup TDS vs placebo (!); could use 200mcg SL bup pills were allowed as rescue meds)
  - 289 enrolled; 32% ‘failed’ initial run in bup phase.
  - Remainder randomized to 70mcg/hr TDS vs placebo patch + Bup BT tabs for 2 wk
  - 10.1016/j.jpainsymman.2007.09.011

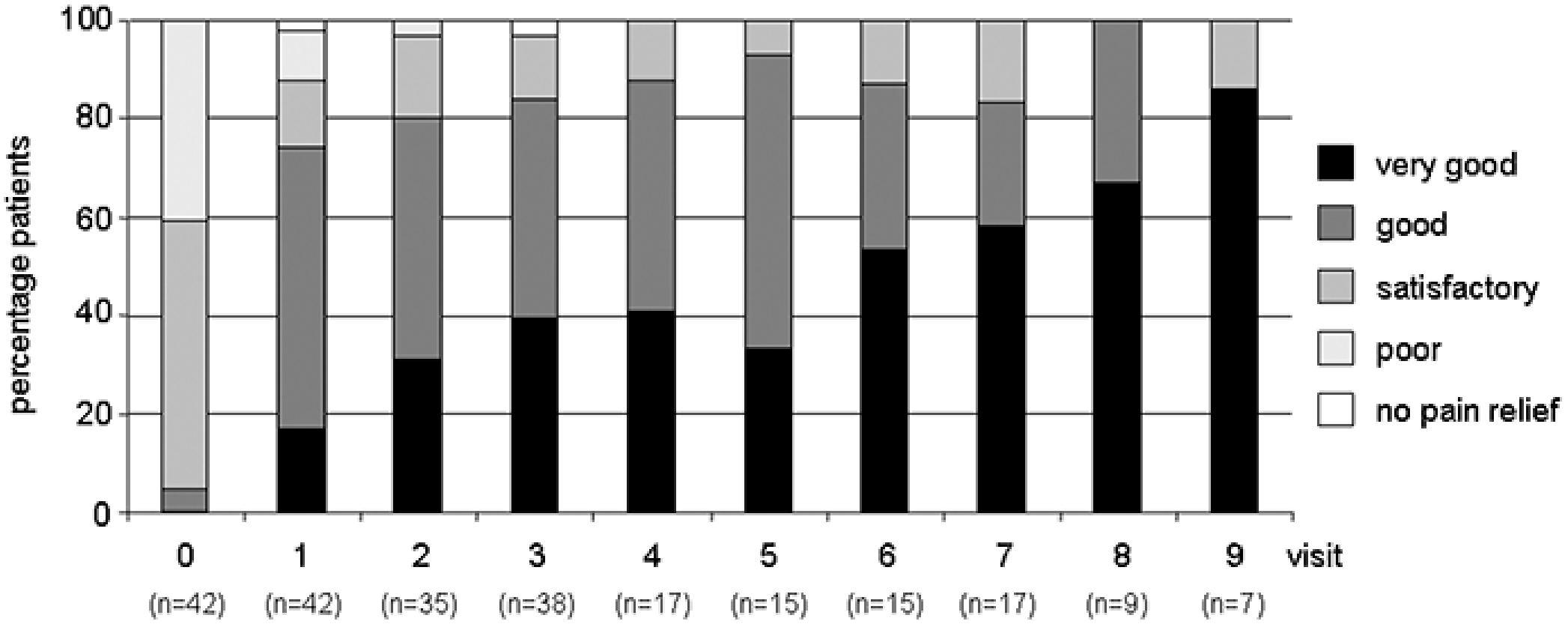
“This was the largest placebo controlled trial of opioids ever for cancer pain”


(a)
Pain Intensity (Score 1-10)
0
1
2
3
4
5
RANDOMIZATION
Placebo
BUP TDS
Run-in Phase
Maintenance Phase
1
7
14
21
28
Days
(b)
Rescue Medication (Tablets/day)
0
1
2
3
RANDOMIZATION
Placebo
BUP TDS
Run-in Phase
Maintenance Phase
1
7
14
21
28
Days

Freye Pain Practice 2007.

- 42 patients with a variety of pain syndromes converted to TD bup from high dose morphine (120-800 mg/d) per physician discretion & closely observed; followed for at least 10 weeks. *Practical, unblinded, 'real life' trial.*
- Pain improved in general:
  - Baseline only 5% of patients had good to very good pain relief
  - On Bup = 76%!!!
- No clear relationship between morphine dose and Bup dose
  - In Europe TD Bup comes as 35, 52, 70 mcg/hr
  - Majority of patients ended up on 52 mcg/hr regardless of baseline morphine dose

https://doi.org/10.1111/j.1533-2500.2007.00119.x


percentage patients
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
9
visit
(n=42)
(n=42)
(n=35)
(n=38)
(n=17)
(n=15)
(n=15)
(n=17)
(n=9)
(n=7)
very good
good
satisfactory
poor
no pain relief

Ruggiero Pediatr Blood Cancer 2013.

