Acūtis

Diagnostics

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Buprenorphine Pharmacology

and Opioid Neurobiology

Objectives

- Summarize the neurobiology of opioid addictive behavior
- List various non-drug sources that are commonly associated with addictive behaviors often requiring cognitive behavior therapy.
- Review basic pharmacology as it applies generally to opioids
- Describe the pharmacology and pharmacokinetics of buprenorphine
- Define the differences between agonist, partial agonist, agonist/antagonist, and antagonist opioids
- Identify differences between the various buprenorphine product formulations, and which are used for medication assisted treatment in combination with cognitive behavior therapy.

Disclosures – Jeffrey Fudin, PharmD, FCCP, FASHP, FFSMB

Affiliation	Role
AcelRx Pharmaceuticals	Advisory Board, Speakers Bureau
Acutis Diagnostics, Inc	Speaker
Astra Zeneca	Speakers Bureau
BDSI	Advisory Board, Consultant
Daiichi Sankyo	Advisory Board, Speakers Bureau
Firstox Laboratories	Consultant
GlaxoSmithKline (GSK)	Advisory Board
Quest Diagnostics	Advisory Board
Scilex Pharmaceuticals	Advisory Board, Speakers Bureau
Salix Pharmaceuticals	Advisory Board

Disclosures – Daniela Zaborskis, PhD

Affiliation	Role
Acutis Diagnostics, Inc	Director of Operations and Senior Scientist

Pretest Question #1

Which of the following are true regarding buprenorphine?

A. Prescribing clinicians are required to complete an eight-hour training course to qualify for a waiver to prescribe buprenorphine for pain
B. All buprenorphine products can be legally prescribed for analgesia by non-certified clinicians with proper DEA license
C. No buprenorphine products are specifically FDA approved for chronic pain management
D. Pharmacologically, buprenorphine is equally dangerous to most other opioids

Pretest Question #2

Which of the following are necessary for addictive behavior?

A. Euphoria, opioids, and benzodiazepines

B. Exposure to drug, vulnerable person, vulnerable time

C. Exposure to drugs and alcohol

D. Opioids taken for longer than 3-months

Pretest Question #3

Select the correct sequence of highest to least baseline addiction vulnerability

A. Alcohol, opioids, nicotine

B. Opioids, alcohol, nicotine

C. Nicotine, alcohol, opioids

D. They all have equal vulnerability

Case Study | Dual Diagnosis

Opioid Use Disorder and Chronic Back Pain

52 Year Old Woman w/ CLBP x 3 years. Works full time as administrative assistant at car dealership.

Urine Screen by IA In-Office Results	
Test	**Result**
Opiate	Negative
Benzodiazepines	Positive
Benzoylecgonine (cocaine metabolite)	Positive

1. Duloxetine (Cymbalta®) 60mg PO QAM
2. Fentanyl (Duragesic®) 50mcg/hr changed Q72 hours
3. Hydrocodone/APAP (Lortab®) 5/325, 1 PO Q4H PRN

Stigma

- A mark of disgrace or infamy; a stain or reproach, as on one's reputation. a mental or physical mark that is characteristic of a defect or disease: the stigmata of leprosy. a place or point on the skin that bleeds during certain mental states, as in hysteria.
- People coping with mental illness have a lot more to deal with than just the disorder itself. Many people report that the stigma of mental illness, and the prejudices they encounter because of it, is nearly as bad as the disorder's symptoms themselves.

1. http://www.dictionary.com/browse/stigma
2. https://www.healthyplace.com/stigma/stand-up-for-mental-health/what-is-stigma/

Empathy

- Empathy means 'the ability to understand and share the feelings of another' (as in both authors have the skill to make you feel empathy with their heroines)
- Sympathy means 'feelings of pity and sorrow for someone else's misfortune' (as in they had great sympathy for the flood victims)

https://en.oxforddictionaries.com/definition/empathy

Addiction (ASAM-short)

- A primary, chronic disease involving brain dysfunction which encompassing reward, motivation, memory and related circuitry.
  - Includes biological, psychological, social and spiritual manifestations.
  - Compulsive reward seeking
    - relief by substance use and other behaviors
    - Examples?

https://www.asam.org/quality-practice/definition-of-addiction

Addiction (continued)

- Inability to abstain
- Impairment in behavioral control and craving
- Diminished recognition of significant problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response.

https://www.asam.org/quality-practice/definition-of-addiction

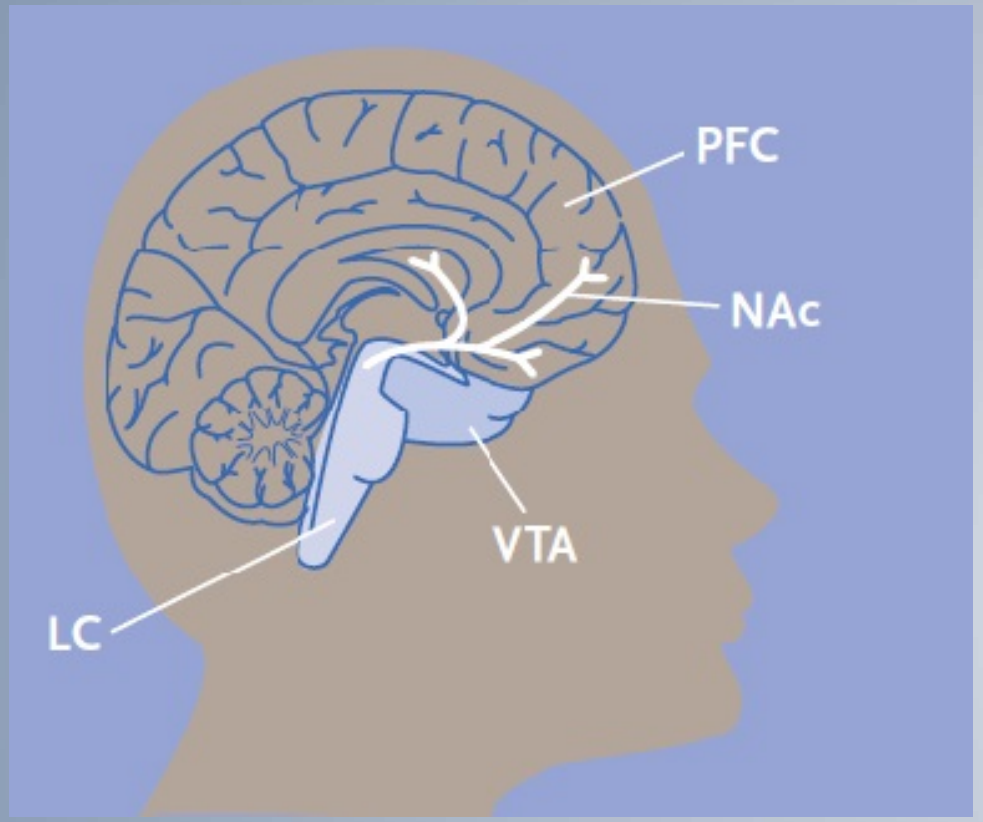
Neurobiology 101

Base Rates of Addiction/Abuse: Vulnerabilities in the Population

- 8.7% Illicit Drugs
- 12.5% Alcohol
- 26.5% Nicotine

SAMHSA 2011 National Survey on Drug use and Health
Hasin DS, et al. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States. Arch Gen Psychiatry. 2007; 64(7): 830-842.

