

Overview of Outpatient Management of Opiate Dependence: Safety and Efficacy of Buprenorphine and Methadone



S. Hughes Melton, MD, FAAFP
Sarah T. Melton, PharmD,BCPP,CGP,FASCP

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Objectives

At the completion of this presentation, the participant will be able to:

1. Explain the rationale and effectiveness of buprenorphine and methadone maintenance therapy in the outpatient treatment of opioid dependence.
2. Contrast the safety profiles of buprenorphine and methadone used in the treatment of opiate dependence.
3. Describe the components and role of nonpharmacological treatments for opioid dependence.
4. Apply clinical tools (e.g., treatment agreements, urine drug screens, pill counts, etc.) needed for an effective outpatient treatment program.



Introduction

- ❖ Estimated 2 million opioid-dependent persons in US in 2009
 - >600,000 involved in opioid maintenance treatment (OMT)
- ❖ Discrepancy between benefits of OMT documented by scientific research vs. public's perception of treatment
 - Perception that OMT is “just substituting one addicting drug for another”
- ❖ Methadone OMT is highly regulated and continues to contribute to stigmatization and barriers to treatment

Negative Attitudes Affect OMT

- ❖ Providers in other medical setting refuse to treat patients on OMT
- ❖ Patients are often told they must withdraw from OMT to receive treatment for other medical conditions
- ❖ Providers may withhold medication for symptomatic relief, causing unnecessary discomfort or pain
- ❖ Providers do not recognize addiction as a chronic disease

Goals of Pharmacotherapy of Opioid Dependence

- ❖ Prevention or reduction of withdrawal symptoms
- ❖ Prevention or reduction of opioid craving
- ❖ Prevention of relapse to use of addictive opioids
- ❖ Restoration to or toward normalcy of any physiologic function disrupted by chronic opioid use



Desirable Profile of Medications used in OMT

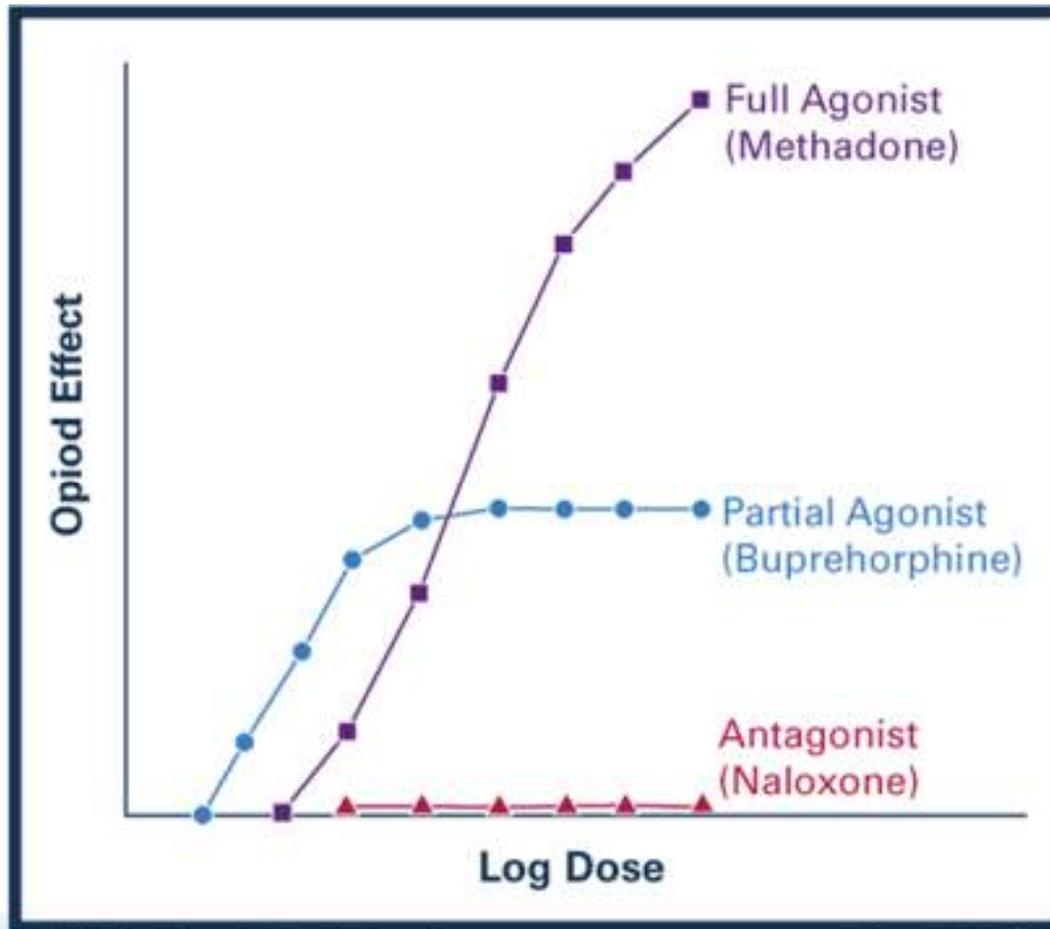
- ❖ Effective after oral administration
- ❖ Long biologic half-life (>24 hours)
- ❖ Minimal side effects with chronic administration
- ❖ Safe (lack true toxic or serious adverse effects)
- ❖ Efficacious for a substantial proportion of persons with opiate dependence