- Observational study of 16 kids with severe cancer pain not controlled with non-opioid therapies
- 11/16 responded, pain 6.3/10→1.4/10. Sleep, play improved.
- Very basic observational study but best we have for kids…..

https://doi.org/10.1002/pbc.24332

- Same author group wrote a review on TD bup for kids in 2021:
  - Attina Drugs Context 2021. https://doi.org/10.7573/dic.2021-6-1

The 2 Main Comparison Studies in Adults

- Corli, Ann Oncol 2016 https://doi.org/10.1093/annonc/mdw097
  - Non blinded RCT adults, cancer pain, none had had ‘strong opioids’ (most had codeine/tramadol), 44 European cancer centers, n=520. Both in+outpatients. Largest opioid trial in cancer ever performed.
  - Randomized to oxyER, morphineER, TD fent, TD bup, followed for 28 d. Clinicians could adjust doses as they felt were clinically indicated.
  - No major differences between groups:
    - Pain ~6→3/10 for all drugs.
    - ~10% classified as nonresponders in all groups.
    - ~35% patients required additional opioids (PRNs)
    - ~20% discontinued initial long acting opioid
    - No major side effect differences
    - They only give end-doses as OMEs (!!) so we don’t know what dose of bup they ended up on!!

The 2 Main Comparison Studies in Adults

- Nosek Drug Des Devel Ther 2017. https://dx.doi.org/10.2147%2FDDDT.S141007
- Sort of a recapitulation of the Corli study, all in Poland, N=52, same patient population, 28 days
- Randomized to one of these drugs, titrated per clinicians' discretion using this protocol

1. Controlled-release morphine administered orally every 12 h: 2×10, 2×20, 2×30, 2×40, 2×60, 2×90, 2×120, 2×150, 2×180, 2×200 mg.
2. Controlled-release oxycodone administered orally every 12 h: 2×5, 2×10, 2×15, 2×20, 2×30, 2×45, 2×60, 2×80, 2×100, 2×120 mg.
3. Fentanyl administered by transdermal route every 48–72 h: 25, 37.5, 50, 75, 100, 125, and 150 µg/h.
4. Transdermal buprenorphine administered every 60–84 h: 35, 52.5, 70, 105, 140, 175, and 210 µg/h.

Nosek study

- Basically same findings as Corli et al.
- Pain improved *similarly between groups*
- The study has lots of secondary comparisons but I think those are best ignored given only 52 patients.
- Presented better day 28 drug doses:
  - Mean 63 mcg/hr bup (1.5 mg/d)
  - Means oxy 32 mg/d, morphine 56 mg/d, Fent 45mcg/hr.

Summary of efficacy data for pain

- In all populations studied, buprenorphine seems to be as effective as full MOR agonists, and is effective compared to placebo
- Like other ‘opioid rotation’ studies for refractory pain, pain generally improves when switching to buprenorphine off higher doses of full MOR agonists
- No clear relationship between ‘baseline’ morphine dose and effective buprenorphine dose
- **Studied dose range for pain mostly <2 mg/day**

Treating acute pain for patients on higher dose buprenorphine for OUD

- There are no RCT; all data observational + expert opinion
- Consensus guidelines + clinical experience = CONTINUE bup, use full MOR agonists, treat the patient like any other HIGHLY OPIOID TOLERANT patient.
- SPECULATION: high affinity opioids are ‘more efficacious’ eg fentanyl?
- CONTROVERSIAL: some experts recommend tapering Suboxone to 12 mg/day
- NO DOUBT: stopping Suboxone increases OUD relapse rate periop!!
- PROBABLY: this is the same approach we should take with cancer pain
- Guideline: Kohan. Reg Anes Pain Med 2021 http://dx.doi.org/10.1136/rapm-2021-103007

Think about it------

What do we know about acute pain management outcomes for opioid tolerant patients?

Eg a patient on 120 mg tid oxycodoneER breaks their hip.

Are you thinking to yourself:

A. *Pain management will be a snap here since they are already on high opioid doses!!*
B. *Ooof, analgesia is going to be rocky...*

- **Pain outcomes are far worse for opioid tolerant patients than opioid naïve patients:**
  - Longer hospital LOS
  - Reduced effectiveness of opioids

  - *There is nothing unique about patients on high dose buprenorphine here!!!*

Who should we use bup for in serious illness?

- My Summary of Consensus Opinion 2023:
  - Bup = first-line opioid for chronic noncancer pain
  - Bup = first-line opioid for frail older patients
  - Bup = first-line opioid for long-term pain in cancer survivors who are expected to live a long time (safer, less hyperalgesia, less risk OUD).
  - Bup = first-line opioid for patients with OUD, or current high-risk substance use, or hx of AUD/OUD (even if long in recovery) who require opioid analgesia (safer, less risk relapse OUD, less risk OD when mixed with alcohol, less harm to community if diverted)
- There are some who think it should be our first-line opioid for everyone

Buprenorphine dosing and formulations

"B" Drugs

- "Lower dose" buprenorphine drugs FDA approved for pain
- Dosed in micrograms
- Max FDA approved dose < 2 mg = 2000 mcg/day
- "Illegal" to Rx for OUD
- *Belbuca* buccal films
- *Butrans* patch

"S" Drugs

- "Higher dose" drugs FDA approved for OUD
- Dosed in milligrams
- 2-12 mg/dose </=24mg/day
- "OK" to Rx "off label" for pain
- Suboxone SL tabs & films
- Subutex SL tabs
- (Zubsolv & a variety of other rarely seen products too)

Why “lower” for pain & “higher” for OUD??

