

Medication Assisted Treatments

A variety of treatment approaches

Definitions

Medication Assisted Treatments (MAT):

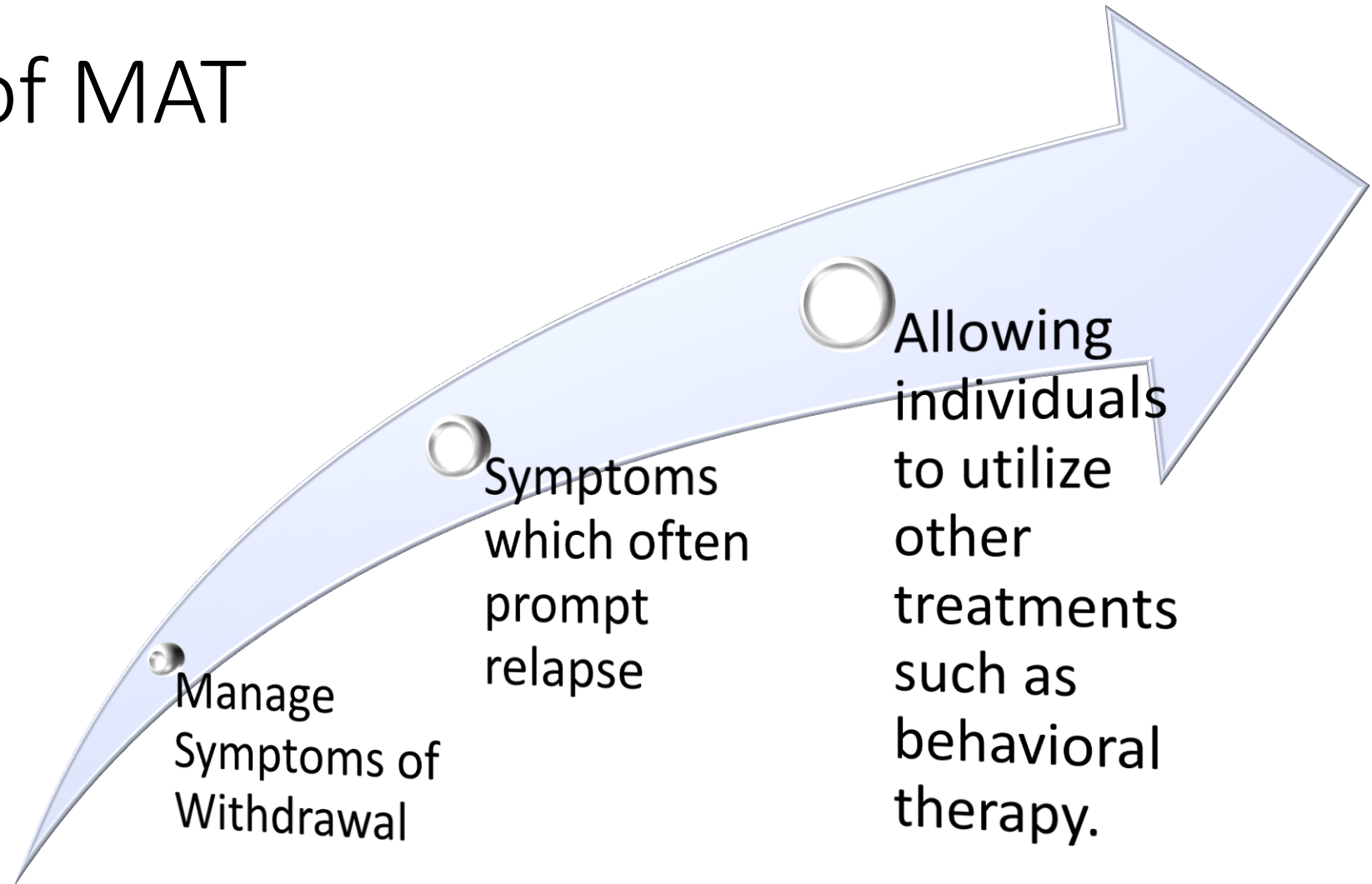
“The use of FDA-approved medications in combination with evidence based behavioral therapies to provide a whole-patient approach to treating substance use disorders (SUDs).”
CMS bulletin in MAT.

Detoxification and Maintenance Phases:

Pharmacological interventions are typically initiated at two different phases of the dependence cycle.

- **Detoxification** can be viewed as an *initial and immediate* goal during which medications are administered to alleviate unpleasant withdrawal symptoms.
- Some medication used in detoxification are also used in maintenance.
- **Maintenance** on pharmacological agents can be viewed as a *longer-term* strategy used to help avoid relapsing to abused drug.
- The distinction between a detoxification and maintenance medication are therefore not always clear.

Benefits of MAT



Also lowering risk of HIV or Hep C

Three Major Strategies

01

Agonist or Substitution Therapy: Examples- methadone or nicotine patch.

02

Antagonist Therapy: Example- naltrexone.

03

Punishment Therapy: Example- Antabuse.