Medications for Opioid Addiction Treatment

- ❖ Methadone
- ❖ Buprenorphine-naloxone
- ❖ Naltrexone



Opioid Effects of Methadone, Buprenorphine, and Naltrexone



HIV Web Study (www.HIVwebstudy.org)

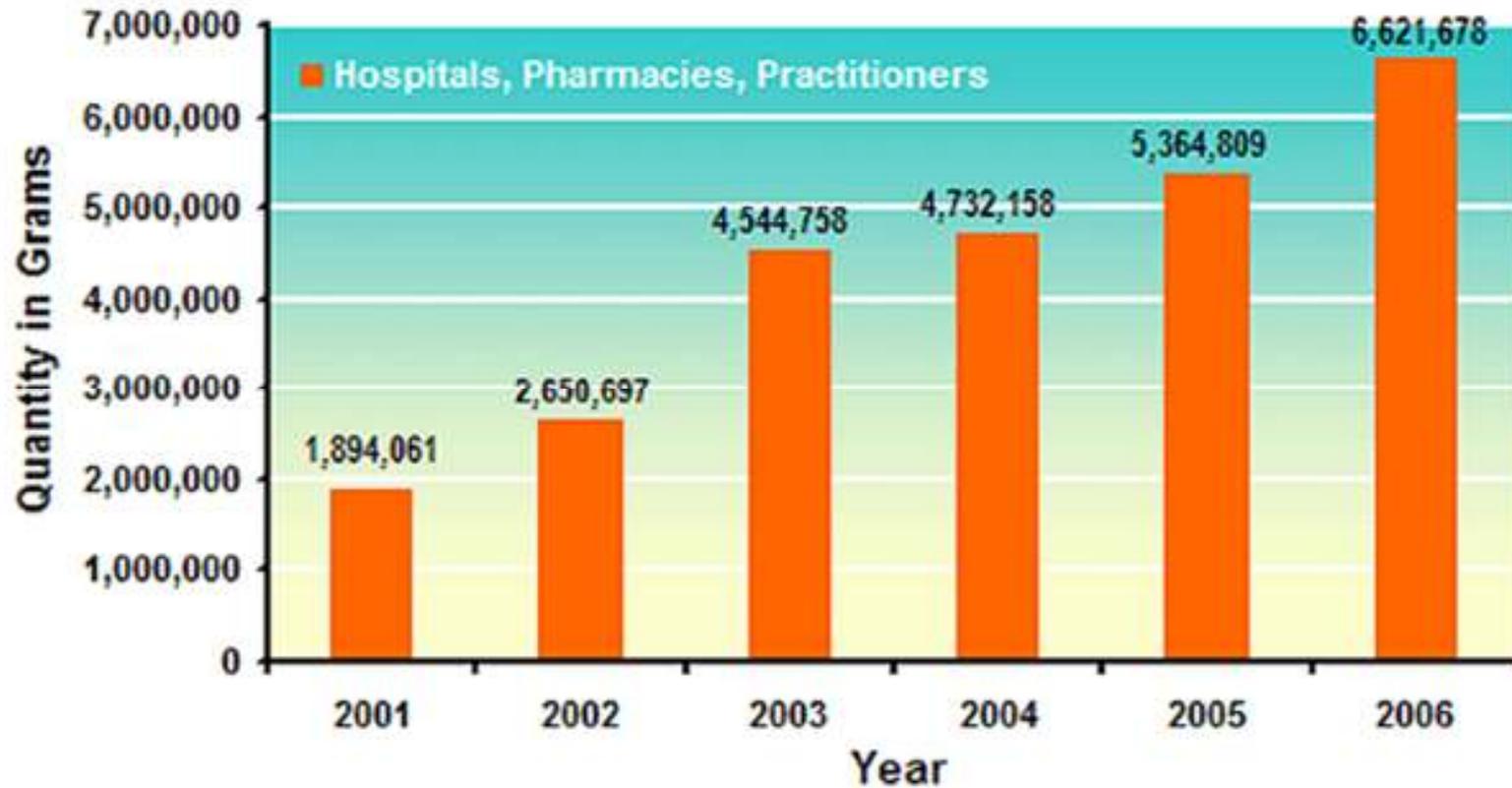
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Methadone: Background