- All opioids: analgesic dose-response curve flattens at higher doses

- Opioid doses for OUD typically are >>> doses for analgesia
  - Methadone ‘sweet spot’ for analgesia is <50 mg day***
  - Methadone for OUD doses often in ~>100 mg range

“B drugs” - Pain only

- Belbuca (‘buccal’ bup films) = 75-900 mcg/film, meant to be taken bid
  - Ok to cut films in half (Not FDA approved to do this)
- BuTrans TD patches = 5-20mcg/hr, changed q7 days

- “Expensive” compared to commonly used FOA: usually I can get one of these covered affordably for my patients
- Lowest doses can be initiated in opioid-naive
- Trend towards lowering $ barriers to these drugs due to improved safety?

- Remove BELBUCA film from the foil package **(see Figure C)**.

Figure C

e BELBUCA buccal film as follows:

1. Use your tongue to wet the inside of your cheek or rinse your mouth with water to moisten the area in your mouth before you place BELBUCA.

2. Hold the BELBUCA buccal film with clean, dry fingers with the yellow side facing up **(see Figure D)**.

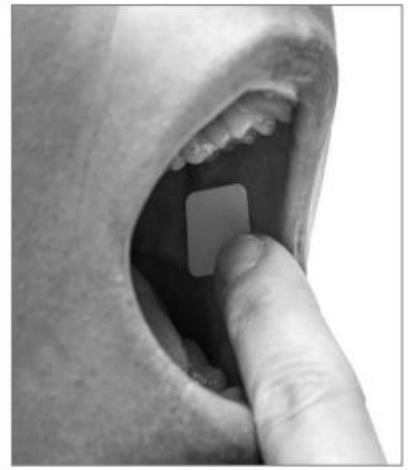


Figure E

4. The BELBUCA buccal film will stick to the inside of your cheek **(see Figure F)**.

Figure F

5. Leave the BELBUCA buccal film in place until it has completely dissolved, usually within 30 minutes after y apply it.
   - **Avoid eating food or drinking liquids until BELBUCA buccal film has dissolved.**
   - **Avoid touching or moving BELBUCA buccal film with your tongue or finger after it is in place.**

“S drugs” for OUD; off-label for pain

- Suboxone = SL bup+naloxone: 2-12 mg bup/film (also a SL tab version)
  - Naloxone is only an abuse-deterrent for if it is injected; inactive when taken orally/SL.
  - Perfectly safe to cut Suboxone films and take ¼, ½, etc: this is not FDA-sanctioned!

- Subutex = SL tab = 2-8 mg; niche is for pregnant patients with OUD
  - Crumbly; not easy to split; best to use Suboxone if splitting films

- **Any clinician with a ‘regular’ DEA registration can Rx these both for pain (off-label) and as MOUD!! No more X-waiver. No training requirement!**
- **I usually don’t have $$ issues with this IF the patient has OUD**

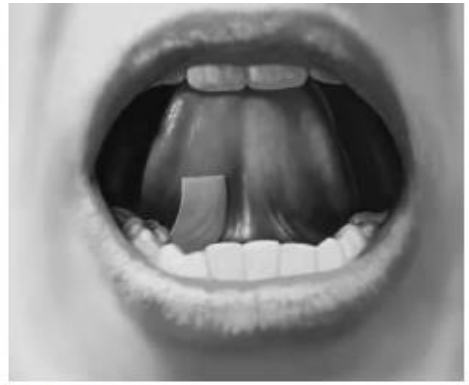


Figure 3

- If your healthcare provider tells you to take 2 films at a time, place the second film under your tongue on the opposite side. Avoid letting the films touch.
- Keep the films in place until they have completely dissolved.
- If your healthcare provider tells you to take a third film, place it under your tongue on either side after the first 2 films have dissolved.

To take SUBOXONE sublingual film on the inside of your cheek (buccal administration):

- Hold the film between two fingers by the outside edges.
- Place one film on the inside of your right or left cheek (see Figure 4).

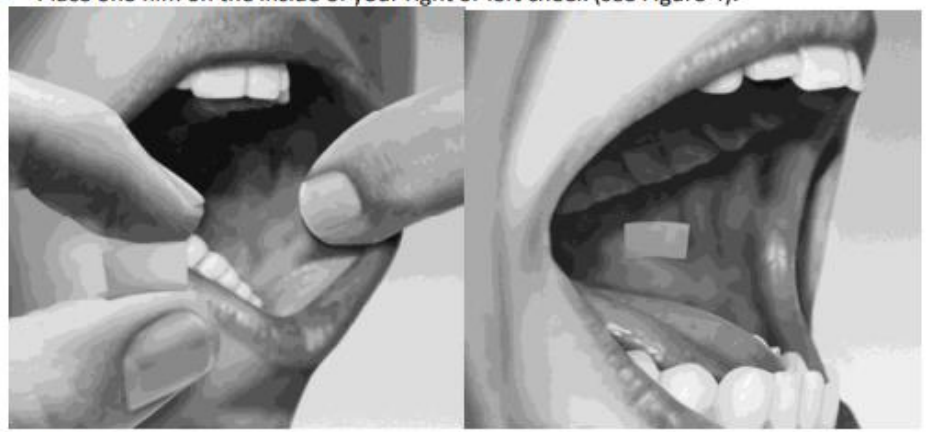


Figure 4

  - If your healthcare provider tells you to take 2 films at a time, place the other film on the inside of the opposite cheek.
  - Keep the films in place until they have completely dissolved.
  - If your healthcare provider tells you to take a third film, place it on the inside of your right or left cheek after the first 2 films have dissolved.
- While SUBOXONE sublingual film is dissolving, do not chew or swallow the film because the medicine will not work as well.
- Talking while the film is dissolving can affect how well the medicine in SUBOXONE sublingual film is absorbed.
- After SUBOXONE is completely dissolved, rinse your mouth with water and swallow. Wait for at least one