Mesolimbic Reward System



VTA: ventral tegmental area
NAc: nucleus accumbens
PFC: prefrontal cortex
LC: locus ceruleus

Stages of Addiction Cycle

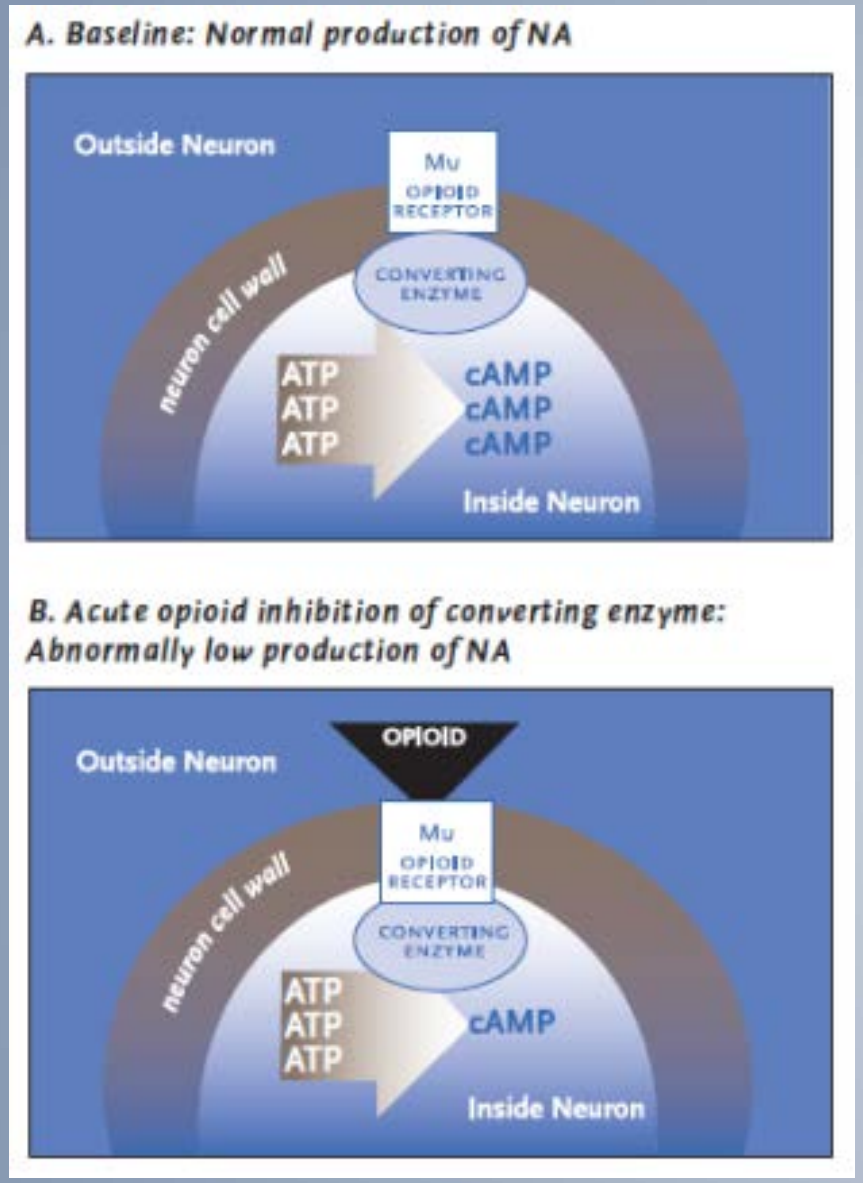
a. Binge and Intoxication
b. Withdrawal and Negative Affect
c. Preoccupation and Anticipation

1. Kosten, T. R., & George, T. P. (2002). The neurobiology of opioid dependence: implications for treatment. *Science & Practice Perspectives*, *1*(1), 13.
2. Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, *374*(4), 363-371.

Stage of Addiction	Neuroadaptive Changes		
Binge and Intoxication	Euphoria	Feeling Happy	Escaping depression, anxiety, or agitation
Withdrawal and negative Affect	Reduced Energy	Reduced Pleasure	Feeling dysphoric
Preoccupation and anticipation	Anticipation	Craving	Obsessing /Planning for Drug