Alcohol

- Acute Alcohol Withdrawal Syndrome: tremors, tachycardia, hypertension, profuse sweating, insomnia, hallucinations and seizures.
 - Often requires inpatient medical management.
- Two goals of acute detoxification:
 - Reduce autonomic hyperactivity
 - Prevent development of seizures

Alcohol-Benzodiazepines and acute EtOH withdrawal



- High cross-tolerance between alcohol and benzodiazepines.
- Benzodiazepines have a longer $t_{1/2}$ than EtOH, and withdrawal can be done safely.
- The neuroinhibitory actions of benzodiazepines potentiate the action of GABA which significantly decreases the risk of seizures.
- Increased autonomic arousal or stress response which comes with EtOH withdrawal is diminished with increased GABAergic transmission.
- Rapid acting benzos are problematic (such as alprazolam) due to abuse potential.

The FDA approved drugs for EtOH abuse and dependence.

- Disulfiram (Antabuse®)
- Naltrexone (Vivitrol®-tablet, Revia®-IM injection)
- Acamprosate (calcium acetylhomotaurinate or Campral®)
- All used for Maintenance treatment
 - Typically used for weeks or months
 - Indefinite maintenance is unusual.

Disulfiram (Antabuse®)

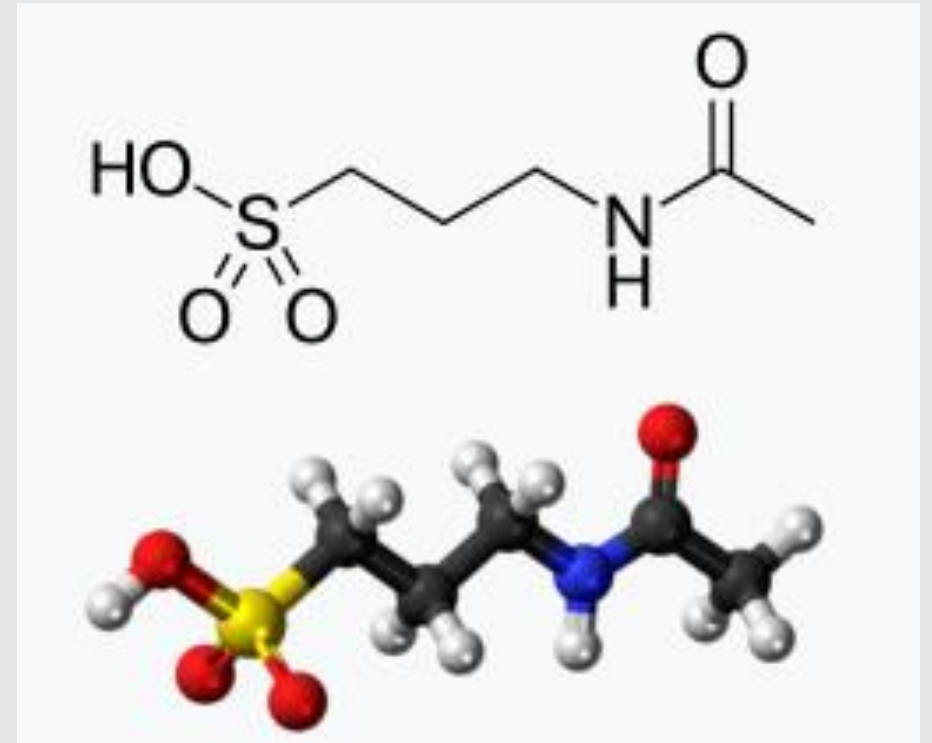
- Unpleasant reaction
 - Flushing, accelerated pulse, throbbing headache, nausea and vomiting
- Increased acetaldehyde in the body due to inhibition of aldehyde dehydrogenase by disulfiram.
- Not shown to be effective in achieving abstinence or delaying relapse.
 - Most individuals simply do not take the medication.

Naltrexone (Vivtrol[®],
Revia[®])

- Initially developed for opioid dependence.
- Found to reduce the days of EtOH drinking per week, reduced rate of relapse, reduced craving.
- Thought that the blockade of opioid receptors, prevents the release of opioid induced dopamine release, which in turn blocks reinforcing effects of EtOH.

Acomprosate (Campral®)

- Action:
 - normalization of basal GABA concentrations, which are disrupted in EtOH dependent individuals.
 - Blocks glutamine increases observed during withdrawal.
- Mechanism of Action: bears structural resemblance to GABA. Opens the chloride ion channel in a novel way as it does not require GABA as a cofactor, making it less liable for dependence than benzodiazepines.
- Half Life: 20-33 hours
- Renally excreted
 - Contraindicated in severe kidney failure (renal failure), and dose reduction necessary for those with impaired kidneys.



Nicotine

- Withdrawal symptoms include: anxiety, depression, dysphoria, irritability, decreased concentration, insomnia, increased food intake and cigarette (nicotine) craving.
- Pharmacotherapies have been used primarily to attenuate withdrawal symptoms.
 - Nicotine replacement therapies
 - Bupropion (Zyban®)
 - Varenicline (Chantix®)

Nicotine Replacement Therapies

- Five FDA approved products:
 - Transdermal Patch
 - Nicotine Gum
 - Nicotine Nasal Spray
 - Nicotine Vapor Inhaler
 - Nicotine Lozenge
- Must not use other nicotine containing products at the same time.
 - Concerns about nicotine toxicity

Bupropion (Zyban[®])

- First non-nicotine pharmacotherapy for smoking cessation.
- Inhibition of dopamine and nor-epinephrine reuptake.
- Blockade of acetylcholine receptors.
- No absolute requirement for user to abstain from nicotine containing product use.
 - Theoretically should be beneficial together with nicotine replacement but studies show no advantage of bupropion addition to nicotine replacement treatment.