Starting bup: opioid naïve---EASY!!

- Belbuca: 75 mcg day 1
  - 75 mcg bid day 2 and onwards
  - OK to titrate dose q4 days: next dose would be 150 mcg bid
  - Next dose steps: 300 mcg bid; then 450-600 mcg bid, then 900 mcg bid
  - Can dose tid and go >900 mcg bid but not FDA-approved
- Butrans: 5 mcg/hr to start (=120 mcg/day); patch lasts 7 days
  - Can adjust dose q7 days
  - Next dose 10 mcg; next dose 15 or 20 mcg/hr depending on judgement
  - Can go higher than 20 but not FDA approved

What if they need a prn dose?

- Option A for Belbuca:
  - Ok to use a "3rd" Belbuca dose as a PRN
  - Ok for patients to split Belbuca film and use that PRN
  - None of this is FDA sanctioned!

- Option B for Butrans or Belbuca
  - Use any of the typical PRN opioids!
  - What dose???
  - Mostly just use 'starting doses' (eg 5-10 mg oxyIR prn etc)
  - For patients on > 1 mg/day buprenorphine: good chance they'll need more!
    - But I'd still start at just a step above 'naïve' doses eg 10 mg oxyIR, 4 mg hydromorphone, 15 mg morphine

3 major approaches to transitioning to bup

1. **Lower dose buprenorphine: stop-n-start**

2. **Higher dose buprenorphine: “lower dose induction” aka “microgram range induction” = no withdrawal method**

3. **Higher dose buprenorphine: “traditional method” aka withdrawal method**

→ *The method used has nothing fundamentally to do with the patient’s dx (OUD vs pain vs both) but to do with the DOSE of buprenorphine you expect the patient to need*

Starting opioid tolerant patients on buprenorphine

- You never start with more than 500-600 mcg/day the first day!!

- If you are anticipating someone will need ‘microgram range doses’
  - =Everyone you are starting on Butrans or Belbuca!
  - =Stop-n-start!!
  - =Easy!

- If you are anticipating someone will be needing >1 mg a day buprenorphine
  - There are 2 major methods; only one involves patient experiencing withdrawal
  - =Everyone who we anticipate will be using an “S-product”
  - =Everyone you are using buprenorphine as MOUD
  - =Some of our opioid tolerant patients who we expect Suboxone will be necessary even if no OUD diagnosis

Stop/Start Method—using a “B product”

- **There is no clear consensus about what BASELINE opioid dose/OME it’s safe to do this with.**
- **The lower the OME the more likely you’ll do stop-start but when the exact transition begins to a ‘higher dose induction’ is UNCLEAR unless the patient has OUD (because you'll be using Suboxone then)**
- **My own practice = I go up to ~100 OMEs using stop-start**
  - This is not standardized, unpredictable, and the recs out there are contradictory, and I always make an individualized judgement.
- Belbuca and Butrans manufactuers have their own guidelines and **who are we to question those!!!?!!**

Belbuca manufacturer recommends:

<30 mg oral MME	30 mg - 89 mg oral MME	90 mg - 160 mg oral MME
Starting dose: **75 mcg***	Starting dose: **150 mcg**	Starting dose: **300 mcg**
once daily or q12h	q12h	q12h

For patients previously taking oral MME >160 mg, consider an alternate analgesic.

All patients should be titrated no more frequently than every 4 days, and dosed in q12h intervals.[1]

Drew's Pro-Tips:

- Manufacturer recommends tapering baseline opioid to OME 30 prior to starting Belbuca: *I do not do this and have never had any problem!*
- > 30 OME I think this Table generally UNDERDOSES patients **(which is probably its intention)**
- Much above 100 OME I usually am starting a higher dose induction with 500 mcg Suboxone day 1
- Just stop the baseline opioid and replace it immediately with Belbuca

Butrans manufacturer recommends

Table 1: Initial BUTRANS Dose

Previous Opioid Analgesic Daily Dose (Oral Morphine Equivalent)	<30 mg	30-80 mg
Recommended BUTRANS Starting Dose	**5 mcg/hour**	**10 mcg/hour**

Drew's Pro-Tips:

- Manufacturer recommends tapering baseline opioid to OME 30 prior to starting Belbuca: *I do not do this and have never had any problem!*
- Just stop the baseline opioid and replace it immediately with Butrans
- Note that with Butrans the serum levels of buprenorphine rise slowly over a couple days and there's virtually zero risk of precipitated withdrawal even if you gave a patient > 20 mcg/hr to start!!
- Note that the 'max day 1' dose with Butrans is 240 mcg; with Belbuca it's 600 mcg day 1

Cases - Break

Part 2

- OUD in patients with serious illness

- Higher dose buprenorphine:
  - Buprenorphine for OUD
  - Buprenorphine for patients without OUD but high risk chemical use/high risk of harm from ‘full opioid agonists’

- Transitioning off buprenorphine
  - So much we don’t know here!