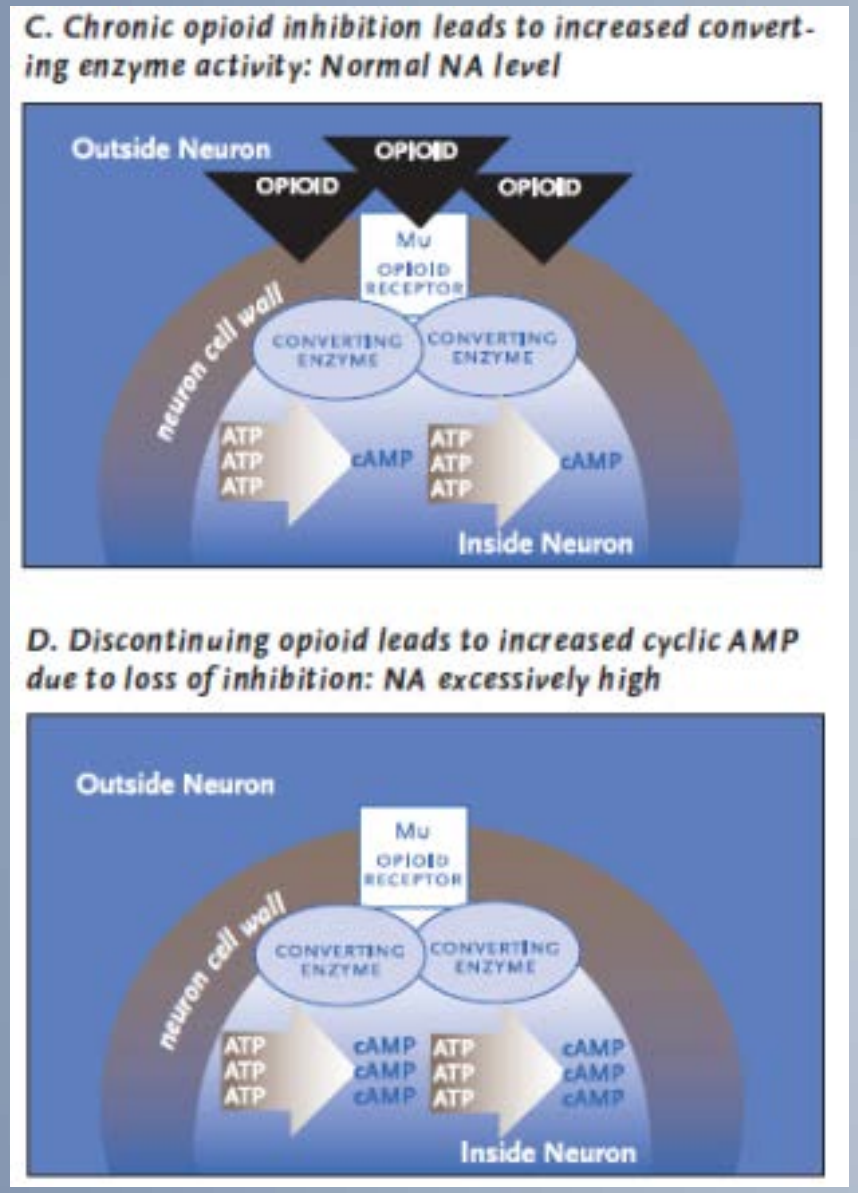
Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, *374*(4), 363-371.

Neurobiological Explanation for Dependence and Withdrawal



What's the impact of diminished noradrenalin?

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, *374*(4), 363-371.



Can we explain the physiological symptomatology?

Volkow, N. D., Koob, G. F., & McLellan, A. T. (2016). Neurobiologic advances from the brain disease model of addiction. *New England Journal of Medicine*, *374*(4), 363-371.

Addiction Comes in All Varieties

Addiction is not Simply a Disease of Exposure

Exposure is necessary but not sufficient

- ✓Exposure to drug
- ✓Vulnerable person
- ✓Vulnerable time

Savage SR, Kirsh KL, Passik SD. Challenges in using opioids to treat pain in persons with substance use disorders. Addiction science & clinical practice. 2008 Jun;4(2):4.

Medical Problems Involving Addiction

- Diabetes (glycemic control RX)
- Obesity (CHO craving; RX v surgery)
  - Bupropion/Naltrexone combo
- Lung Cancer (Nicotine products)
- GERD (Are PPIs in patient's best interest?)[1]

1. Yoshikawa I, et al. Long-term treatment with proton pump inhibitor is associated with undesired weight gain. World J Gastroenterol. 2009; 15(38): 4794-4798.

Does formulation selection matter?

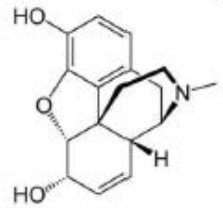
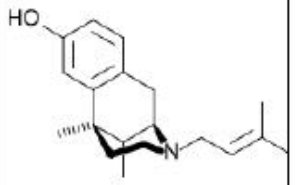
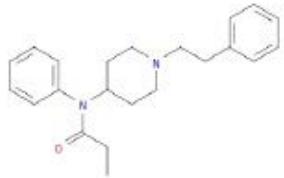
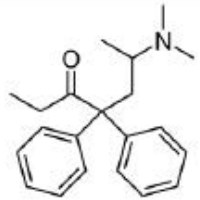
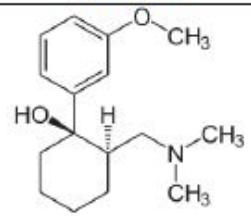
Fentanyl Patch

Fentanyl TIRF

Included with permission from Dr. Steven Passik with revisions

Breaking Down Opioids by Chemical Class

Chemical Classes of Opioids

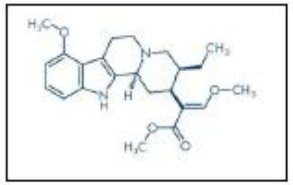
PHENANTHRENES	BENZOMORPHANS	PHENYLPIPERIDINES	DIPHENYLHEPTANES	PHENYLPROPYL AMINES
				
MORPHINE	PENTAZOCINE	FENTANYL	METHADONE	TRAMADOL
Buprenorphine* Butorphanol* Codeine Dextromethorphan* Dihydrocodeine Heroin (diacetyl-morphine) Hydrocodone* Hydromorphone* Levorphanol* Methylnaltrexone** Morphine (Opium, conc) Nalbuphine* Naloxone* Naloxegol* Naltrexone** Oxycodone* Oxymorphone*	Diphenoxylate Loperamide Pentazocine	Alfentanil Fentanyl Meperidine Remifentanil Sufentanil **Illicit Fentanyl** Furanyl fentanyl Acetyl fentanyl Fluoro-fentanyl Carfentanil	Methadone Propoxyphene	Tapentadol Tramadol
CROSS-SENSITIVITY RISK				
PROBABLE	POSSIBLE	LOW RISK	LOW RISK	LOW RISK

*Agents lacking the 6-OH group of morphine, possibly decreases cross-tolerability within the phenanthrene group
**6-position is substituted with a ketone group and tolerability is similar to hydroxylation

Jeffrey Fudin, BSPharm, PharmD, DAIPM, FCCP, FASHP, FFSMB

http://paindr.com/wp-content/uploads/2018/02/Opioid-Structural-Classes-Figure_-updated-2018-02.pdf

Mitragynine (Kratom)



http://paindr.com/wp-content/uploads/2016/11/Opioid-Structural-Classes_edited-November-2016.pdf

Immunoassay: Not created equally

- Pros = simple, automated, rapid results
- Cons = cross-reactivity, false-positives, false negatives
- Buprenorphine screen
  - -cross reactants = morphine, methadone, codeine, dihydrocodeine, tramadol, amisulpiride, sulpiride

Journal of Analytical Toxicology 2014;38:387–396 doi:10.1093/jat/bku075 Alec Saitman1*, Hyung-Doo Park1,2 and Robert L. Fitzgerald1 False-Positive Interferences of Common Urine Drug Screen Immunoassays: A Review

Opioid Pharmacology 101

- Opioid pharmacology
  - Agonist, partial agonist, agonist/antagonist, antagonist
- There are three opioid receptors (μ, δ, and κ) that are distributed throughout the body and CNS, and elicit different responses when activated
- CO_2 accumulation and diminished chemoreceptor response may lead to the lethal effect of respiratory depression

