BUPRENORPHINE

INDICATIONS FOR PAIN MANAGEMENT

Marc C Mentel DO

Board Certified Addiction Medicine

OBJECTIVES

- Understand the unique pharmacology of Buprenorphine
- Review the goals of pain management
- Understand Buprenorphine's role in pain management

HISTORY- A BETTER MORPHINE

Patented in 1965 by Reckitt and Colman

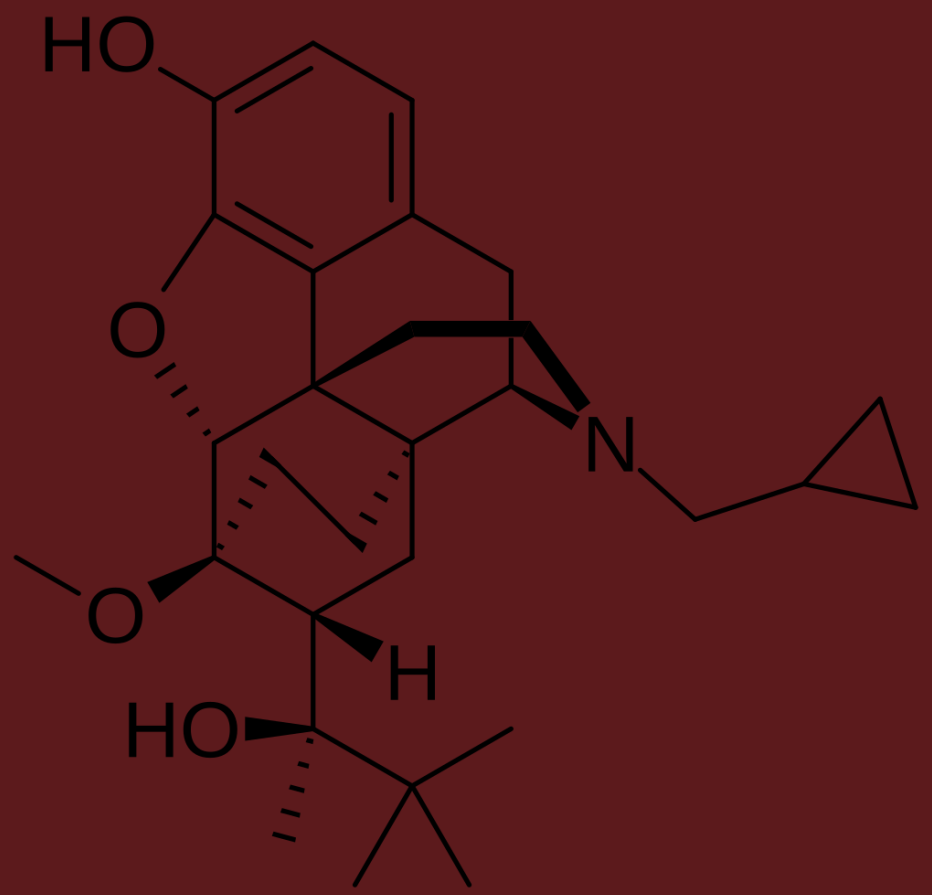
Named Buprenorphine in 1969

Human trials began in 1971

Launched in the UK to treat severe pain in 1978

Sublingual Formulation released in 1982

Approved for OUD in the US 2002



BASICS

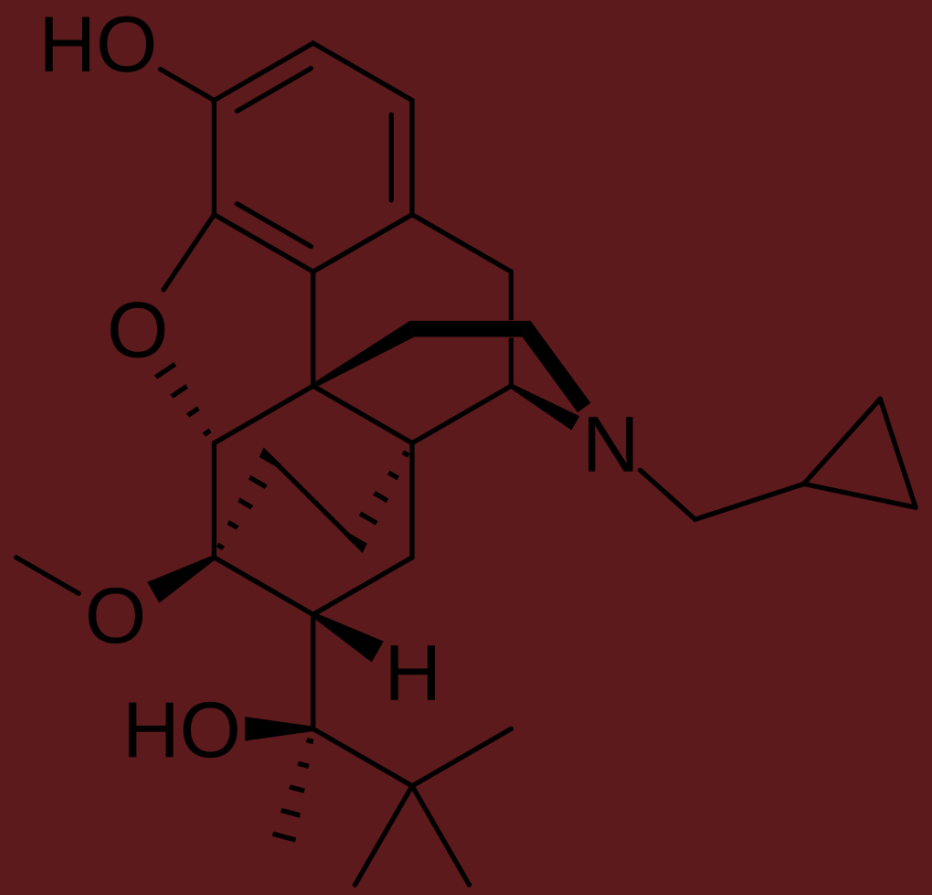
FDA approved Opioid Dependence

FDA approved Moderate to Severe pain

DEA Schedule III

WHO's list of Essential Medicines