"Past" Attitudes about OUD

- Who cares if the patient gets addicted—they're going to die anyway!
- Cancer = Opioids are indicated and safe!
- Opioids = Compassion. Patients *deserve* opioids
- Opioid addiction is a terminal illness—patients never get better—there's nothing you can do for them—why bother
- This patient is "drug seeking" = I am not going to care for them anymore
- Opioid addiction is not my problem -- it belongs to [PCP, AM, etc]

Current Perspectives

- OUD/SUD is commonplace
- Caring for patients with OUD with skill and compassion is something all of us can / must do
- OUD is treatable + it is normal for patients to relapse/remit
- Our role is to provide effective supportive care for patients with OUD that promotes safety and well-being
  - But does not require some abstract concept of 'totally safe', 'abstinence’
  - Opioids have risks, benefits, contra/indications like any other drug
  - Everything is a risk-balance decision
  - Harm reduction....

Scope of the problem

- US prevalence of OUD ~0.5%; high risk opioid use much higher
- ?~10% of patients prescribed long-term opioids develop OUD?
- Unclear prevalence of OUD and high risk chemical use in US cancer centers
- My referral practice: about 5 % of my practice
  - However my patients with OUD/high risk chemical use are a high-stress, high-stakes, time-intensive population

JAMA Netw Open. 2021;4(12):e2139968. doi:10.1001/jamanetworkopen.2021.39968

What are we talking about when we say "opioid use disorder" "opioid dependence" "addiction" "nonmedical opioid use"

DSM-5 diagnostic criteria for 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 the opioid, use the opioid, or recover from its effects.
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 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.
    b. A 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 (refer to Criteria A and B of the criteria set for opioid withdrawal, pp. 547 to 548).
    b. Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

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

- 2-3 = mild OUD, 4-5 mod; 6+ severe

Addiction & Complex Persistent Dependence

- Discussion right now whether mild OUD is 'addiction'
- "CPD" - Criteria 1 & 2 alone + patient not necessarily distressed
  - Opioids taking longer or larger amounts than "intended"
  - Persistent desire and/or unsuccessful effort to cut down use
- I think of CPD as patients that I am distressed by and I want them to cut down opioid use but they cannot/do not
- "Stuck on opioids": poor pain relief, significant functional impairment from pain, "despite" chronic opioid use, cannot taper down....

Manhapra, A., Sullivan, M.D., Ballantyne, J.C. *et al.* Complex Persistent Opioid Dependence with Long-term Opioids: a Gray Area That Needs Definition, Better Understanding, Treatment Guidance, and Policy Changes. *J GEN INTERN MED* **35,** 964–971 (2020)

Opioid/chemical use exists on a spectrum

- "By the books" Rx opioid use in pt not on any other CNS depressants +/- higher ‘physiologic risk’ eg OSA
- "By the books" Rx opioid use + higher risk chemical use (alcohol, BZD)
- Opioid use for non-analgesic purposes: stress, relaxation, to 'zone out'
  - With or without any objective, actual harmful consequences
  - We all tolerate/encourage this at the very end of life!!
  - May occur a couple times---may be habitual
- "Nontherapeutic opioid dependence" without addiction—patients on COT, hyperalgesic, can't cut down, but opioid reductions cause immediate worsening of pain, mood, functioning—but not compulsively using opioids, and no objective health/social harms
- Addiction: mod to severe OUD

R

I

S

K

Harm Reduction

- A set of practices aimed at promoting the health, safety, well-being for patients who use drugs
- Which are not predicated upon prioritizing recovery/abstinence as a criteria for ongoing care/help
- "Helping patients be safer, healthier" even if/as they continue to use drugs
  - Naloxone, Clean injection supplies, Non-adulterated drug supply, Monitored injection facilities; Housing & Food; Mental Health Care; Virus Care
- *Our 'higher risk' patients with cancer, pain, and high risk substance use/OUD often are receiving prescription opioids*

‘Harm reduction’ for our patients with cancer

- Universal opioid safety precautions

- Being comfortable with risk—we cannot 'eliminate risk' from harm with opioids
  - Stopping Rx opioids may not be in best interest
    - Even if patient won't receive treatment eg MOUD (eg Suboxone)
    - Will this patient be better off if I stop opioids entirely (or BZD?)