- ❖ Most effective (??) and widely used treatment in the world for opiate addiction (Cochrane Collaboration, 2008)
- ❖ Approved by the FDA in 1972 for treatment of opiate addiction, CII schedule
- ❖ Over past 10 years, use of methadone has skyrocketed for treatment of chronic pain
- ❖ Availability:
 - Oral concentrate 10 mg/ml
 - Oral solution (5 and 10 mg/5 ml)
 - Tablet (5, 10, 40 mg)
 - Injectable (10 mg/ml)
 - Powder (50, 100 and 500 mg/bottle for compounding)



Increases in legitimate distribution of methadone, 2001-2006



Drug Enforcement Agency

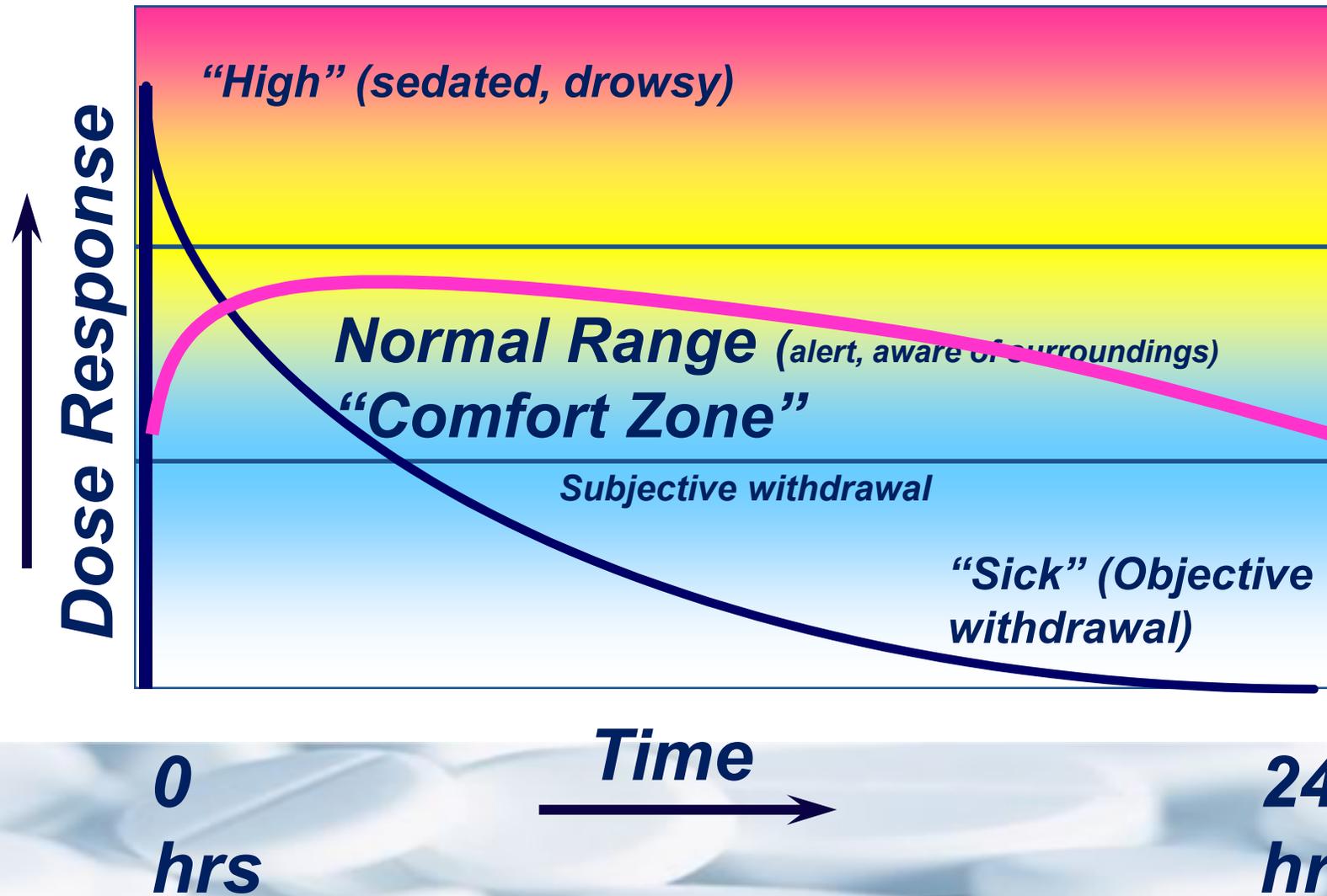
Methadone Pharmacology

- ❖ Synthetic opioid, 2 racemic enantiomers
 - Active l(R) enantiomer half-life of 36-48 hours
 - Inactive d(S) enantiomer half-life of 16 hours
- ❖ Systemic bioavailability >90% after oral administration
- ❖ Detectable in plasma in 30 minutes, peak levels in 2-4 hours
- ❖ Full μ -opioid agonist; N-methyl-D-aspartate (NMDA) receptor antagonist; inhibits monoamine reuptake
- ❖ Metabolized by CYP-450 systems, excreted in urine and feces

Increase in Methadone Overdose Deaths

- ❖ Most lethal drug in Virginia
- ❖ In US, most fatal poisoning was from patients filling prescriptions , not from OMT
 - Source and formulation could not be determined in 70% of cases
 - Tablet form implicated in 25% of reported cases
- ❖ 35% of methadone deaths characterized as resulting from an abuse episode
- ❖ 66% of methadone deaths involved use of multiple drugs (e.g., benzodiazepines, alcohol, antidepressants)

Rationale for Use: Methadone Simulated 24 Hr. Dose and Response at Steady-state in Tolerant Patient



Phases of Treatment with Methadone ODT

❖ Induction (most critical phase)

- Maximum first dose set at 30 mg by regulation
- Overdose mortality most likely to occur during first 10-14 days of treatment with high induction doses and use of concurrent sedatives
- Patients present to dosing window 24 hours after first dose are usually uncomfortable (withdrawal)
- If comfortable during first 4-12 hours after first dose, dosage is not increased
- Induction lasts until steady state (4-5 days)