186th most common drug prescribed US



BASICS

PHARMACOLOGY

Metabolized primarily by the liver

Metabolite Norbuprenorphine

CYP450:3A4

UGT1A1/UGT2B7

Excretion: feces 69%/urine 30%

Half life 20 -44 hours

Analgesia effects up to 6-8 hours

FORMULATIONS

Sublingual

Buccal

Transdermal

Subcutaneous Injection

Intravenous

Implants

PHARMACOLOGY

Affinity

Potency

Efficacy

PHARMACOLOGY

AFFINITY

Buprenorphine has a very low K value which means it has a very high affinity for the opioid receptor

K VALUE

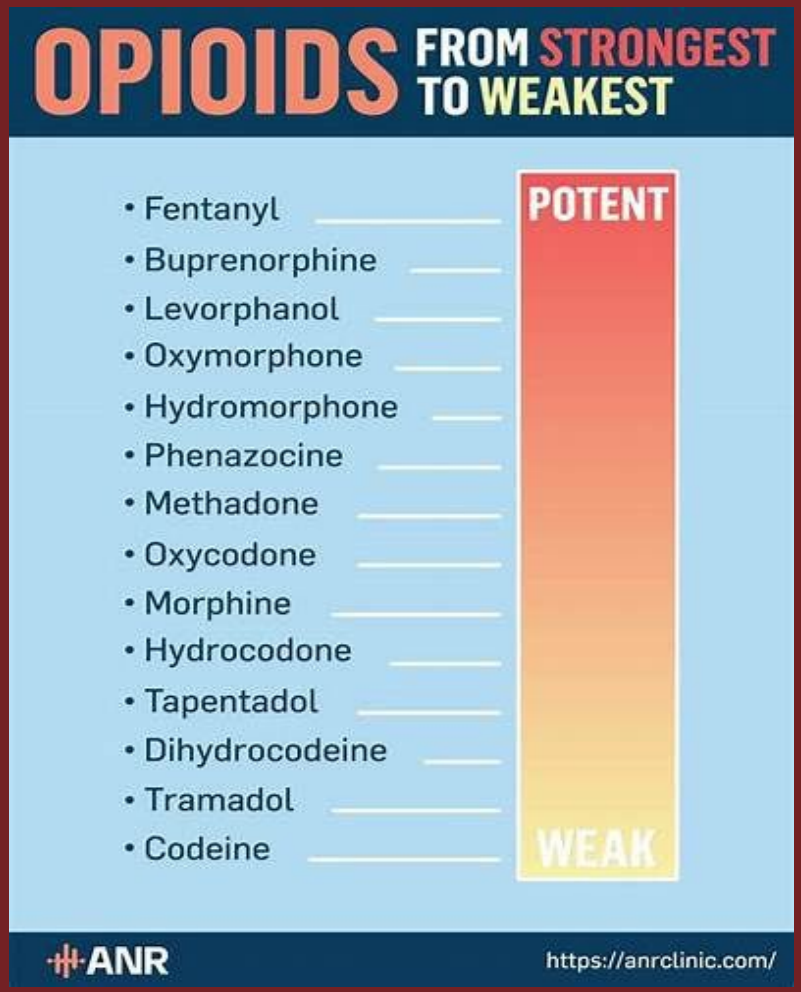
Medication	K_i (nM)
Codeine	734.2
Meperidine	450.1
Oxycodone	25.87
Methadone	3.378
Naloxone	1.518
Fentanyl	1.346
Morphine	1.168
Hydromorphone	0.3654
Buprenorphine	0.2157
Sufentanil	0.1380