Varenicline (Chantix®)

- The latest FDA approved smoking cessation medication.
 - A partial nicotinic-receptor agonist.
 - Even at large doses, it doesn't produce the full response of nicotine.
- Reduce withdrawal and cravings.
- Found to be more effective than placebo or bupropion.

Stack, N.M. "Smoking Cessation: An Overview of Treatment Options with a Focus on Varenicline". *Pharmacotherapy* 27 (2007), 1550-57.



Opioids- approach to withdrawal

Historically: belladonna was used (strong anticholinergic drugs) to produce delirium, lasting for several days, at which time the dependent person would emerge cured of dependence without remembering dreadful withdrawal.

Newer: “Rapid opioid detoxification”, where dependent patients are anesthetized, given opioid antagonists when unconscious, so withdrawal occurs while unconscious. After 24 hours, patient released to counseling and continued opioid antagonist treatment.

FDA Approved Opioid Dependence Treatments

With minimum 8 hours of training for providers. The Drug Addiction Treatment Act of 2000 enabled physicians to provide office based treatment for opioid addiction.

- **Methadone:** long duration of action, developed in WWII as an analgesic. Reduces cravings by activating opioid receptors in the brain. CII.
- **Buprenorphine:** partial opioid agonist, with a large margin of safety, low overdose potential. Reduces or eliminates opioid withdrawal symptoms, including cravings without producing the euphoria or dangerous side effects of opioids such as heroin. Low abuse potential, high availability for *office use*. High cost and possibly not effective for patients requiring high methadone doses. CIII.
- **Naltrexone:** long acting opioid antagonist for treating opioid dependence. Naltrexone is used for preventing relapse in adults following complete detoxification from opioids.
 - **Naloxone** is a short acting opioid antagonist with greater affinity for brain opioid receptors than most opioid agonists, including heroin. Used for treating opioid overdose. Quickly reverses or blocks effects of other opioids, restores normal respiration.
- **Buprenorphine/Naloxone:** opioid agonist and antagonist. Not recommended for use during induction for long acting opioids or methadone. CIII.

Buprenorphine-partial agonist
Naltrexone-antagonist

- Buprenorphine is a partial agonist, thus receptor activation increases as the dose increase until it reaches a PLATEAU.
 - When displacing other opioids, it can cause withdrawal symptoms.
 - Withdrawal less severe after discontinuation.
- Full opioid agonists, such as methadone and heroin, continue to create increased receptor activation as dose increase, never reaching a plateau.
- Antagonists will not produce receptor activation regardless of dosing.

Because of patient activation, chronic opioid users are less likely to abuse buprenorphine.

