Buprenorphine Treatment (Suboxone)

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Disclosures

- No financial reimbursement for this lecture
- Consultant for various pharmaceutical companies including Indivior, Pfizer, BioDelivery Sciences, and Orexo.
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We've Got a Big Opioid Problem…

- Americans (4.6% of worlds population) consume :
- **80% of the global opioid supply.**
- 99% of the global Hydrocodone supply
- "The Opioid Epidemic of Our Age"

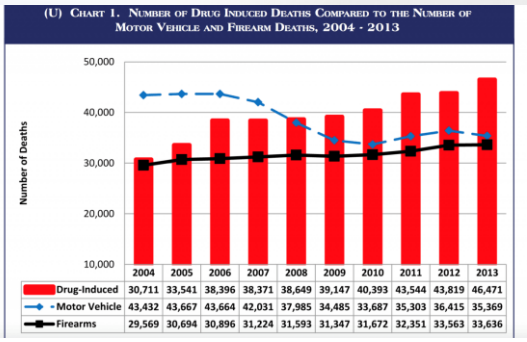
Opioids

- Why are we having an epidemic of prescription pain pills?
  - Powerful pain medications→ changing brain chemistry
  - Rx habits of doctors
  - Legal drug (if prescribed) vs. cocaine (clearly illegal)
  - Society or culture → "pills solve our problems"
- Why is heroin increasing?
  - When people get addicted to pain pills their addiction worsens. When they can't find pain pills → start heroin to prevent withdrawal, it's powerful, and it's cheaper !

Opioids

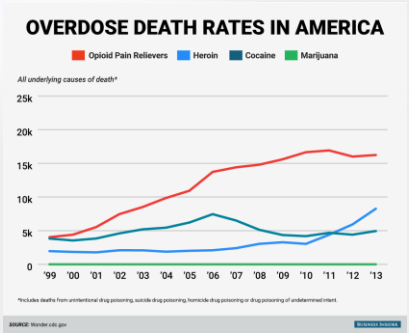
- How do opioids work?
  - Bind to Mu-opioid receptors in brain→ causing pain relief, sedation, tranquility. Many people get a "high" or euphoria. People who get a significant euphoria most likely are genetically susceptible to addiction.
  - Increased dopamine release when used recreationally→ reward
- So, why can't they just stop?
  - Opioid Withdrawal- sweating, pounding heartbeats, diarrhea, headaches, shakes upon discontinuation of opioid. Happens as soon as a few hours.

Opioids Death Rate Vs. Motor Vehicle Deaths

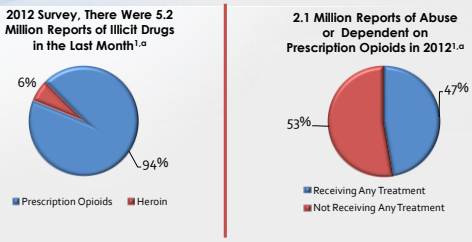


	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Drug-Induced	30,711	33,541	38,396	38,371	38,649	39,147	40,393	43,544	43,819	46,471
Motor Vehicle	43,432	43,667	43,664	42,031	37,985	34,485	33,687	35,303	36,415	35,369
Firearms	29,569	30,694	30,896	31,224	31,593	31,347	31,672	32,351	33,563	33,636

Overdose Death by Drug In US (99-2013)



More Than Half of Patients With Opioid Addiction Are Not Receiving Treatment



1. US Department of Health and Human Services. http://www.samhsa.gov/data/NSDUH/2k12MH_FindingsandDetTables/2K12MHF/NSDUHmhfr2012.pdf. Accessed July 7, 2014. 2. Office of the President of the United States. http://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/rx_abuse_plan.pdf. Accessed July 7, 2014.