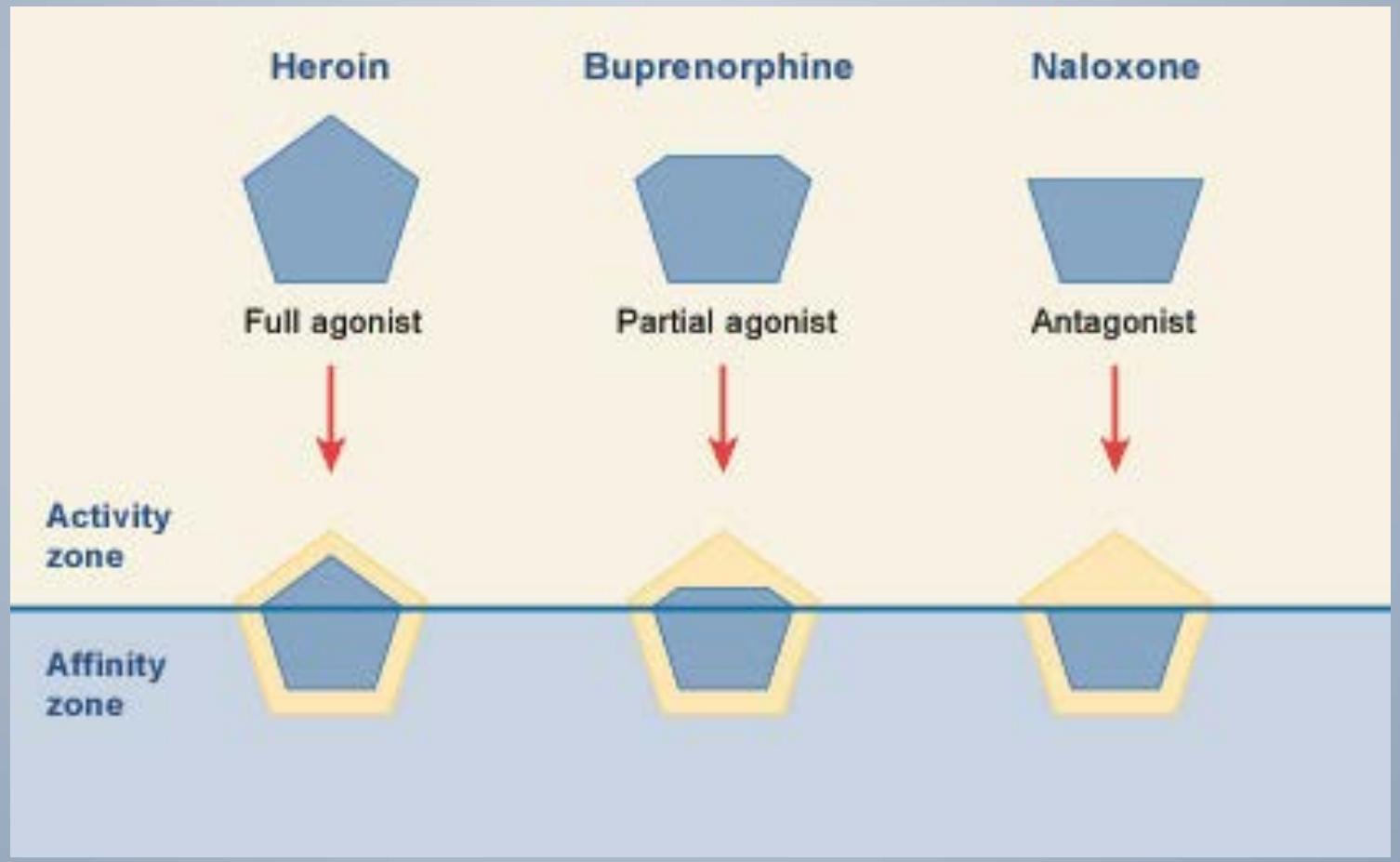
Opioid Receptor	Desired Activity	Disadvantages when activated
μ	Peripheral Analgesia, euphoria?	Sedation, euphoria, respiratory depression, bradycardia, N/V, and decreased GI motility
δ	Spinal and supraspinal analgesia	Decreased GI motility
κ	Spinal analgesia	Diuresis and dysphoria

Williams J. Rev Pain. 2008 Mar; 1(2): 2-5.

Opioid Pharmacology Schematic

Important Qualities

1. Affinity (pull towards receptor)
2. Binding Strength (ki, “rubber v metal”)
3. Receptor Dissociation
   - Consider methadone
4. Potency (chemical configuration)



Mu Receptor Binding Affinity of Buprenorphine

Opioids	Range of Ki Value
Buprenorphine	0.21- 1.5
Naltrexone	0.4-0.6 (antagonist effects)*
Fentanyl	0.7-1.9
Methadone	0.72-5.6
Naloxone	1.0-3.0 (antagonist effects)*
Morphine	1.02-4
Pentazocine	3.9-6.9
Codeine	65-135