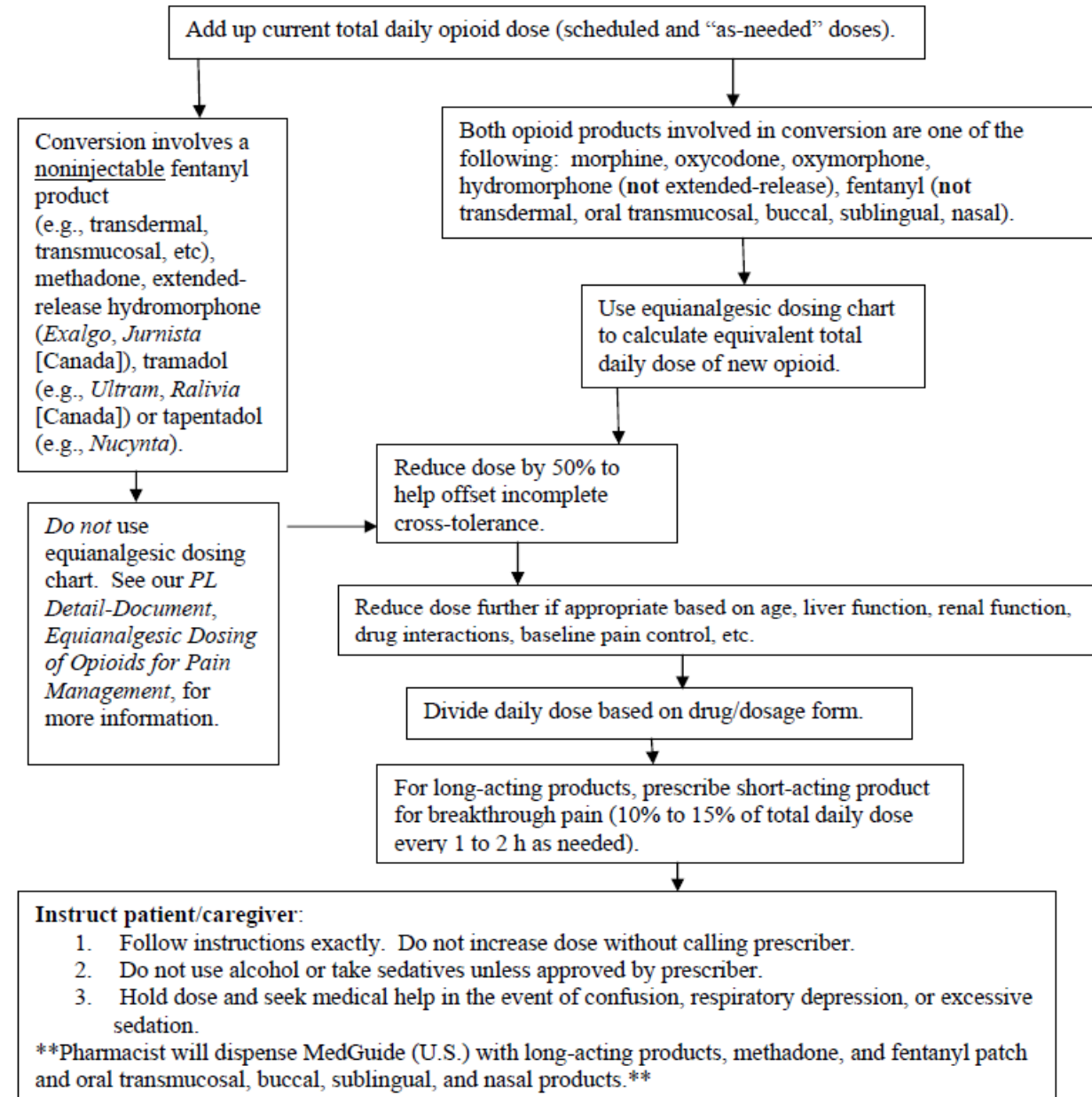
Equal analgesic Conversion

- [Equal Analgesic Conversion Table\(s\)](#)
- [Methadone Conversion](#)
 - Must exercise extreme caution
 - Experienced clinicians recommended- analgesic duration shorter than the half life; toxicity builds up easily.
- [Fentanyl Conversion](#)
 - Must exercise extreme caution

M.K. is a 78-year-old female with severe rheumatoid arthritis and renal insufficiency (CrCl 20 mL/min). She has been taking *OxyContin* 120 mg twice daily for the past six months, methotrexate, and carbamazepine. Her new insurance plan will not cover *OxyContin*, but it will cover *MS Contin*. To how much *MS Contin* should she be switched?

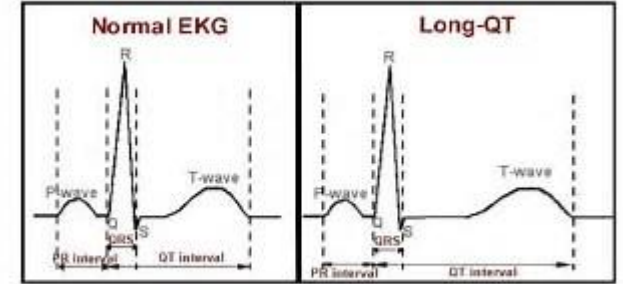
Opioid Conversion Algorithm

Equianalgesic doses are approximate, and should be used only as a guideline. Dosing must be titrated to individual response. Response may vary depending on tolerance, age, renal and hepatic function, other conditions, drug interactions, and genetics. Also consider pain control at time of switch. Below is a stepwise guide for estimating opioid dose conversions.¹⁻⁴



Methadone

- Indications
 - Detoxification of opioid dependence
 - Pain management, for which alternative treatment options are inadequate.
- Initial dosage:
 - 20 to 30 mg (as a single dose) when there are no signs of sedation or intoxication and patients shows symptoms of withdrawal. Lower doses should be considered in patients with low tolerance at initiation (eg, absence of opioids for at least 5 days); an additional 5 to 10 mg may be provided if withdrawal symptoms have not been suppressed or if symptoms reappear after 2 to 4 hours; total daily dose on the first day should not exceed 40 mg.
- Dose adjustment: **Do not increase dose without waiting for steady-state to be achieved. Levels will accumulate over the first few days; deaths have occurred in early treatment due to cumulative effects.**
- Maintenance dosage:
 - 80 to 120 mg/day (titration should occur cautiously). Titrate to a dosage which prevents opioid withdrawal symptoms for 24 hours, prevents craving, attenuates euphoric effect of self-administered opioids, and tolerance to sedative effects of methadone.



Methadone

 [Print this section](#)

Diskets 40 mg tablets for suspension, **Methadose** 40 mg tablets for suspension, and **Methadose** 10 mg/mL concentrated oral liquid are for detoxification and maintenance only. Use with caution.

Methadose 10 mg/mL concentrated oral liquid may contain sucrose.

Gluten Free Dye Free Alcohol Free

Click on a desired **product name** or **strength** below for more product details