Opioid Addiction Studies Demonstrate:

- Chronic Long Term Brain and Behavioral Changes with Opioid Addiction[1]
  - Hypodopaminergic effects leading to increase impulsivity and more addictive behaviors [2,3]
  - Increase pain and pain perceptions
  - Ongoing cravings [4]
  - These effects can persist even with long term abstinence from opioids

1. Blum K et al. *J Genet Syndr Gene Ther.* 2012;3(4):1-13. 2. Koob GF, Volkow ND. *Neuropsychopharmacology.* 2010;35(1):217-238. 3. Belin D et al. *Curr Opin Neurobiol.* 2013;23(4):564-572. 4. Filbey FM et al. In: Adinoff B, Stein EA, eds. In: *Neuroimaging in Addiction.* Oxford, UK: John Wiley & Sons. Ltd; 2011:133-156. 5. Sell LA et al. *Drug Alcohol Depend.* 2000;60(2):207-216.

Treatment of Opiate Addiction

Medication assisted treatment

Behavioral interventions

Treatment: One Size Does Not Fit All

- No one treatment is right for everyone
- Treatment should be easily available
- Retention and engagement is needed for treatment to be effective
- Counseling is a critical component of treatment
- Medications can be important for stabilization, reducing illicit drug use, and reducing risk of death
- Recovery is usually long-term and may involve multiple treatments and relapses

USDHHS. http:dpt.samhsa.gove/pdf/oo121Baccred.pdf

Buprenorphine

- Suboxone (Buprenorphine/Naloxone)- approved since 2002. Partial opioid. Helpful in cessation of opioid use and prevention of withdrawal and cravings
  - Office based (convenient)
  - Prescription pickup at pharmacy
  - Act of Congress- DATA 2000
  - Weekly visits to monthly as appropriate

11. USDHHS. http:dpt.samhsa.gove/pdf/oo121Baccred.pdf

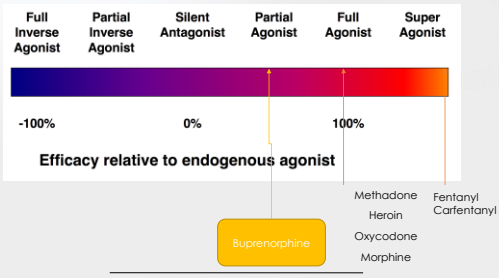
Buprenorphine Products For Addiction

DRUG	APPROVAL
Suboxone (Buprenorphine/Naloxone)	opioid dependence, induction & opioid dependence, maintenance. Approved for addiction in 2002. Film, Sublingual, Orange taste
Zubsolv (Buprenorphine/Naloxone)	opioid dependence, induction & opioid dependence, maintenance in 2013. Tablet, Sublingual, Menthol taste
Buprenorphine	mod-severe pain and opiate dependence induction only. - *Off label* for opiate user disorder in pregnancy). - Approved for pain in 1981 - Tablet, Sublingual
Bunavail (Buprenorphine/Naloxone)	(Buprenorphine/naloxone in buccal formulation) approved for induction and maintenance in 2014. Buccal. Film
Buprenorphine/Naloxone Generic Tablets	Opioid dependence, maintenance Tablets, Sublingual
Probuphine Implant (Buprenorphine Implant)	Buprenorphine Implant FDA approved in 2016. Subdermal in the arm. 80mg. 6 months of buprenorphine with equivalence of about 8mg of Buprenorphine per day.

Prescribing Buprenorphine Limits

- Physician, NP/PA certified to rx Buprenorphine has patient limits. Physicians limited to 100-275 patients if prescriber and clinic requirements met. PA/NP more limited to patient limits than physicians.
- DEA audits, auditing requirements for patients, availability to refer to therapy requirements exist

Buprenorphine

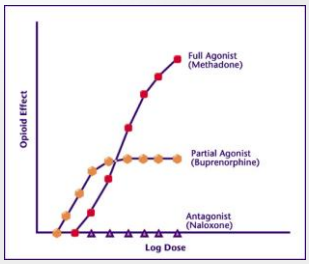


Buprenorphine

Buprenorphine was expected to have limited abuse potential and increased safety due to:

- "*Ceiling*" at moderate doses (16 -24mg).
- Being a *partial agonist with strong affinity*
- Dependence to buprenorphine, if developed, was associated with a *mild withdrawal syndrome*.
- Lower risk of respiratory depression

Buprenorphine Ceiling Effect



Buprenorphine: pharmacokinetics

- oral *bioavailability*: Buprenorphine: *30–55%* when given sublingually & 10% if swallowed.
- oral Bioavailability: Naloxone: 2%.
- The mean time to maximum plasma concentration for SL form: 40 minutes to 3.5 hours.
- Large volume of distribution.
- 96% protein bound.

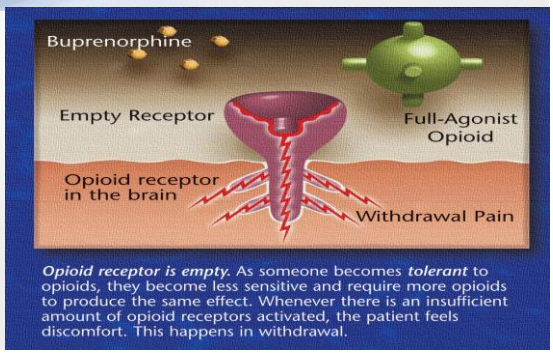
http://www.ncbi.nlm.nih.gov/pubmed/15966752

Buprenorphine: Pharmacokinetics

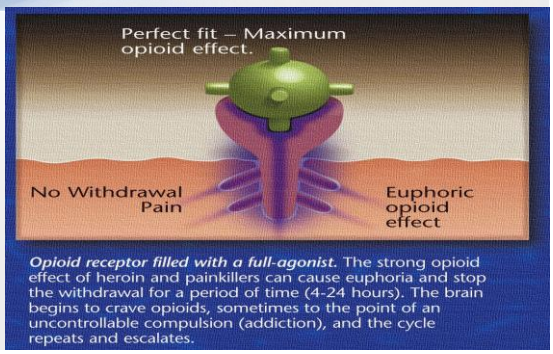
- Metabolism in liver: N-dealkylation to norbuprenorphine primarily through cytochrome *P450 (CYP) 3A4*.
- **Half-life**: 3-5 hours in first phase and up to 24 hours in second phase. *24-42 hours average*.
- Buprenorphine crosses the placenta during pregnancy and also crosses into breast milk.

http://www.nps.org.au/publications/health-professional/nps-radar/2011/september-2011/brief-item-buprenorphine-with-naloxone-sublingual-film

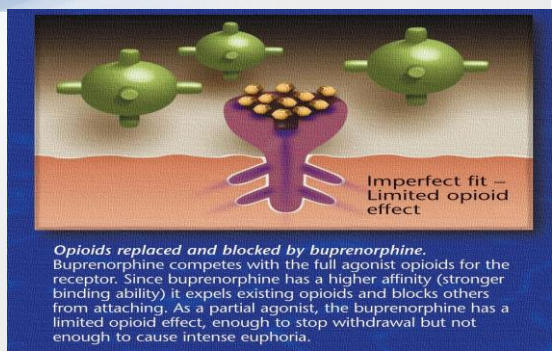
Pharmocodynamics- Empty Opioid Receptor



Pharmocodynamics- Full Opioid Agonist

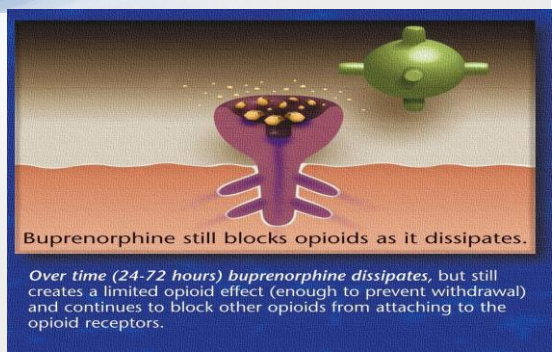


Pharmocodynamics- Buprenorphine- blocking



Opioids replaced and blocked by buprenorphine. Buprenorphine competes with the full agonist opioids for the receptor. Since buprenorphine has a higher affinity (stronger binding ability) it expels existing opioids and blocks others from attaching. As a partial agonist, the buprenorphine has a limited opioid effect, enough to stop withdrawal but not enough to cause intense euphoria.