  - Treating psychiatric comorbidities; counseling/psychotherapy; chemdep resources

Universal Opioid Safety Practices

- Risk assessment for "everyone"
- Opioid Safety Education / Discussion / Consent with all our patients
  - Risk of intoxication, falls, addiction
  - Risks of using opioids for emotional calming, sleep, anything other than pain
  - Disposal
  - No alcohol or BZDs (without explicit discussion)
- PDMP for every fill
- Naloxone for
  - Everyone we think has above-average risk from harm from opioids
  - Everyone Epic tells us to Rx naloxone (MEDD > 50, or on a BZD)

Risk Assessment

- No evidence-based consensus on how to do this in patients w/ cancer
- All the 'tools' have limited evidence and none specifically validated for us (ORT, SOAPP, etc)
- But! Broad consensus of the risk factors—**Just take a good hx!**
  - Personal SUD hx; close family SUD hx
  - Depression, anxiety, OCD, bipolar d/o, schizophrenia, ADD, PTSD
  - Significant trauma hx**
  - Age <45 y
  - "**How many times** in the past year have you used an illegal drug or used a prescription medication for non-medical reasons?"

Risk Assessment

- Purpose is not to help me decide who to prescribe opioids for or not!
- Or to eliminate risk!
- Or to diagnose OUD!
- But to help me identify who I will have the most intense risk mitigation practices for!
  - Naloxone, more elaborate informed consent discussion, smaller Rx, shorter follow up, try to use exclusively buprenorphine, etc

Initiating higher dose buprenorphine

- Patient has OUD: we will be using an “S product”
  - Goal of tx in OUD: reduce craving, reduce use of the ‘opioid of abuse’, reduce overdose risk, improve qol

- Pain patient who is highly opioid tolerant and we are expecting they’ll need >1-2 mg buprenorphine a day
  - Goal of tx: important to establish this with your patient. Is it improved pain? Is it increased safety? How worried are we about chemical use—are we ok with them using prn Rx full opioid agonists, etc.

“Traditional” “Withdrawal” Method

- How initiating bup for OUD was originally conceived and practiced
- **Based on observation that if a patient is ALREADY IN WITHDRAWAL, starting a HIGH DOSE of buprenorphine ALLEVIATES THE WITHDRAWAL**
- Conceived of as an in-clinic practice on day 1 **but long has been done at home by patients by themselves**
- I think this has MINIMAL role for those of us in palliative care/caring for patients with serious illness (definitely has a role in addiction medicine) since we have an alternate method that does not require forcing our patients to withdraw.

- **<u>Traditional method</u>**:
  - Stop opioids, wait for COWS 12+ withdrawal
  - Then initiate 2 mg Suboxone (for patients on heroin or very high doses; 4 mg); this way bup *relieves* w/d, not *trigger* it
  - Various protocols: mostly patients advised to take up to q4h the first day (up to 8 mg total)
  - Patients should redose with 2-4 mg q4h until withdrawal sx subside on day 1. Patients are in control of this!
  - In coming days should be titrated to reduce cravings too.
  - Requires daily contact first several days

Wesson & Ling, J Psychoactive Drugs. 2003 Apr-Jun;35(2):253-9.

COWS Clinical Opiate Withdrawal Scale

Resting Pulse Rate: _____beats/minute *Measured after patient is sitting or lying for one minute* 0 Pulse rate 80 or below 1 Pulse rate 81-100 2 Pulse rate 101-120 4 Pulse rate greater than 120	GI Upset: *over last 1/2 hour* 0 No GI symptoms 1 Stomach cramps 2 Nausea or loose stool 3 Vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting
Sweating: *over past 1/2 hour not accounted for by room temperature or patient activity.* 0 No report of chills or flushing 1 Subjective report of chills or flushing 2 Flushed or observable moistness on face 3 Beads of sweat *on* brow or face 4 Sweat streaming off face	Tremor *observation of outstretched hands* 0 No tremor 1 Tremor can be felt, but not observed 2 Slight tremor observable 4 Gross tremor or muscle twitching
Restlessness *Observation during assessment* 0 Able to sit still 1 Reports difficulty sifting still, but is able to do so 3 Frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds	Yawning *Observation during assessment* 0 No yawning 1 Yawning once or twice during assessment 2 Yawning three or more times during assessment 4 Yawning several times/minute
Pupil size 0 Pupils pinned or normal size for room light 1 Pupils possibly larger than normal for room light 2 Pupils moderately dilated 5 Pupils so dilated that only the rim of the iris is visible	Anxiety or irritability 0 None 1 Patient reports increasing irritability or anxiousness 2 Patient obviously irritable anxious 4 Patient so irritable or anxious that participation in the assessment is difficult
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 Not present 1 Mild diffuse discomfort 2 Patient reports severe diffuse aching of joints/ muscles 4 Patient is rubbing joints or muscles and is unable to sit still because of discomfort	Gooseflesh skin 0 Skin is smooth 3 Piloerrection of skin can be felt or hairs standing up on arms 5 Prominent piloerrection
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 Not present 1 Nasal stuffiness or unusually moist eyes 2 Nose running or tearing 4 Nose constantly running or tears streaming down cheeks	Total Score _____ The total score is the sum of all 11 items Initials of person completing Assessment:_____

Score: 5-12 mild; 13-24 moderate; 25-36 moderately severe; more than 36 = severe withdrawal

“Microgram dose range induction”