PHARMACOLOGY

POTENCY

Buprenorphine is 80 times more potent than morphine SL

Buprenorphine is 100 times more potent than morphine TD

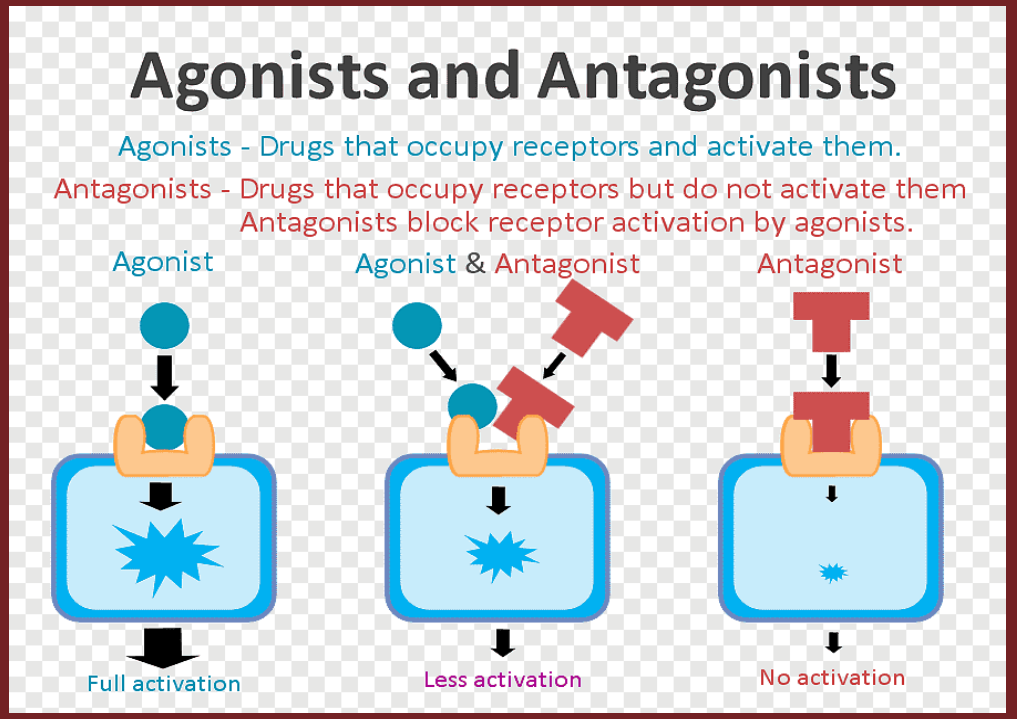


PHARMACOLOGY

MECHANISM OF ACTION

Buprenorphine is partial agonist at the mu receptor, an agonist at the delta receptor, and an antagonist at the kappa receptor

EFFICACY



PHARMACOLOGY

MECHANISM OF ACTION

Buprenorphine is partial agonist at the mu receptor

Brain areas with high concentrations of mu receptors include the nucleus accumbens, ventral tegmental area, dorsal raphe nucleus, and locus coeruleus

MU RECEPTORS 1,2,3

mu receptors are responsible for analgesia, depression, euphoria, dependence, sedation, and respiratory depression

PHARMACOLOGY

MECHANISM OF ACTION

Buprenorphine is a weak agonist at the delta receptor

delta receptors are most concentrated in the basal ganglia and neocortical regions of the brain