PHARMACODYNAMICS- Dissipation



Over time (24-72 hours) buprenorphine dissipates, but still creates a limited opioid effect (enough to prevent withdrawal) and continues to block other opioids from attaching to the opioid receptors.

USES OF BUPRENORPHINE (SUBOXONE)

- *Induction:* suppress opioid withdrawal as rapidly as possible.
- *Maintenance:* prevent the emergence of opioid withdrawal symptoms, suppress craving for opioids, and reduce risk of or use of any illicit opioids.
- *Detoxification:* In short- and long-term medical withdrawal (ie, detoxification)

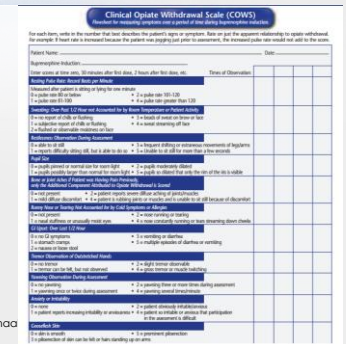
http://www.naabt.org/documents/Suboxone_Dosing_guide.pdf

CRITERIA

- Opioid dependency (quantity, frequency, type of opioid, duration).
- Time when the person last administered an opioid
- Social support, past quit attempts, past withdrawals
- Concurrent medical and mental health conditions and use of other drugs, particularly benzodiazepines and alcohol.

http://www.nps.org.au/publications/health-professional/nps-radar/2011/september-2011/brief-item-buprenorphine-with-naloxone-sublingual-film

INDUCTION



https://www.naa

INDUCTION

Drug	Parental Dose (MG) Equivalent to 10 MG IV Morphone	Oral Dose Equivalent to 30 MG Oral Morphine	Bioavailability of Oral Dosage Form	Dosing Interval (HRS)
Morphine	10	30	0.3	3
Anileridine (Leritine)	25	75	0.3	3
Codeine	100	300	0.3	3
Diamorphine (Heroin)	8	12.5	0.4	3

Drug	PO Dose	SC / IV Dose
Morphine	10 mg	5 mg
Codeine	100 mg	50 mg
Oxycodone	5 mg	-
Hydromorphone	2 mg	1 mg
Methadone	1 mg	Too irritating
Fentanyl IV or Patch	Check mfg. instructions	100 mcg

http://www.uofapain.med.ualberta.ca/en/ForHealthProfessionals/OpioidConversionGuide.aspx

INDUCTION

- Start Buprenorphine:
  6-12 hours after last heroin or opioid use. Should start in active withdrawal
- At least several days (6 day) after last methadone dose. Generally aim for methadone doses of < 40 mg.
- Never attempt to transfer at Methadone dose of 60 or higher.

http://www.nps.org.au/publications/health-professional/nps-radar/2011/september-2011/brief-item-buprenorphine-with-naloxone-sublingual-film

INDUCTION

- DAY 1: Maximum of 4-8 mg SL film.
  - Start at 2-4 mg & observe patient for 2 hours and then give 2-4 mg.
- DAY 2: Titrate to effective dose
- DAY 3: continue dose used on day 2 if dose sufficiently suppressed cravings and withdrawals

http://www.uofapain.med.ualberta.ca/en/ForHealthProfessionals/OpioidConversionGuide.aspx

MONITORING

- Important of drug testing and frequency
- High rates of clinically false negatives with UDS/ Immunoassay compared to confirmed methods
- Monitor for hepatitis-Liver toxicity, precipitated withdrawals, confusion, constipation, and headache

http://www.asam.org/docs/default-source/public-policy-statements/drug-testing-a-white-paper-by-asam.pdf