Rx/OTC/ Schedule	Product Name View Selected	Labeler Name	Generic Name	Route	Doseform	Strengths View Selected	Market Status
c-ii	<input type="checkbox"/> Dolophine	WEST-WARD	Methadone HCl	Oral	Tablet	<input type="checkbox"/> 5 MG	Active
						<input type="checkbox"/> 10 MG	Active
c-ii	<input type="checkbox"/> Methadone HCl	Various	Methadone HCl	Oral	Tablet	<input type="checkbox"/> 5 MG	Active
						<input type="checkbox"/> 10 MG	Active
c-ii	<input type="checkbox"/> Methadone HCl	Various	Methadone HCl	Oral	Tablet Soluble	<input type="checkbox"/> 40 MG	Active
c-ii	<input type="checkbox"/> Methadone HCl	Various	Methadone HCl	Oral	Solution	<input type="checkbox"/> 5 MG/5ML	Active
						<input type="checkbox"/> 10 MG/5ML	Active
c-ii	<input type="checkbox"/> Methadone HCl	Various	Methadone HCl	Oral	Concentrate	<input type="checkbox"/> 10 MG/ML	Active
c-ii	<input type="checkbox"/> Methadone HCl	Various	Methadone HCl	Injection	Solution	<input type="checkbox"/> 10 MG/ML	Active
c-ii	<input type="checkbox"/> Methadone HCl Intenso!	WEST-WARD	Methadone HCl	Oral	Concentrate	<input type="checkbox"/> 10 MG/ML	Active
c-ii	<input type="checkbox"/> Methadose	AMERICAN HEALTH PACKAGING	Methadone HCl	Oral	Tablet Soluble	<input type="checkbox"/> 40 MG	Active
c-ii	<input type="checkbox"/> Methadose	MALLINCKRODT PHARM	Methadone HCl	Oral	Tablet Soluble	<input type="checkbox"/> 40 MG	Active
c-ii	<input type="checkbox"/> Methadose	MALLINCKRODT PHARM	Methadone HCl	Oral	Concentrate	<input type="checkbox"/> 10 MG/ML	Active
c-ii	<input type="checkbox"/> Methadose Sugar-Free	MALLINCKRODT PHARM	Methadone HCl	Oral	Concentrate	<input type="checkbox"/> 10 MG/ML	Active

Buprenorphine Dosage Forms (CIII)

- **Belbuca**®
 - Buccal Film is mainly for pain management. Breakthrough pain for those on round the clock, long term opioid treatment.
 - Peak effect 2.5-3 hrs.
- **Buprenex**®
 - IM and IV injection for quick onset with one hour peak effect and 6 hour duration of action.
- **Generic Buprenorphine HCl**
 - Sublingual tablet and injection.
 - SL tablet time to peak is 30 minutes to 1 hour.
 - SL tablet used for opioid dependence treatment (vs film for breakthrough pain)
- **Butrans**®
 - Weekly patch, used for pain requiring round the clock long term opioid treatment.
 - Time to peak is approximately 3 days
- **Probuphine**®
 - Implantable buprenorphine for opioid dependence for those stable on low to moderate doses of trans mucosal product fo 3 months or longer.
 - [Insertion](#)
 - [Med-Guide](#)

BUPRENORPHINE TRANSDERMAL

Product List

Butrans 5 mcg/hour patch contains a total of buprenorphine 5 mg. **Butrans** 7.5 mcg/hour patch contains a total of buprenorphine 7.5 mg. **Butrans** 10 mcg/hour patch contains a total of buprenorphine 10 mg. **Butrans** 15 mcg/hour patch contains a total of buprenorphine 15 mg. **Butrans** 20 mcg/hour patch contains a total of buprenorphine 20 mg.

Belbuca buccal films may contain saccharin.

Gluten Free Dye Free Alcohol Free


Click on a desired **product name** or **strength** below for more product details

Rx/OTC/ Schedule	Product Name <input type="button" value="View Selected"/>	Labeler Name	Route	Doseform		Generic Name/Strengths <input type="button" value="View Selected"/>		Market Status
						Buprenorphine	BUPRENORPHINE HYDROCHLORIDE	
c-iii	<input type="checkbox"/> Belbuca	BIODELIVERY SCIENCES	Buccal	Film	<input type="checkbox"/>		75 MCG	Active
					<input type="checkbox"/>		150 MCG	Active
					<input type="checkbox"/>		300 MCG	Active
					<input type="checkbox"/>		450 MCG	Active
					<input type="checkbox"/>		600 MCG	Active
					<input type="checkbox"/>		750 MCG	Active
					<input type="checkbox"/>		900 MCG	Active
c-iii	<input type="checkbox"/> Buprenex	INDIVIOR INC	Injection	Solution	<input type="checkbox"/>		0.3 MG/ML	Active
c-iii	<input type="checkbox"/> Buprenorphine HCl	Various	Sublingual	Tablet Sublingual	<input type="checkbox"/>		2 MG	Active
					<input type="checkbox"/>		8 MG	Active
c-iii	<input type="checkbox"/> Buprenorphine HCl	Various	Injection	Solution	<input type="checkbox"/>		0.3 MG/ML	Active
c-iii	<input type="checkbox"/> Butrans	PURDUE PHARMA LP	Transdermal	Patch Weekly	<input type="checkbox"/>	5 MCG/HR		Active
					<input type="checkbox"/>	7.5 MCG/HR		Active
					<input type="checkbox"/>	10 MCG/HR		Active
					<input type="checkbox"/>	15 MCG/HR		Active
					<input type="checkbox"/>	20 MCG/HR		Active
c-iii	<input type="checkbox"/> Probuphine Implant Kit	BRAEBURN PHARMACEUTICAL	Subcutaneous	Implant	<input type="checkbox"/>		74.2 MG	Active

Refer to the general discussion in the [Opioid Agonist-Antagonist Analgesics](#) introduction.