Phases of Treatment with Methadone ODT

❖ Stabilization and Steady State

- Average half-life of 24-36 hours
- Significant portion of previous dose remains in tissue stores, so levels of methadone increase daily even without increase in dose
- Change doses only after 7 days, in 5-10 mg increments

Phases of Treatment with Methadone ODT

❖ Maintenance

- Begins once stable dose is obtained that eliminates craving and prevents withdrawal
- Most patients do well on dose range of 80-120 mg/day
- Most can maintain dose for years with no need to escalate dose

Phases of Treatment with Methadone ODT

❖ Duration of therapy

- For most patients, a chronic care approach is appropriate and supported by addiction experts
- Patients withdrawn from methadone too early often have poor prognosis
 - Relapse to injectable opiate use
 - Increase risk of HIV infection
- Overall recommendation: treatment should continue as long as patient continues to benefit from treatment, wishes to remain in treatment, remains at risk for relapse, and suffers no significant adverse effects

Methadone: Evidence-Based Efficacy

- ❖ Decreases mortality
- ❖ Reduces illicit drug use
- ❖ Reduces seroconversion to HIV
- ❖ Reduces criminal activity
- ❖ Improves pregnancy outcomes
- ❖ Improves retention in treatment
- ❖ Increases engagement in socially productive activities

Methadone: Evidence-based Efficacy

- ❖ Approximately 25% of patients do not respond to methadone (Gossop et al, 2003)
- ❖ In the US, 1-year retention rates range from 25-60% (Fischer et al, 2005)

Methadone: Safety

❖ Risk factors for adverse events

- Simultaneous use of benzodiazepines, other opiates, alcohol, cocaine
- Interactions between medications
- Accumulation in body to toxic levels
- Peak respiratory depressant effects
- Poor clinical practice during the start of methadone treatment (induction)
- Cardiac effects
- Diversion

Methadone Chronic Adverse Effects

- ❖ Most studies show that blocking doses of methadone do not impair psychomotor and cognitive function
 - Patients can function well in work and social environments
 - Some patients describe effects as being disabling, tiring and numbing
- ❖ Constipation (tolerance usually occurs within 3 years)
- ❖ Sweating (persists in 50% of patients)
- ❖ Sexual dysfunction
- ❖ QTc prolongation
 - Hypokalemia
 - Structural heart disease
 - Arrhythmia
 - History of prolonged QT syndrome

Methadone Drug Interactions

- ❖ Inhibit CYP enzymes and increase methadone levels
 - Fluconazole, voriconazole, ciprofloxacin, clarithromycin
 - Fluoxetine, fluvoxamine, amitriptyline, quetiapine
- ❖ Induce CYP enzymes and decrease methadone levels and may lead to withdrawal
 - Darunivir, efavirenz, nelfinavir
 - Rifampin
 - St. John's wort
- ❖ Pharmacodynamic interactions
 - Benzodiazepines, alcohol

Improving Patient Safety

- ❖ Updating induction protocols
 - Most patients need much less than 20-30 mg for first dose (initial dose cannot exceed 30 mg)
 - Patients are in critical phase during inductions, requiring intensive monitoring
 - Assess medical conditions that affect respiration
- ❖ Improving procedures for take-home medications
 - 8 regulatory requirements for unsupervised meds
 - Sign release for OTP to contact other providers

Improving Patient Safety

- ❖ Assess each patient for use of other medications
 - Prescription drug monitoring
 - Records from other providers
 - Urine drug screens
- ❖ Patient and family education
 - Safe use and storage of take-home methadone
 - Take exactly as prescribed
 - Interactions with prescription and OTC medications
 - Signs of methadone overdose

Buprenorphine Characteristics

- ❖ Slowly metabolized- long duration of action
- ❖ Slow dissociation from mu opioid receptor- prolonged therapeutic effect for opioid dependence treatment (contrasts to its relatively short analgesic effects)
- ❖ Used in the United States to treat opiate dependence since 2003