DELTA RECEPTOR

delta receptors are responsible for analgesia, anxiety reduction, positive affect, and decreased GI motility

PHARMACOLOGY

MECHANISM OF ACTION

Buprenorphine is a weak antagonist at the kappa receptor

kappa receptors are most concentrated in the cerebral cortex and the substantia gelatinosa of the dorsal horn

KAPPA RECEPTOR

kappa receptors are responsible for analgesia, diuresis, dysphoria, and stress like responses

PAIN MANAGEMENT

CDC RECOMENDATIONS

OPIOIDS ARE NOT 1ST LINE FOR ACUTE PAIN

Recommendation 1

- **Nonopioid therapies are at least as effective as opioids for many common types of acute pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider opioid therapy for acute pain if benefits are anticipated to outweigh risks to the patient. Before prescribing opioid therapy for acute pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy (recommendation category: B; evidence type: 3).**

OPIOIDS ARE NOT 1ST LINE FOR SUBACUTE AND CHRONIC PAIN

Recommendation 2

- **Nonopioid therapies are preferred for subacute and chronic pain. Clinicians should maximize use of nonpharmacologic and nonopioid pharmacologic therapies as appropriate for the specific condition and patient and only consider initiating opioid therapy if expected benefits for pain and function are anticipated to outweigh risks to the patient. Before starting opioid therapy for subacute or chronic pain, clinicians should discuss with patients the realistic benefits and known risks of opioid therapy, should work with patients to establish treatment goals for pain and function, and should consider how opioid therapy will be discontinued if benefits do not outweigh risks (recommendation category: A; evidence type: 2).**

NEVER START TREATING PAIN WITH LONG-ACTING OPIOIDS

Recommendation 3

- **When starting opioid therapy for acute, subacute, or chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release and long-acting (ER/LA) opioids (recommendation category: A; evidence type: 4).**

USE THE LOWEST EFFECTIVE DOSE

Recommendation 4

- **When opioids are initiated for opioid-naïve patients with acute, subacute, or chronic pain, clinicians should prescribe the lowest effective dosage. If opioids are continued for subacute or chronic pain, clinicians should use caution when prescribing opioids at any dosage, should carefully evaluate individual benefits and risks when considering increasing dosage, and should avoid increasing dosage above levels likely to yield diminishing returns in benefits relative to risks to patients (recommendation category: A; evidence type: 3).**

NEVER ABRUPTLY STOP OPIOID TREATMENT FOR PATIENTS WHO ARE OPIOID DEPENDENT

Recommendation 5

- **For patients already receiving opioid therapy, clinicians should carefully weigh benefits and risks and exercise care when changing opioid dosage. If benefits outweigh risks of continued opioid therapy, clinicians should work closely with patients to optimize nonopioid therapies while continuing opioid therapy. If benefits do not outweigh risks of continued opioid therapy, clinicians should optimize other therapies and work closely with patients to gradually taper to lower dosages or, if warranted based on the individual circumstances of the patient, appropriately taper and discontinue opioids. Unless there are indications of a life-threatening issue such as warning signs of impending overdose (e.g., confusion, sedation, or slurred speech), opioid therapy should not be discontinued abruptly, and clinicians should not rapidly reduce opioid dosages from higher dosages (recommendation category: B; evidence type: 4).**

DON'T USE OPIOIDS LONGER THAN EXPECTED FOR ACUTE PAIN

Recommendation 6

- **When opioids are needed for acute pain, clinicians should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids (recommendation category: A; evidence type: 4).**

- **Important information: Michigan Open Website**
- **6-10%** of opioid-naive patients undergoing common surgical procedures continue filling opioid prescriptions 3-6 months after surgery.[1] [2]
- **92%** of opioids prescribed by surgeons go unused by patients.[2]

MONITOR YOUR PATIENTS - BENEFICENCE

Recommendation 7

- **Clinicians should evaluate benefits and risks with patients within 1–4 weeks of starting opioid therapy for subacute or chronic pain or of dosage escalation. Clinicians should regularly reevaluate benefits and risks of continued opioid therapy with patients (recommendation category: A; evidence type: 4).**

MONITOR YOUR PATIENTS - NONMALEFICENCE

Recommendation 8

- **Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk for opioid-related harms and discuss risk with patients. Clinicians should work with patients to incorporate into the management plan strategies to mitigate risk, including offering naloxone (recommendation category: A; evidence type: 4).**