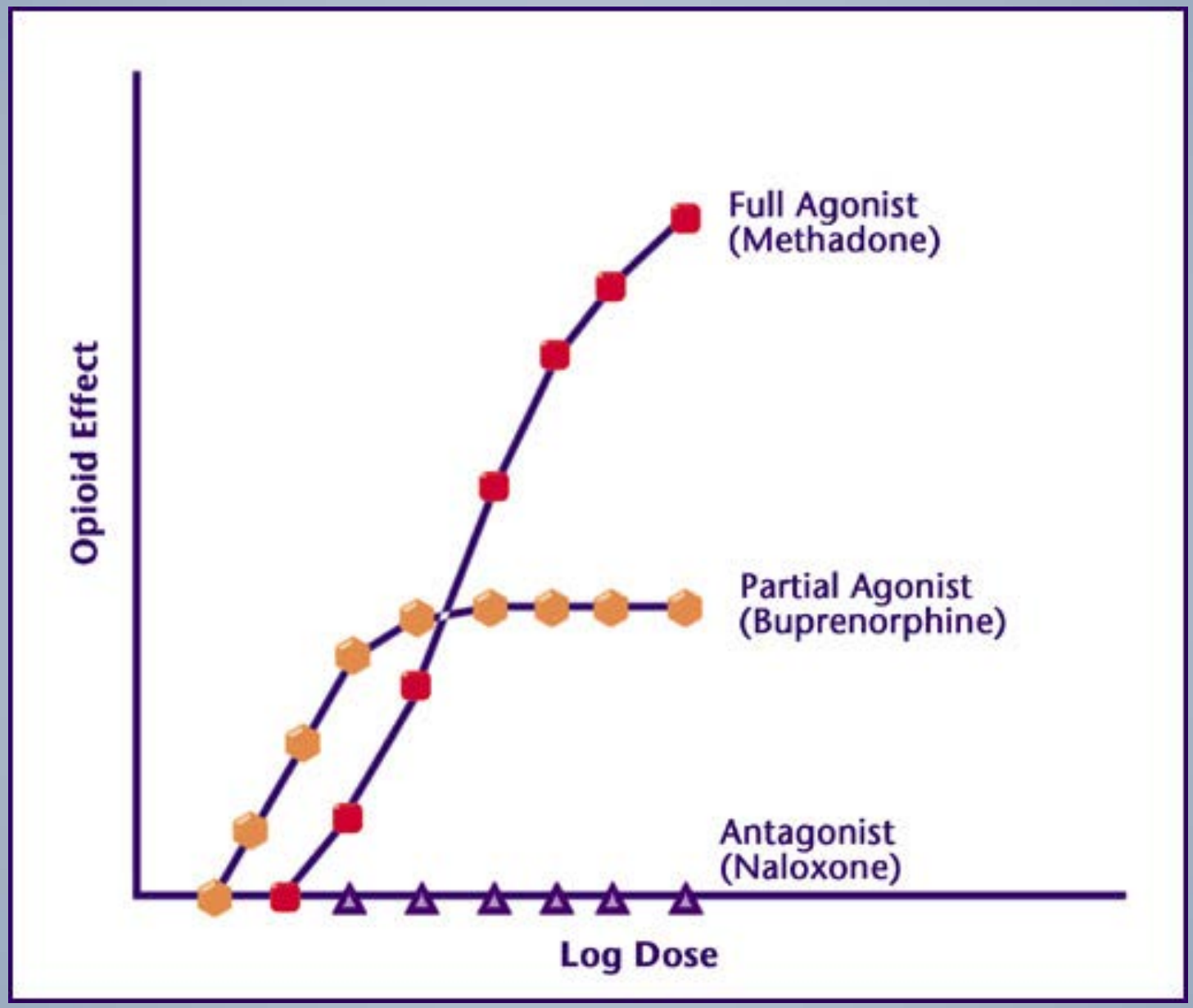
**Wang D, Sun X, Sadee W. Different effects of opioid antagonists on μ-, δ-, and κ-opioid receptors with and without agonist pretreatment. Journal of Pharmacology and Experimental Therapeutics. 2007 May 1;321(2):544-52.
Fudin J, Chu R, Ciani A, Raouf M. Opioid Agonists, Partial Agonists, Antagonists: Oh My! Pharmacy Times. January 6, 2018. Available at http://www.pharmacytimes.com/contributor/jeffrey-fudin/2018/01/opioid-agonists-partial-agonists-antagonists-oh-my

Pharmacology of Buprenorphine

- Partial agonist at the μ-receptor and a potent antagonist at the κ-receptor
  - Lower intrinsic activity at μ-receptors in comparison to full μ-agonists
- Flattened dose-response curve (ceiling effect):
  - At lower dosages there are dose-related increases in efficacy
  - Eventually escalating doses result in plateaued efficacy
- Ceiling on euphoria and CO_2 accumulation decreases
  - Abuse liability
  - Risk of OIRD and overdose

Walsh SL et al. Clin Pharmacol Ther. 1994; 55(5): 569-80.

Conceptual Dose-Response Curves of Three Opioids



McNicholas L. US Department of Health and Human Services. 2004. Pages 11-24.

Pharmacology & PK of Buprenorphine

- Highest affinity for the μ-receptor compared to all other opioid **agonists** and **antagonists**
  - Higher than _____?
- Slow dissociation rate from the μ-receptor
- Competitive binding of buprenorphine at low doses
  - Not displaced by full agonists at moderate to high doses
  - Considerations for surgery?
- Undergoes extensive N-dealkylation via CYP3A4 into norbuprenorphine, and glucuronidation into buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide (all inactive metabolites)
- Half-life ≈ 26 hours

McNicholas L. US Department of Health and Human Services. 2004. Pages 11-24.

Buprenorphine Metabolism

- Buprenorphine → Norbuprenorphine CYP450 3A4 and 2C8
- Norbuprenorphine concentrations higher than buprenorphine within a few hours
- Urine drug concentrations – vary due to differences in dose, uptake, distribution, metabolism and excretion.
- Concentration of drug in urine ≠ estimation of intake time
- Metabolite/parent compound ratio → unaffected by urine dilution

Available Doses of Buprenorphine/Naloxone Combination Products

Suboxone SL Tablet	Suboxone SL Film	Zubzolv SL Tablet	Bunavail Buccal Film
2 / 0.5 mg	2 / 0.5 mg	1.4 / 0.36 mg	----------
4 / 1 mg	4 / 1 mg	----------	2.1 / 0.3 mg
8 / 2 mg	8 / 2 mg	5.7/ 1.4 mg	4.2 / 0.7 mg
12 / 3 mg	8 / 2 mg + TWO 2 / 0.5mg films	----------	6.3 / 1 mg

Fudin J, Cleary J, Gottwald J. A Brief Review of Buprenorphine Products. Pharmacy Times. March 22, 2016. Available at http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/03/a-brief-review-of-buprenorphine-products

Buprenorphine Product Bioavailability

PRODUCT	Available Strengths	PERCENT BIOAVAILABILITY
Buprenorphine – buccal film (Belbuca)	75, 150, 300, 450, 600, 750, 900mcg	45-65 %
Buprenorphine – TD patch (Butrans)	5, 7.5, 10, 15, 20 mcg/hr	15 %
Subutex (SL) Suboxone/Bunavail/ Zubsolv	See previous slide	29 +/- 10 %
Buprenex (injectable)	0.3mcg/mL	100%

Revised from:

Bettinger JJ, Fudin J, Argoff C. Buprenorphine and Surgery: What's the Protocol? In Kean N, 2nd ed., Opioid Prescribing and Monitoring—How to Combat Opioid Abuse and Misuse Responsibly. Chap. 6. Pg. 73-78. Pub. Vertical Health, LLC. September 2017.

Case Study | Tablet Scraping

What do these results mean?