Naltrexone (Revia[®], Vivtrol[®])

- Opioid antagonist with highest affinity for mu receptor.
- Has little or no opioid agonist activity.
- Naltrexone blocks the effects of opioids by competitively binding opioid receptors.
 - This makes blockade potentially surmountable with opioid use, which can cause other non-opioid receptor mediated symptoms such as histamine release.

Rx/OTC/ Schedule	Product Name 	Labeler Name	Route	Doseform	Generic Name/Strengths		Market Status
	View Selected				View Selected		
	Naltrexone HCl	Various	Oral	Tablet	<input type="checkbox"/>	Naltrexone NALTREXONE HYDROCHLORIDE	Active
Rx	<input type="checkbox"/> Naltrexone HCl	Various	Oral	Tablet	<input type="checkbox"/>	50 MG	Active
Rx	<input type="checkbox"/> ReVia	TEVA/WOMENS HEALTH	Oral	Tablet	<input type="checkbox"/>	50 MG	Discontinued
Rx	<input type="checkbox"/> Vivtrol	ALKERMES	Intramuscular	Suspension Reconstituted	<input type="checkbox"/>	380 MG	Active

Naltrexone- Warnings

- **Contraindicated in persons who fail to pass naloxone challenge or positive urine screen for opioids.**
 - Especially when using naloxone for EtOH treatment (can overlook concurrent, undisclosed, opioid use)
- **Must be opioid free for minimum of 7-10 days for patients previously dependent on short acting opioids.**
- **Must be opioid free (including tramadol) before starting to use naltrexone.**
- **There is no completely reliable way to determine if patient has had adequate opioid free period (even if urine tox. screen looks OK).**
 - Be prepared to manage withdrawal symptomatically always.
- **Patients on naltrexone involved in an accident and requiring pain relief pose a special challenge.**
 - Non-opioid pain management
 - Local pain blockade
 - High dose hydromorphone (Dilaudid®) is used with extreme caution (and only in hospital)

Naltrexone- Warnings

- Patients at end of dosing interval, discontinued treatment, or missed dose
 - Have very sensitive opioid receptors
 - Dangerous if exposed to even small doses
 - Dangerous if exposed to high doses as used before treatment (or using during treatment and naltrexone dose wears off)
- Naltrexone blocks the effects of exogenous opioids for approximately 28 days after administration.
- Discontinue extended release IM naltrexone at least 30 days prior to surgery.

Naltrexone-misc. information

- Monitoring:
 - Opioid withdrawal
 - Injection site reactions
 - Hepatotoxicity
 - Depression and/or suicidal thinking
- Single doses of up to 784mg were administered to 5 healthy subjects. There were no serious or severe adverse reactions.
- May causes cross-reactivity with some opioid immunoassay methods.

Patient Counseling Tool

VIVITROL® (naltrexone for extended-release injectable suspension)

Risk of sudden opioid withdrawal during initiation and re-initiation of VIVITROL

Using any type of opioid including street drugs, prescription pain medicines, cough, cold or diarrhea medicines that contain opioids, or opioid dependence treatments buprenorphine or methadone, in the 7 to 14 days before starting VIVITROL may cause severe and potentially dangerous sudden opioid withdrawal.

Risk of opioid overdose

Patients may be more sensitive to the effects of lower amounts of opioids:

- After stopping opioids (detoxification)
- When the next VIVITROL dose is due
- If a dose of VIVITROL is missed
- After VIVITROL treatment stops

Patients should tell their family and people close to them about the increased sensitivity to opioids and the risk of overdose even when using lower doses of opioids or amounts that they used before treatment. Using large amounts of opioids, such as prescription pain pills or heroin, to overcome effects of VIVITROL can lead to serious injury, coma, and death.

Risk of severe reactions at the injection site

Remind patients of these possible symptoms at the injection site:

- Intense pain
- The area feels hard
- Large areas of swelling
- Lumps
- Blisters
- Open wound
- Dark scab

Some of these injection site reactions have required surgery. Tell your patients to contact a healthcare provider if they have any reactions at the injection site.

Risk of liver injury, including liver damage or hepatitis

Remind patients of the possible symptoms of liver damage or hepatitis.

- Stomach area pain lasting more than a few days
- Dark urine
- Yellowing of the whites of eyes
- Tiredness

Patients may not feel the therapeutic effects of opioid-containing medicines for pain, cough or cold, or diarrhea while taking VIVITROL.

Patients should carry written information with them at all times to alert healthcare providers that they are taking VIVITROL, so they can be treated properly in an emergency.

A Patient Wallet Card or Medical Alert Bracelet can be ordered from: 1-800-848-4876, Option #1.

PLEASE SEE PRESCRIBING INFORMATION AND MEDICATION GUIDE.



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www.vivitrol.com

Vivitrol®
(naltrexone for extended-release injectable suspension)

Buprenorphine- Naltrexone (Suboxone®)®®

Bunavail buccal film may contain saccharin. **Suboxone** sublingual film may contain maltitol. **Zubsolv** sublingual tablets may contain mannitol and sucralose.