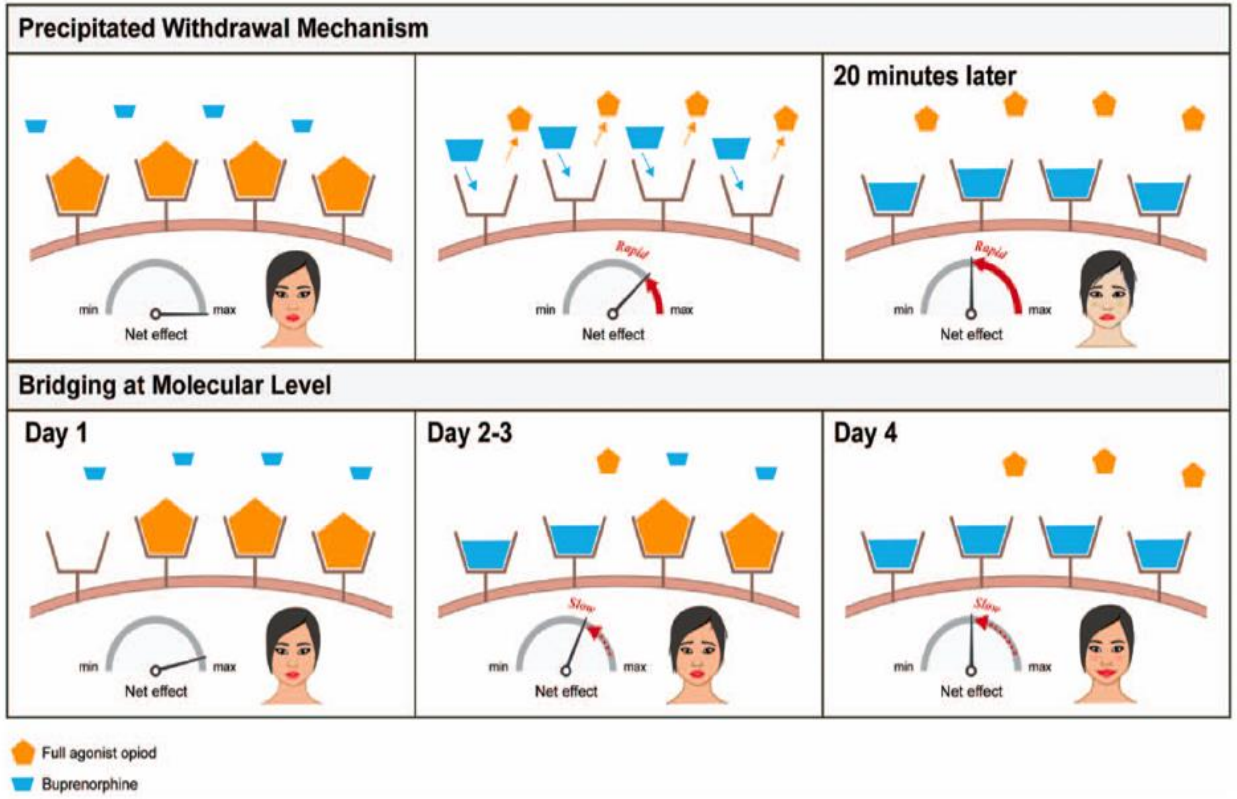
- “Microinduction” “Lower dose induction” ~~“Microdose induction”~~

- Slow increase of bup over several days gives enough time for the bup levels to rise and *slowly* displace the full MOR agonist and so **no withdrawal**

- Patient **continues the baseline full MOR agonist** until they are on a ‘good dose’ of buprenorphine *which is a complex clinical assessment and there is no arbitrary dose!*

Bernese method: Repeat administration of very small Bup doses with sufficient dosing intervals should not precipitate opioid withdrawal

- As full agonist dissociates
- Bupe slowly accumulates on opioid receptors because of long receptor binding time
- over time, Bupe will replace an increasing amount of a full agonist



Bup initiation can be independent from full agonist dose/ timing

Ghosh 2019; Hämmig R et al. 2010, 2016. Slide from Zach Sagar MD

“Microgram dose range induction”

- Some patients will just stop the other opioids once they are on > 4 mg/d “just don’t need it anymore”.
- We typically wait until they are on at least 4 mg a day and then taper or stop baseline full MOR agonist
- This is a new practice–just described <5 y ago and we are still figuring it out
- Buprenorphine is forgiving! It’s really not that bad: main thing is making sure patient can follow directions (because if they take too much early on→withdrawal!)

“Microgram Dose Induction”

- Start at 0.5 mg
  =500 mcg or ¼ film
  - Double dose every day
  - Plateau at 4 mg tid
  - This is geared towards OUD=expecting high doses of Suboxone (eg 12mg+)
  - For patients with pain not OUD need to adjust this—sometimes we stop at eg 2mg bid or tid.
  - I often just stop the baseline opioid and not taper it

- DOESN’T induce withdrawal

Robbins. J Am Board Fam Med 2021: JM-JABF200266 141..146 (jabfm.org)

Table 2. Outpatient Microinduction Protocol Using Sublingual 2 mg Buprenorphine/Naloxone Tablets or Films

Day	Bup/Nlx Dose and Frequency	Full Agonist Opioid
1	0.5 mg daily (1/4 tablet or film)	No change
2	0.5 mg BID	No change
3	1 mg BID (half-tablet or film)	No change
4	2 mg BID	No change
5	2 mg TID	No change
6	4 mg TID	No change
7 and beyond	Per provider discretion	Taper by 25% weekly

“Microgram Dose Induction”