Patient		Matrix - Urine		Provider	
Name	Passmytest, Tryingto	Accession #	376851	Doctor	Test, Test
ID	1-102303	Collection Date	10/10/2018 1:00 PM	Organization	Acutis Diagnostics
Gender	Male	Received Date	10/10/2018		
Birth	9/18/1984	Reported Date	10/10/2018		

Summary

Prescribed drug found (CONSISTENT) - Parent drug or metabolite was detected

Reported Prescription	Anticipated Positives(s)	Test Outcome	Detection Window
Suboxone	Buprenorphine	POSITIVE	2 - 24 hours
	↳ Norbuprenorphine	NEGATIVE	2 - 48 hours
	↳ Naloxone	POSITIVE	1 - 3 days

Prescribed drug not found (INCONSISTENT) - Parent drug or metabolite was not detected

Reported Prescription	Anticipated Positive(s)	Test Outcome	Detection Window

Non-prescribed drug found (INCONSISTENT) - Suggests illicit or non-prescribed drug taken

Detected Analyte	Illicit	Result	Cutoff	Test Outcome	Detection Window
N/A	N/A	N/A	N/A	N/A	N/A

↳ Indicates drug metabolite or additional drug component. Relationship is not shown for any non-prescribed drugs found.

Case Study | Tablet Scraping

What do these results mean?

Patient

Name	Passmytest, Tryingto
ID	1-102303
Gender	Male
Birth	9/18/1984

Matrix - Urine

Accession #	376851
Collection Date	10/10/2018 1:00 PM
Received Date	10/10/2018
Reported Date	10/10/2018

Provider

Doctor	Test, Test
Organization	Acutis Diagnostics

Detailed

Test Name	Outcome	Result [ng/mL]	Cutoff	Detection Window	Status
Natural & Semi-Synthetic Opiates					
Buprenorphine	Positive	3416	10	2 - 24 hours	Consistent result
Norbuprenorphine	Negative	-	10	2 - 48 hours	Consistent result
Naloxone	Positive	854	10	1 - 3 days	Consistent result

The presence of parent drug in the absence of metabolites is unusual and may indicate that the drug was added directly to the urine. It is also possible the patient is unable to metabolize drugs due to genetic variation, impaired liver function or drug-drug interactions.

Case Study | Tablet Scraping

Positive for Prescribed Medications w/no metabolites

- No norbuprenorphine present
- Ratio of buprenorphine to naloxone is 4:1
- Adulteration of samples may occur from placement of medication directly into the sample

Opioids Requiring Special Considerations Perioperatively

- Methadone
- Buprenorphine

1. Fudin J, Raouf M, Wegrzyn WL. Pharmacological Considerations Regarding Equianalgesic Dosing. A White Paper from the Academy of Integrative Pain Management. September 2017.
2. Fudin J, Pratt Cleary J, Schatman ME. The MEDD myth: the impact of pseudoscience on pain research and prescribing-guideline development. Journal of Pain Research. 2016 March; 9:153-156.
3. Macintyre PE, Huxtable CA, Flint SL, Dobbin MD. Costs and consequences: a review of discharge opioid prescribing for ongoing management of acute pain. Anaesthesia and intensive care. 2014 Sep 1;42(5):558.

Buprenorphine, Surgery, Acute Injury or Pain Flare-up

What's the Protocol?

Moral and Ethical Obligations

- First do no harm!
- Prevent Panic
- Patients may self-taper
- Real live examples

1. Macintyre PE, Huxtable CA, Flint SL, Dobbin MD. Costs and consequences: a review of discharge opioid prescribing for ongoing management of acute pain. Anaesthesia and intensive care. 2014 Sep 1;42(5):558.
2. Marcucci C, Fudin J, Thomas P, Sandson NB, Welsh C. A new pattern of buprenorphine misuse may complicate perioperative pain control. Anesthesia & Analgesia. 2009 Jun 1;108(6):1996-7.
3. Fudin J. Bupes, and Subs, and Surgery, Oh My. Paindr.com Blog. April 2013. Available at: http://paindr.com/bupes-and-subs-and-surgery-oh-my/ (Over 150 comments)
4. Fudin J. Buprenorphine, so misunderstood. Paindr.com Blog. April 2016. Vailable at http://paindr.com/buprenorphine-so-misunderstood/ (Over 90 comments)

Dilemmas When Treating Acute Pain for Patients Requiring Buprenorphine

- Full opioid agonists (e.g. morphine, oxycodone) will not displace buprenorphine from the MOR
- Starting an opioid agonist in Emergency Department
  - Patient falsely accused of drug seeking
  - High tolerance is misleading to clinicians
- Risks of individualized opioid titration in ED with 3-day supply
  - Recall T1/2 of buprenorphine
  - As soon as the patient's body eliminates all of the buprenorphine, the new opioid will be able to occupy all available MORs.
  - Abrupt transition receptors occupation by high-dose full agonist => OIRD
- Institution should have policies in place
  - ED visits
  - Elective and Emergency Surgery
  - UNIVERSAL SCREENS PRIOR TO SURGERY

1. Bettinger JJ, Fudin J, Argoff C. Buprenorphine and Surgery: What's the Protocol? In Kean N, 2nd ed., Opioid Prescribing and Monitoring—How to Combat Opioid Abuse and Misuse Responsibly. Chap. 6. Pg. 73-78. Pub. Vertical Health, LLC. September 2017.
2. Macintyre PE, Russell RA, Usher KA, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesthesia and intensive care. 2013 Mar 1;41(2):222.

Considerations for Acute Pain

- Elective versus Emergency Surgery?
- Patients may require higher-than-usual postoperative opioid
  - Acute pain / Physical tolerance
  - Receptors are occupied
- May transition to another opioid shortly after a major surgical procedure requiring conscious sedation with sedative hypnotics and/or general anesthesia
- Converting to or adding another opioid is generally manageable in the majority of cases
  - This requires careful consideration and a team approach

Bettinger JJ, et. Al. 2017.

Elective versus Emergency Surgery

- Elective surgery
  - Ample time prior to the surgery for preparation
  - Why is patient receiving buprenorphine (OUD or analgesia or both)?
  - How long should patient be off buprenorphine prior to surgery?
- History of Opioid Used Disorder
  - Careful Patient Assessment
    - Taper in advance?
      - Benefits versus risks
      - Continue buprenorphine?
      - Benefits versus risks
    - Is there team support?
      - Behavior Health, Pharmacy, Medicine
      - What other meds can be used?

Bettinger JJ, et. Al. 2017.

Buprenorphine was Prescribed for Pain

- Stop 2-4 weeks prior to surgery
- Offer short-acting opioid agonists
  - e.g. hydrocodone, oxycodone, or morphine PRN
- Upon admission for surgery
  - pre-, intra-, and postoperative patient pain management plan according to its institutional policies
  - Post-op when opioids are no longer necessary
    - Buprenorphine may be reintroduced and titrated until an adequate dose is achieved

Bettinger JJ, et. Al. 2017.