USE THE PRESCRIPTION DRUG REGISTRY

Recommendation 9

- **When prescribing initial opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for chronic pain, clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or combinations that put the patient at high risk for overdose (recommendation category: B; evidence type: 4).**

CONSIDER URINE DRUG MONITORING

Recommendation 10

- **When prescribing opioids for subacute or chronic pain, clinicians should consider the benefits and risks of toxicology testing to assess for prescribed medications as well as other prescribed and nonprescribed controlled substances (recommendation category: B; evidence type: 4).**

BE VERY CAREFUL WITH BENZODIAZEPINES

Recommendation 11

- **Clinicians should use extreme caution when prescribing opioid pain medication and benzodiazepines concurrently and consider whether benefits outweigh risks of concurrent prescribing of opioids and other central nervous system depressants (recommendation category: B; evidence type: 3).**

DO TREAT OPIOID USE DISORDER

Recommendation 12

- **Clinicians should offer or arrange treatment with evidence-based medications to treat patients with opioid use disorder. Detoxification on its own, without medications for opioid use disorder, is not recommended for opioid use disorder because of increased risks for resuming drug use, overdose, and overdose death (recommendation category: A; evidence type: 1).**

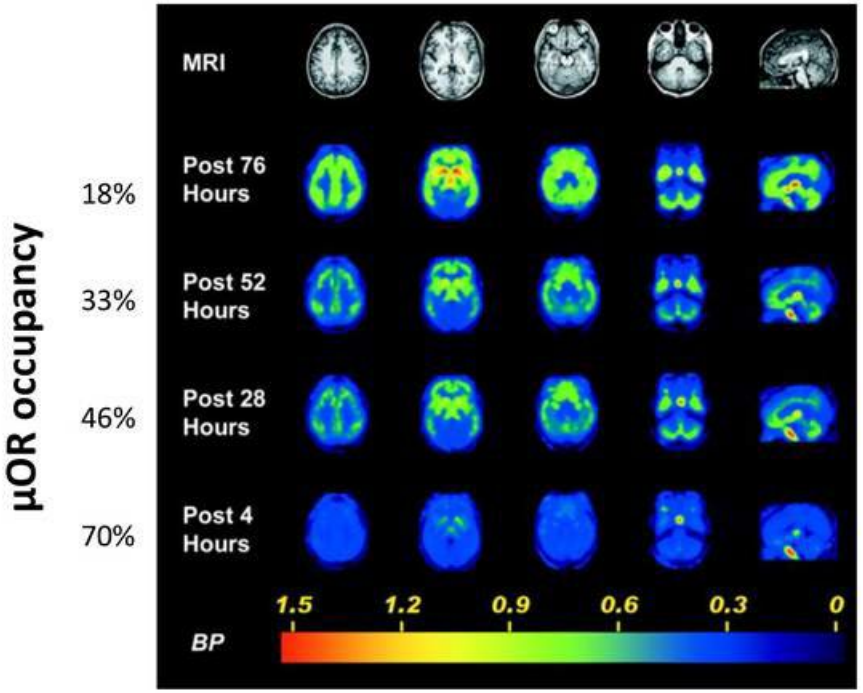
NOT THE GOAL

PAIN MANAGEMENT WITH BUPRENORPHINE

A case study

BUPRENORPHINE IN ACTION FOR OUD

PHARMACODYNAMIC ACTION OF BUPRENORPHINE DECREASES WITH A DECREASE IN PLASMA CONCENTRATIONS & BRAIN μOR OCCUPANCY



- Acute sublingual (SL) buprenorphine duration of pharmacodynamic action (*estimated by abstinence, suppression of withdrawal and craving, and blockade of the effects of an opioid agonist such as hydromorphone*) decreases over time and is highly correlated with plasma concentrations of buprenorphine and μOR occupancy.
- Agonist symptoms produced by hydromorphone were blocked at 4 hours after acute SL BUP 16 mg, but recovered increasingly as time elapsed together with withdrawal symptoms and craving as plasma concentrations of buprenorphine and μOR occupancy progressively decreased.

Parametric images of brain μOR availability as assessed by $^{[11C]}$Carfentanil PET from a representative opioid-dependent volunteer at different times (4, 28, 52, and 76 hours) after the sublingual administration of a maintenance dose of buprenorphine 16 mg. Anatomical MRI images are shown on top. Images show a clear time-dependent increase in μOR availability (i.e., a decrease in μOR occupancy) post-buprenorphine administration that was associated with a progressive increase in withdrawal symptoms, cravings and agonist effects produced by an opioid agonist.