Gluten Free Dye Free Alcohol Free

Click on a desired **product name** or **strength** below for more product details

Rx/OTC/ Schedule	Product Name View Selected	Labeler Name	Route	Doseform	Generic Name/Strengths View Selected		Market Status
					BUPRENORPHINE HYDROCHLORIDE	NALOXONE HYDROCHLORIDE DIHYDRATE	
c-iii	<input type="checkbox"/> Bunavail	BIODELIVERY SCIENCES	Buccal	Film	<input type="checkbox"/> 2.1 MG	0.3 MG	Active
					<input type="checkbox"/> 4.2 MG	0.7 MG	Active
					<input type="checkbox"/> 6.3 MG	1 MG	Active
c-iii	<input type="checkbox"/> Buprenorphine HCl-Naloxone HCl	Various	Sublingual	Tablet Sublingual	<input type="checkbox"/> 2 MG	0.5 MG	Active
					<input type="checkbox"/> 8 MG	2 MG	Active
c-iii	<input type="checkbox"/> Suboxone	INDIVIOR INC	Sublingual	Film	<input type="checkbox"/> 2 MG	0.5 MG	Active
					<input type="checkbox"/> 4 MG	1 MG	Active
					<input type="checkbox"/> 8 MG	2 MG	Active
					<input type="checkbox"/> 12 MG	3 MG	Active
c-iii	<input type="checkbox"/> Zubsolv	OREXO US	Sublingual	Tablet Sublingual	<input type="checkbox"/> 0.7 MG	0.18 MG	Active
					<input type="checkbox"/> 1.4 MG	0.36 MG	Active
					<input type="checkbox"/> 2.9 MG	0.71 MG	Active
					<input type="checkbox"/> 5.7 MG	1.4 MG	Active
					<input type="checkbox"/> 8.6 MG	2.1 MG	Active
					<input type="checkbox"/> 11.4 MG	2.9 MG	Active

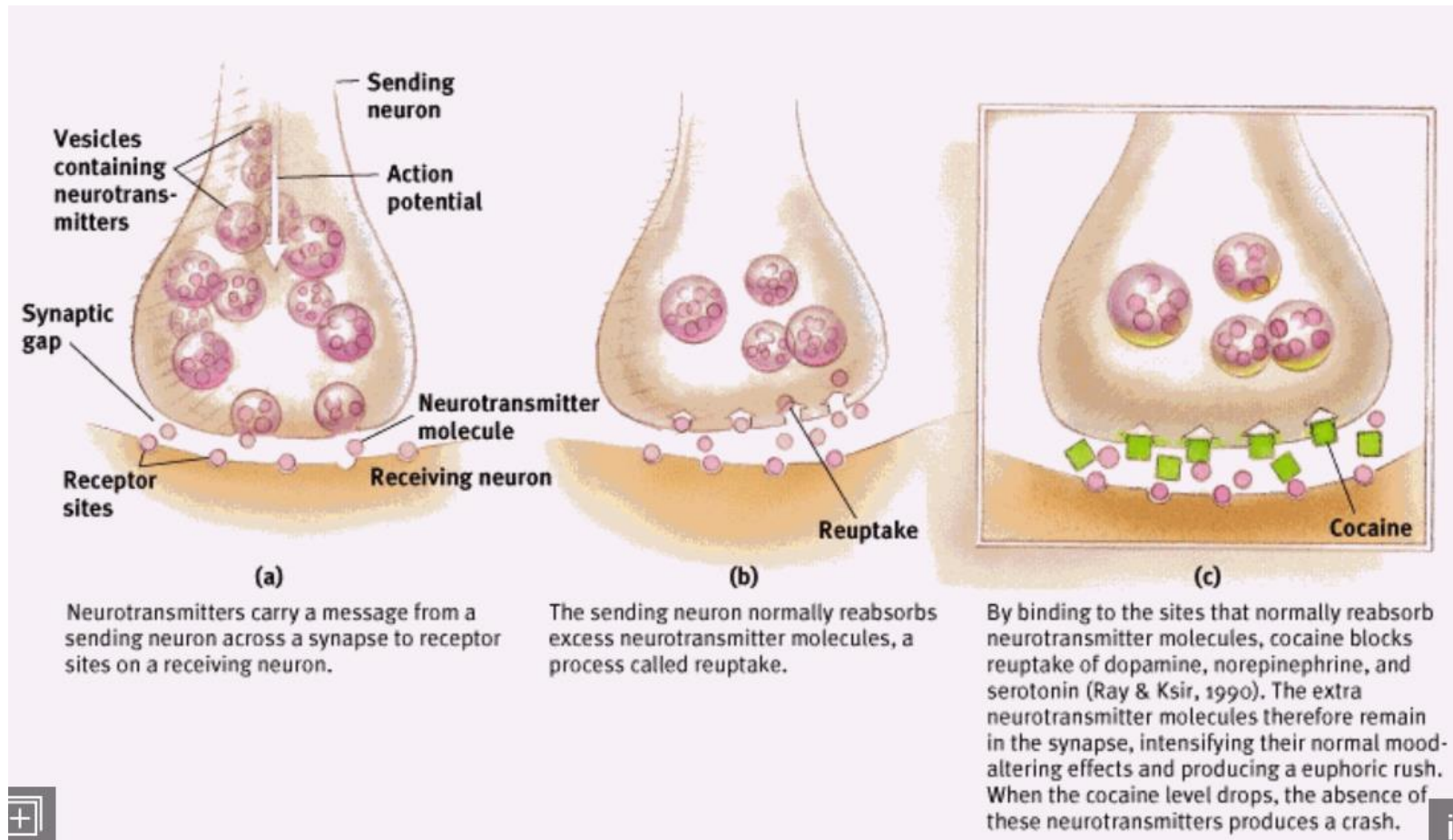
Cautions and Monitoring (Suboxone®)