Buprenorphine was Prescribed for OUD

- Choice was to continue buprenorphine
  - Counseling and reassurance by interdisciplinary team
- Options perioperatively
  - Preemptive Analgesia
    - Pregabalin, SNRIs, TCAs, COX-2 selective agents
    - IV buprenorphine v fentanyl v high dose hydromorphone
      - Competitive binding v unoccupied receptors

Buprenorphine was Prescribed for OUD (continued)

- Intraoperative
  - › Nerve blocks, Propofol, Ketamine, IV opioids as above
- Postoperative
  - › Increase baseline bupe dose
  - › Adjuvants if appropriate, as listed above
    - Nociceptive (somatic: e.g. skin, bones or visceral: e.g. organs), Neuropathic pain (peripheral v central), Idiopathic (usually head, shoulders, or pelvic)

Can a certified (DEA Waiver) bupe prescriber offer Suboxone and similar products to treat pain off label?

- What are you to do?

Testing Protocols

Buprenorphine

- Buprenorphine and its metabolites
- Detection windows and cut off
- Urine vs. oral fluid
- Buprenorphine and naloxone (Suboxone) vs. buprenorphine (Butrans)
- Adulterated vs. unadulterated samples

Buprenorphine Products to Treat Pain

FDA Approved as Analgesics
How do they compare?

Injectable Buprenorphine

- FDA Indication
  - Relief of moderate to severe pain
- Formulation
  - Parenteral
- Dosage and Administration:
  - 0.3mg (1mL) intramuscularly or slow (at least 2 minutes) intravenous injection
    - Single doses up to 0.6mg to adults depending on pain
    - Dosed every 6-8 hours

1. Buprenex: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
2. Fudin et al. Pharmacy Times. 2016.

Injectable Buprenorphine

- **Oral Morphine Equivalent Per Day**
  - 0.3mg Buprenex = Approximately 10mg oral morphine sulfate
    - High doses of buprenorphine cannot be compared to pure agonists
- **Bioavailability**
  - 100%
- Half-life
  - Mean of about 2.2 hours
- **Time to effects**
  - Occur as soon as 15 minutes post-injection, and persist for 6 or more hours
  - Peak effects are observed within one hour
- **Practical Considerations**
  - Ileus
  - Surgery (emergency v scheduled)

1. Buprenex: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
2. Fudin et al. Pharmacy Times. 2016.

Buprenorphine Transdermal

- FDA Indication
  - For the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- Formulation
  - Transdermal patch
    - *Administration:* apply buprenorphine (Butrans) to upper outer arm, upper chest, upper back, or side of the chest (8 total sites) every 7 days. Wait a minimum of 21 days before reapplying to the same site.
- Dosage and Administration:
  - *Opioid-Naïve Patients:* initiate with buprenorphine (Butrans) 5mcg/hour; dose titrations occur after a minimum of 72 hours.
  - *Conversion from Other Opioids:*
    - Oral morphine equivalent <30mg → 5mcg/hour Butrans
    - Oral morphine equivalent >30mg → 10mcg/hour
  - Maximum dose of 20mcg/hour

1. Butrans: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
2. Fudin et al. Pharmacy Times. 2016.

Buprenorphine Transdermal

- Oral morphine equivalent per day
  - Buprenorphine (Butrans) to opioid: Questionable?
- Bioavailability
  - 15%
- Half-life
  - About 26 hours
- Time to effects:
  - Peak effects are observed after about 60 hours, and steady state is reached at 72 hours

1. Butrans: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
2. Fudin et al. Pharmacy Times. 2016.

Buprenorphine Transdermal

- QTc Prolongation[1,2]
  - Study demonstrated no clinically meaningful QTc effect at a buprenorphine (Butrans) dose of 10mcg/hour, however a Butrans dose of 40mcg/hour yielded a maximum QTc prolongation of 9 msec.
  - Buprenorphine (Butrans) (USA, Europe)
    - 5, 7.5, 10, 15, 20 mcg/hour
- Higher Strengths
  - Buprenorphine (Transtec) [Europe] Transdermal 3-day patch[3]
    - 35, 52.5, 75 mcg/hour
    - Chronic moderate – severe pain

Buprenorphine Buccal Film

1. Butrans: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
2. Fudin et al. Pharmacy Times. 2016.
3. Yang A, Demirkol A, Khor KE, Nielsen S, Lintzeris N. Safety and Efficacy of Buprenorphine Patch in the Management of Chronic Pain. Clinical Medicine Reviews in Therapeutics. 2015 Jan 13;2015(7):1-0.
4. Freye E, Anderson-Hillemacher A, Ritzdorf I, Levy JV. Opioid Rotation from High-Dose Morphine to Transdermal Buprenorphine (Transtec®) in Chronic Pain Patients. Pain Practice. 2007 Jun 1;7(2):123-9.

Buprenorphine (Belbuca)

- Oral morphine equivalent per day
  - Buprenorphine (Belbuca) to opioid: Questionable?
- Bioavailability
  - 45-60%
- Half-life:
  - About 27.6 hours
- Time to effects:
  - Peak effects are observed after about 2.5-3 hours, and steady state is reached at about 72 hours (prior to the 6th dose)