MONITORING: false positives

AMPHETAMINES	BARBITURATES	METHADONE	PHENCYCLIDINE (PCP)
Amantadine (Symmetrel) (Parkinson's EQ)	Ibuprofen, Naproxen (Anti-inflammatories)	Chlorpromazine (Thorazine) (Antipsychotic)	Dextromethorphan (Dextrotrim) (ADHD, Stimulant)
Bupropion (Wellbutrin, Zyban) (Antidepressant, Smoking cessation)	Phenytoin (Dilantin) (Seizures)	Clomipramine (Anafranil) (Antidepressant)	Doxylamine/Diphenhydramine (Unisom) (Insomnia)
Chloroquine (Aralen) (Anti-malarial)	Primidone (Mysoline) (Seizures)	Diphenhydramine (Benadryl) (Antihistamine)	Diphenhydramine (Benadryl) (Antihistamine)
Chlorpromazine (Thorazine) (Antipsychotic)	BENZODIAZEPINES	Doxylamine (Unisom) (Insomnia)	Doxylamine (Unisom) (Insomnia)
Desipramine (Norpramine) (Antidepressant)	Clozapinozin (Diazpam) (Anxiety)	Ibuprofen (Advil) (Anti-inflammatory)	Ibuprofen (Advil) (Anti-inflammatory)
Dextromethamphetamine (Desoxtrim) (ADHD, Stimulant)	Sertraline (Zoloft) (Antidepressant)	Quetiapine (Seroquel) (Antipsychotic)	imipramine (Tofranil) (TCA antidepressant)
Ephedrine (Ephedra, Ma Huang) (Stimulant)	CANNABINOIDS	Thioridazine (Mellaril) (Antipsychotic)	Ketamine (General anesthetic)
Labetalol (Trandate) (Hypertension)	Dronabinol (Marinol) (Nausea, Appetite stimulant)	Verapamil (HTN, Anti-arrhythmic)	Meperidine (Demerol) (Pain)
Mexiletine (Anti-arrhythmic)	Efavirenz (Sustiva) (HIV)	OPIATES / OPIOIDS	Tramadol (Ultram) (Pain)
Procainamide (Anti-arrhythmic)	Hemp seed oil, Cannabis seed, Hemp oil, Hemp food	Dextromethorphan (Delsym, Robitussin) (Anti-tussive)	Venlafaxine (Effexor) (SNRI Antidepressant)
Phentermine (Adipex, Supretrex) (Diuretic)	NSAIDs (ibuprofen, naproxen, ketoprofen, piroxicam, etc)	Diphenhydramine (Benadryl) (Antihistamine)	LSD
Promethazine (Phenergan) (Nausea)	Pantoprazole (Protonix) (GERD, Peptic ulcer dz)	Fluoroquinolones (Levaquin, Avelox, Cipro, Floxin)	Amitriptyline (Elavil) (TCA antidepressant)
Propranolol (Inderal) (HTN, Migraines, Anti-arrhythmic, Essential tremor, Stage Fright)	Promethazine (Phenergan) (Nausea)	Poppy seeds and oil (Yummy bagels and bread)	Dicyclomine (Bentyl) (Anticholinergic for IBS)
Pseudoephedrine (Sudafed) (Nasal decongestant)	COCAINE	Quinine (Anti-malarial)	Ergotamine (Migraines)
Ranitidine (Zantac) (GERD, Peptic ulcer)	Amoxicillin (Amoxil) (Antibiotic)	Rifampin (Tuberculosis)	Promethazine (Phenergan) (Nausea/Vomiting)
Selegeline (Zelapar, Eldepryl) (Parkinson's Disease)	Coca leaf teas	OXYCODONE	Sumatriptan (Imitrex) (Migraine)
Trazodone (Desyrel) (Antidepressant, Insomnia, Migraines)	Tonic water	Hydrocodone, Oxymorphone Hydromorphone, Codeine,	
Wellbutrin (Antidepressant)			

http://thepainsi ns/

MAINTENANCE

- Long-term maintenance prescribing of Buprenorphine is aimed at:
- Reducing the intensity, frequency, and length of relapse to use of illicit opioids.
- Promoting psychosocial adjustment and limiting overdose risk, criminal activity, and HIV/Hepatitis infection.