Adapted from: Greenwald MK, Johanson CE, Bueller J, Chang Y, Moody DE, Kilbourn MR, Koeppe RA, Zubieta JK (2007) Buprenorphine duration of action: Mu-opioid receptor availability, pharmacokinetic and behavioral indices. Biological Psychiatry 61: 101-110.

GOALS

Improve Analgesia

Improve Affect

Improve Activity

Decrease Adverse reactions

Stop Aberrant behaviors

Improve Sleep

CASE STUDY

HXCC: R.M is 68yo male who presents to establish care for his Opioid Dependence and ongoing pain disorder. He has been on opioids for a long-standing history of back pain. His dose of morphine has been rapidly reduced to 90MME per day. He had been on a daily of dose 300mg daily. He is not been doing well with the dose decrease. His pain is averaging 7-8/10. He is irritable, anxious, moody, has aches all over, and seems to be sweating more than usual. He did have a syndrome of Hyperalgesia in the past.

When on the higher dose of morphine his pain was averaging 3/10. He was able to walk his dog, sit for a longer periods of time, stand for prolonged periods and he had a better mood. He was also sleeping better. He remains engaged with exercising, chiropractor, and PT>

MOOD: He currently relates feeling poorly and depressed. He would describe his mood as being mostly cloudy if it were a weather pattern. He also feels about 40% charged if he were a battery He is sleeping poorly. No SI/HI, but he questions if life is worth living if he is always going to feel this way

PMHX: A-Fib, HTN, Hypothyroidism, BPH, Chronic Back Pain/Sciatica

PSYCHHX: Depression/Anxiety

PSHX: Cardioversion

CASE STUDY

MEDS: Losartan 25mg QD, Eliquis 5mg BID, Fluoxetine 40mg QD, Levothyroxine 75mcg once day, Testosterone 200mg every 2 weeks, Suboxone 8/2mg ½ strip BID, Tamsulosin 0.4mg QD, Flecainide 100mg BID, Supplements, pregabalin 100mg as needed for pain

ALLERGIES: NKDA

FAMHX: Father deceased aged 84 from CHF, Mother deceased aged 72 from emphysema, 1 Brother in fair health with liver issues from drinking, 1 sister in good health, 1 brother passed from a motorcycle accident.

SOCHX: Married to K. for the past 41 years, 2 boys from a previous marriage, 2 grandchildren ages 10 and 12. Currently lives in Missoula in their own home. Still working part time in the HR business.

DEVELOPMENTALHX: BA in Social Work

SUBSTANCE USE HX: His substance dependence started with chronic low back pain when he still worked at Plum Creek in the early 2000's. He started with pain medications around 2010 when prescribed by his provider. He did use Alcohol heavily in his early life but stopped in 1989. Non-tobacco user. No methamphetamine, marijuana in his history

MILITARY HX: None

LEGAL HX: None

DISCUSSION

OUTCOME

HISTORY: R.S. is a 71yo male who presents for follow up of his Opioid Dependence Disorder and chronic pain. Since his last visit, he injured his back while putting a dog gate into his vehicle. The back pain has since resolved. His oral surgeries continue to go well. He rarely uses his remaining 10 tablets for his post-op care. He has been switched to BiPAP, and it is working well. He and his wife attend the New Directions PT Program at the university. He continues to reduce his stress by meditating and doing self-study. He continues to walk his dog and exercise for self-care. His energy level remains good. The pain management program is going well for him. He relates his average pain with Suboxone 2mg QID is 3/10 and without the pain medication would be 7/10. He did try taking Suboxone TID. This experiment did not go well, and he was having break through pain. His quality of life remains at 7/10. He feels stable on the fluoxetine 40mg QD. He was on Season 5 episode 6 of Yellowstone as a background extra.

MOOD: He feels his mood is good most of the time. He rates his anxiety at 2/10. He would still describe his mood as being mostly sunny with about 20% cloud cover and predicted to clear if it were a weather pattern. He also feels about 80% charged if he were a battery. He has been sleeping well for the most part, however he is getting up to urinate. No SI/HI

AUDIENCE CASES

THANK YOU

Marc C Mentel DO

406 Recovery

marc.mentel@406recovery.care

406-219-7233