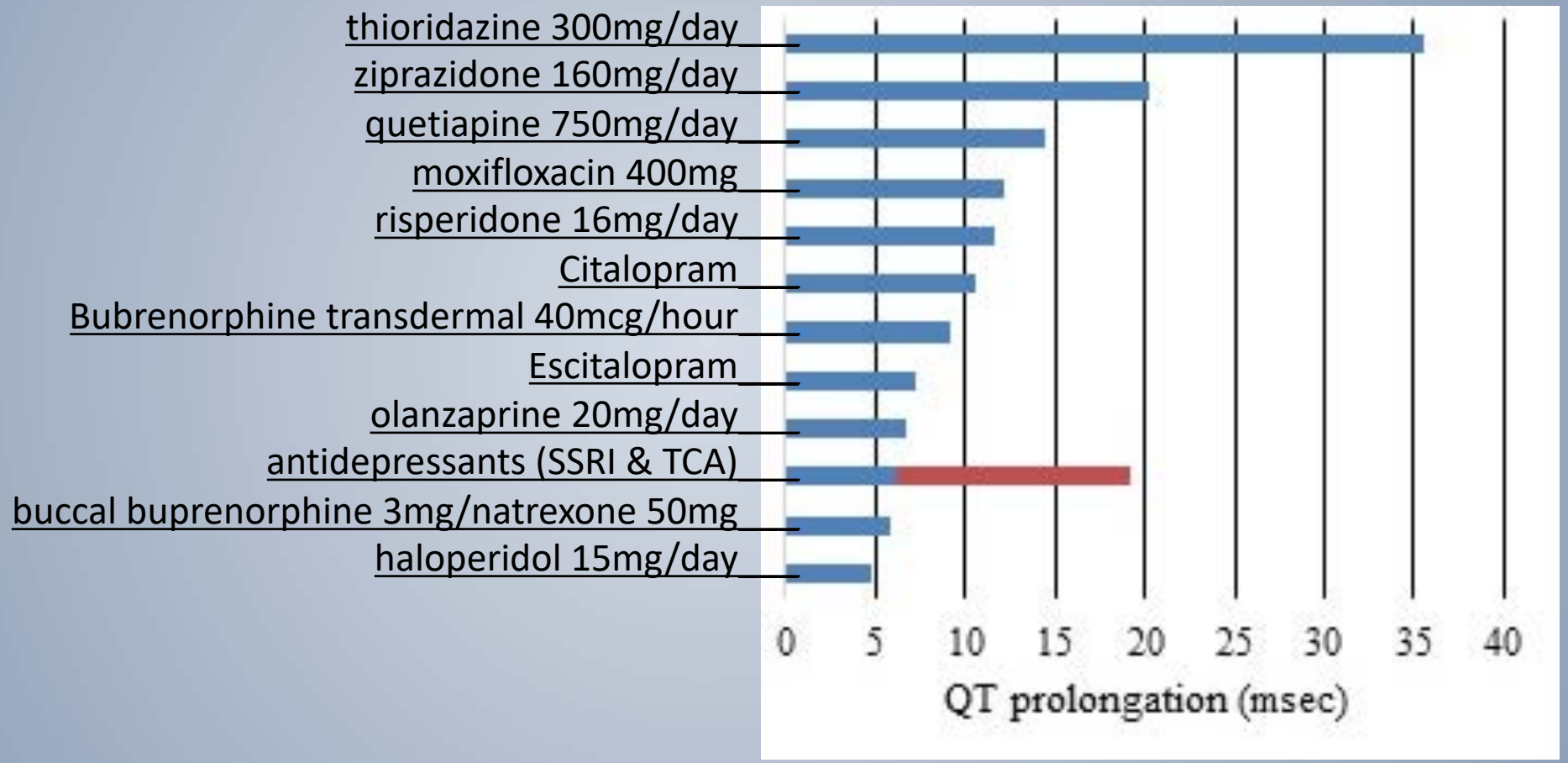
Belbuca: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
Fudin et al. Pharmacy Times. 2016.

Buprenorphine (Belbuca)

- QTc Prolongation: doses at 900mcg every 12 hours resulted in QTc values between 450 msec to 480 msec.

Belbuca: Package Insert [Internet]. Bethesda (MD): National Library of Medicine.
Fudin et al. Pharmacy Times. 2016.

QT Prolongation of Various Medications



Fudin J, Cleary J, Gottwald J. A Brief Review of Buprenorphine Products. Pharmacy Times. March 22, 2016. Available at http://www.pharmacytimes.com/contributor/jeffrey-fudin/2016/03/a-brief-review-of-buprenorphine-products

Buprenorphine Extended Release Injection

- Buprenorphine Extended Release Injection (BERI) is indicated for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days
- BERI (Sublocade[1]) should be used as part of a complete treatment plan that includes counseling and psychosocial support
- Strengths: 100, 300mg
- Dosage and Administration
  - Prescription use of this product is limited under the Drug Addiction Treatment Act. SUBLOCADE should only be prepared and administered by a healthcare provider.
  - SUBLOCADE is administered monthly only by subcutaneous injection in the abdominal region.
  - The recommended dose is two monthly initial doses of 300 mg followed by 100 mg monthly maintenance doses.
  - Increasing the maintenance dose to 300 mg monthly may be considered for patients in which the benefits outweigh the risks.
- Practical Considerations for Future Products[2]

1. Highlights of Prescribing Information. Sublocade (buprenorphine extended-release) injection, for subcutaneous use. North Chesterfield VA. Available at: https://www.sublocade.com/Content/pdf/prescribing-information.pdf
2. Breen C. There's a New Buprenorphine on the Block. Paindr.com Blog. Feb. 2018. Available at: http://paindr.com/theres-a-new-buprenorphine-on-the-block/

Case Study | Chronic Back Pain

Opioid Use Disorder and Chronic Back Pain
52 Year Old Woman w/ CLBP x 3 years. Works full time as administrative assistant at car dealership.

IA In-Office Results	
Test	**Result**
Opiate	Negative
Benzodiazepines	Positive
Benzoylecgonine (cocaine metabolite)	Positive

Chromatography [send out] Results	
Test	**Result**
Fentanyl	Positive
Hydrocodone	Negative
Alpha-hydroxyalprazolam	Positive
Benzoylecgonine	Positive

Duloxetine (Cymbalta®) 60mg PO QAM
Fentanyl (Duragesic®) 50mcg/hr changed Q72 hours
Hydrocodone + APAP (Lortab®) 5/325, 1 PO Q4H PRN

Case Study | Unexpected Results

Negative for Prescribed Medications | Positive for illicits not prescribed

- Lack of hydrocodone PRN use (trading for cocaine / alprazolam?)
- Pharmacokinetics (when was urine collected?)
- Noncompliance (illegally obtained drugs)
- Test is not specific for the drug tested (opiate vs. synthetic, in this case fentanyl)
- Drug-drug, drug-disease, drug-food/supplement interactions
- Genetic polymorphism

Case Study| Chronic Low Back Pain

- Speak with patient
- Give patient an opportunity to explain
- Assessment: Document justification for plan
- Devise actionable medical plan based on lab findings
  - Change in drug therapy (Patch, ADF, no opioid)
  - Justification for f/u lab testing
  - Justification for alternative therapies
  - Justification for behavioral health

Conclusion and Take Home Points

- Addiction is a neurobiological disease with REAL pathology
- Buprenorphine has an extremely unique pharmacology, exhibiting partial agonist activity at the μ-receptor and antagonist activity at the κ-receptor, the highest binding-affinity toward the μ-receptor compared to all other opioids, and a slow dissociation rate from the μ-receptor.
- Buprenorphine has a ceiling effect on CO2 accumulation
- There are many formulations of buprenorphine that differ in formulation, indication, strength, and pharmacokinetics.
- No buprenorphine products are interchangeable in terms of exact dosage equivalent
- Conversion of buprenorphine to morphine equivalents is not practical

Acūtis

Diagnostics