http://findings.org.uk/PHP/dl.php?file=Veilleux_JC_1.txt

Withdrawal

- Can happen via 2 mechanisms:

1. Spontaneous Withdrawal
1. Precipitated Withdrawal

http://www.buppractice.com/withdrawalversusprecipitatedwithdrawal

Discontinuation

. *Tapering down:*

. Educate about risk for overdose deaths due to low tolerance.

. Naloxone for emergency purposes.

. Detox in inpatient setting vs outpatient.

The Maudsley Prescribing Guidelines in Psychiatry, 12th Edition. David Taylor, Carol Paton, Shitij Kapur. 760 pages. June 2015, Wiley-Blackwell

Discontinuation

DAILY BUP DOSE	REDUCTION RATE
above 16 mg	4 mg every 1-2 weeks
8-16 mg	2-4 mg every 1-2 weeks
2-8 mg	2 mg per week or fortnight
below 2 mg	reduce by 0.4-0.8 mg per week

The Maudsley Prescribing Guidelines in Psychiatry, 12th Edition. David Taylor, Carol Paton, Shitij Kapur. 760 pages. June 2015, Wiley-Blackwell

Discontinuation

-Prepare the patient for possible feelings of *less energy, lower appetite, irritability, difficulty sleeping*, etc.

-*Slow down* or *stop* the dose reductions if: - patient has opioid cravings, mild withdrawal symptoms, feels unstable emotionally

The Maudsley Prescribing Guidelines in Psychiatry, 12th Edition. David Taylor, Carol Paton, Shitij Kapur. 760 pages. June 2015, Wiley-Blackwell

Bup vs Methadone: Studies

Johnson et al. (1992) n=162
BUP 8 mg vs. METH 20 mg vs. METH 60 mg

Strain et al. (1994) n=164
BUP 8 mg vs. METH 50 mg for 26 weeks

Ling et al. (1996) n=225
BUP 8 mg vs. METH 30 mg vs. METH 80 mg for 52 weeks

Mattick et al. (2014) Cochrane Database of Systematic Reviews.

(slide courtesy of Herbert D. Kleber, M.D., Professor of Psychiatry, Columbia University College of Physicians & Surgeons)

Bup vs Methadone: Studies

Primary outcome measures in most studies:

- Treatment retention.
- Decrease in frequency and dose of illicit opioid use.
- Negative urine drug screens.
- Decrease in high-risk behaviors.

Bup vs Methadone: Studies

-**Buprenorphine > placebo** in retention of participants at all doses examined. (**high quality** of evidence).

-16 mg or higher doses of buprenorphine > placebo** in suppressing illicit opioid use measured by urinalysis (**moderate quality** of evidence).

Bup vs Methadone: Studies

- Objective evidence for **Low-dose, and medium-dose buprenorphine is not better than placebo (moderate quality** of evidence).

- Methadone > Bup in participant retention(**high quality of evidence).**

Bup vs Methadone: Studies

For those retained in treatment:

- **Methadone = Bup** in suppression of opioid use as measured by urinalysis (**moderate quality** of evidence).

- **Low-dose Methadone (≤ 40 mg) > low dose Bup** (2-6 mg)to retain participants.

Bup vs Methadone: Studies

- However, **medium-dose buprenorphine (7 - 15 mg) = medium-dose methadone (40 - 85 mg) in retention, in suppression of illicit opioid, and in self report of illicit opioid use.

- **High-dose buprenorphine (≥ 16 mg) = high-dose methadone (≥ 85 mg) in retention or suppression of self-reported heroin use.

Questions?

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