- Start at 0.5mg
  - Could use 300-600 mcg/d Belbuca to start!
  - Could use 20 mcg/hr Butrans for a few days to start!
  - As long as you start low this can be very flexible!
  - I often find patients themselves stop / reduce baseline opioid agonists once above 4-6 mg bup/d

Table 2. Outpatient Microinduction Protocol Using Sublingual 2 mg Buprenorphine/Naloxone Tablets or Films

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Robbins. J Am Board Fam Med 2021: JM-JABF200266 141..146 (jabfm.org)

"Microgram dose induction"

- What is important are the underlying principles NOT the exact protocol

  - Start 500-600 mcg day 1
  - Ok to double it daily for several days
  - Continue 'baseline opioids' until patient is on a 'therapeutic dose' of bup
  - Then stop/back off the baseline opioid

Adjusting dose of buprenorphine for pain

- Like any other opioid, ok to adjust dose by ~~25-50% depending on severity of pain (or eg ongoing cravings/OUD activity)

- Once the "induction" is over; I'll adjust the dose of Suboxone q4days just like Belbuca: SAME PHARMACOKINETICS!

Use of PRN FOA for patients on high dose bup

- Avoided in OUD, but sometimes necessary!
- Perfectly fine to do for patients with pain without OUD: *current practice model is really to try to use bup as the ONLY opioid analgesic however it's ok to use it as a 'long-acting' and then use prn opioids as with any other patient on long-acting opioids needing a prn*
- What starting dose do you use?

Use of PRN FOA for patients on high dose bup

- What starting dose do you use?
- There is no answer to this: it is empiric, pretend you have a patient on 60 mg a day methadone who all of a sudden needs PRNs: what would you do??
- I still start at "one-step up" starting doses,
  - 10 mg oxy, 4 mg hydromorphone, 15 mg morphine
  - Plan to rapidly (same day even) increase by 50-100%
  - *Key is not 'guessing the right dose'* but *starting somewhere and rapidly adjusting!!*

Transitioning off buprenorphine entirely

- Intolerable side effects
- Ineffective
- Hospice won't cover it
- Etc

- Ask yourself: if you had someone on 60 mg methadone how do you transition them off of it?

Transitioning off buprenorphine entirely

- If the patient is on PRN 'full opioid agonist' opioids
  - Can stop the bup and liberalize the PRN dose and give them 4-5 days to see where they land!
  - Can stop the bup and choose a 'long-acting opioid' dose BASED SOLELY ON THE PRN DOSE.
  - Eg patient on 8 mg bid Suboxone and 120mg/day prn morphineIR
    - Stop Suboxone
    - Start 60 mg bid MSContin (etc—use your judgment—but dose here is based on PRN morphine dose ignoring the bup!!)
    - Close fu and dose adjustment is key!!!!
- If they are not on a prn; start one; give it a week; then stop bup!!

References

General:

- Webster et al: Understanding bup for use in chronic pain: Expert Opinion. Pain Med 2020; 21(4);714-23
- Davis M: Twelve Reasons for considering bup as a frontline analgesic. Supp Onc 2012; 10(6);209-19

Most Pharmacology Information:

- Case et al. Treating chronic pain with bup—the practical guide. Curr Treat Options in Oncol. 2021; 22:116.
- Gudin et al. A Narrative Pharmacological Review of Bup. Pain Ther 2020; 9:41-54
- Eu J Pain 2009. doi:10.1016/j.ejpain.2008.04.011

Induction:

- Microinduction: there are dozens of protocols out there, all pretty similar.
  - I like this one due to its ease: Robbins. J Am Board Fam Med 2021: JM-JABF200266 141..146 (jabfm.org)
- ASAM pocket guide: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-pocketguide.pdf
- Buprenorphine Quick Start Guide (samhsa.gov)
- AMSA Patient Guide to Starting Suboxone at Home: unobserved-home-induction-patient-guide.pdf (asam.org)
- This is the ASAM "Bible" on MOUD: The ASAM National Practice Guideline Supplement.pdf

- Informal SUD/buprenorphine in palliative care Peer network: MAPPIT—email me if you want to join it
- Online bup for OUD training at: ASAM.org
- A series of blog posts about my evolving thoughts about opioids https://www.pallimed.org/2019/10/a-series-of-observations-on-opioids-by.html
- Center to Advance Palliative Care has modules on this https://www.capc.org/training/pain-management/
- Consensus Guideline on managing cancer pain in setting of OUD: *JAMA Oncol.* 2022;8(8):1107-1114. doi:10.1001/jamaoncol.2022.2191 https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2787463
- Practical Review papers on using bup in palliative/cancer settings:
  - https://www.liebertpub.com/doi/full/10.1089/jpm.2022.0399
  - https://www.jpsmjournal.com/article/S0885-3924(19)30870-X/fulltext
- Microinduction: there are dozens of protocols out there, all pretty similar.
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- ASAM pocket guide: https://www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-pocketguide.pdf
- This is the ASAM "Bible" on MOUD: The ASAM National Practice Guideline Supplement.pdf
- I am giving a 4 h bup workshop at the 2023 Great Lakes Palliative Care Conference https://ocpe.mcw.edu/medicine/11thGreatLakesPalliativeCareConference#group-tabs-node-course-default2