- Buprenorphine/naloxone is not recommended for use during the induction period for long-acting opioids or methadone; initial treatment should begin using buprenorphine monotherapy under supervision.
- Patients should be switched to the combination product for maintenance and unsupervised therapy.
- Initiate treatment with sublingual buprenorphine/naloxone or buprenorphine monotherapy during the induction period for short-acting opioids or heroin;
 - initiate treatment when signs of moderate opioid withdrawal appear and not less than 6 hours after last opioid use.
 - Titrate to adequate maintenance dose as rapidly as possible based on control of acute withdrawal symptoms.

Cocaine Detoxification Treatment

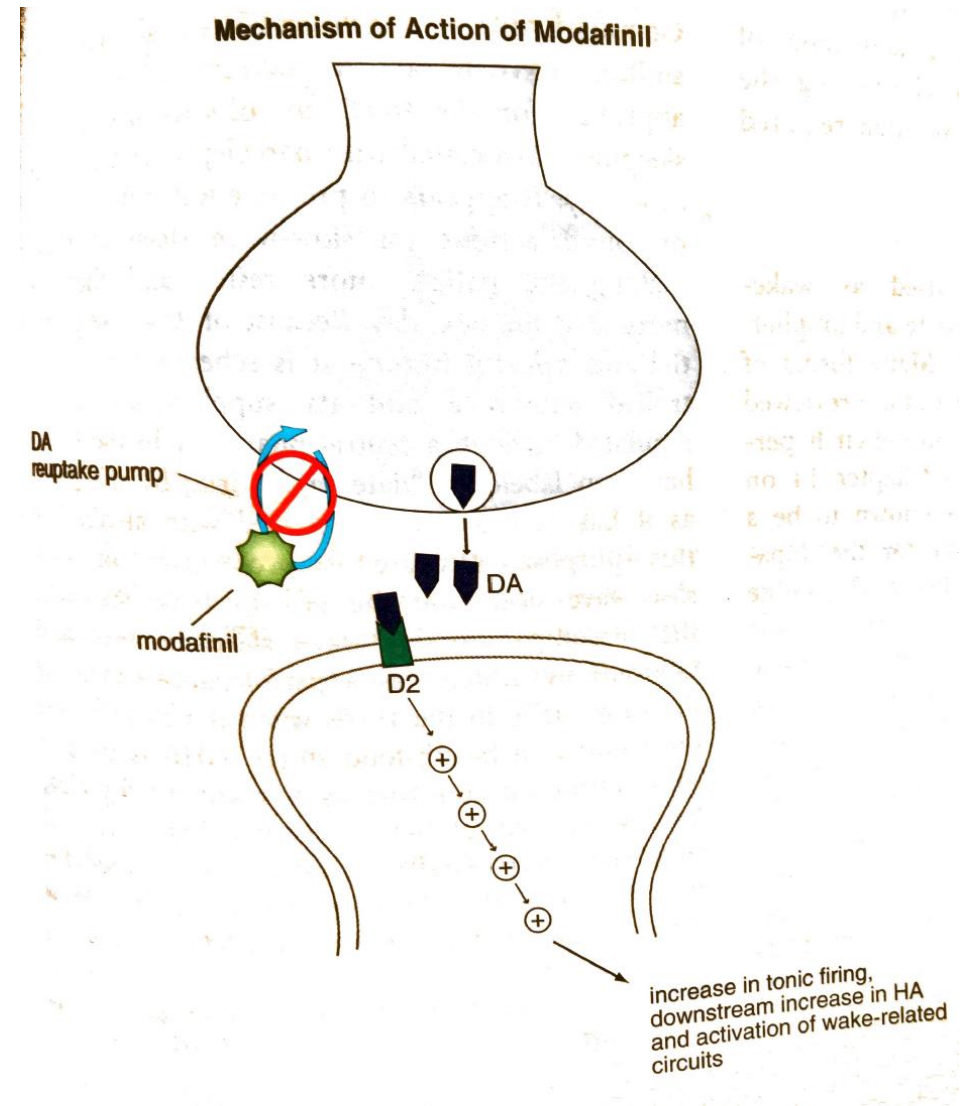
- Withdrawal doesn't seem to be a major feature of cocaine dependence.
- Some documented symptoms:
 - Depression
 - Nervousness
 - Dysphoria
 - Anhedonia
 - Fatigue
 - Irritability
 - Sleep and activity disturbances
 - Craving for cocaine

Monoaminergic activity of cocaine



Modafinil (Provigil®) for cocaine withdrawal treatment.

- Modafinil is known to bind to dopamine transporter (DAT).
- Increased synaptic DA leads to increased tonic firing and downstream release of neurotransmitters involving wakefulness: orexin and histamine.



Cannabis

Most consume infrequently, small proportion of users become dependent (1:11)

Withdrawal characteristics:

irritability

anxiety

sleep disruption

aches



The only effective treatment studied thus far: dronabinol (oral THC or Marinol®)

Substitution of a longer acting pharmacologically equivalent drug.

End MAT

- Thank You!