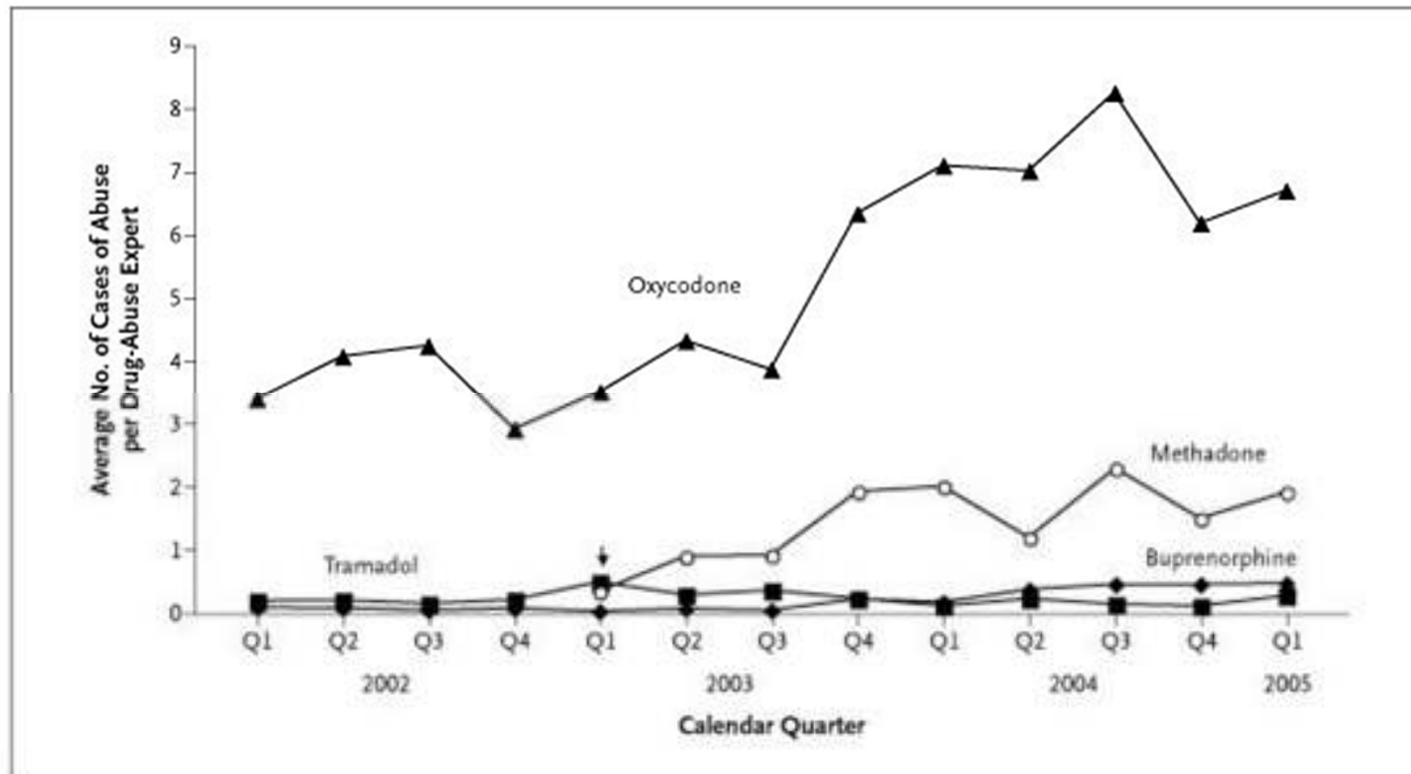


Buprenorphine: Safety

- ❖ Less overdose risk
- ❖ Preserved cognitive function
- ❖ No psychomotor performance impact
- ❖ Less abuse potential- blocks other opioids, short and muted agonist effect, combination with Naloxone



Average Number of Cases of Abuse of Buprenorphine Products, Methadone, Tramadol, and Oxycodone per Drug-Abuse Expert

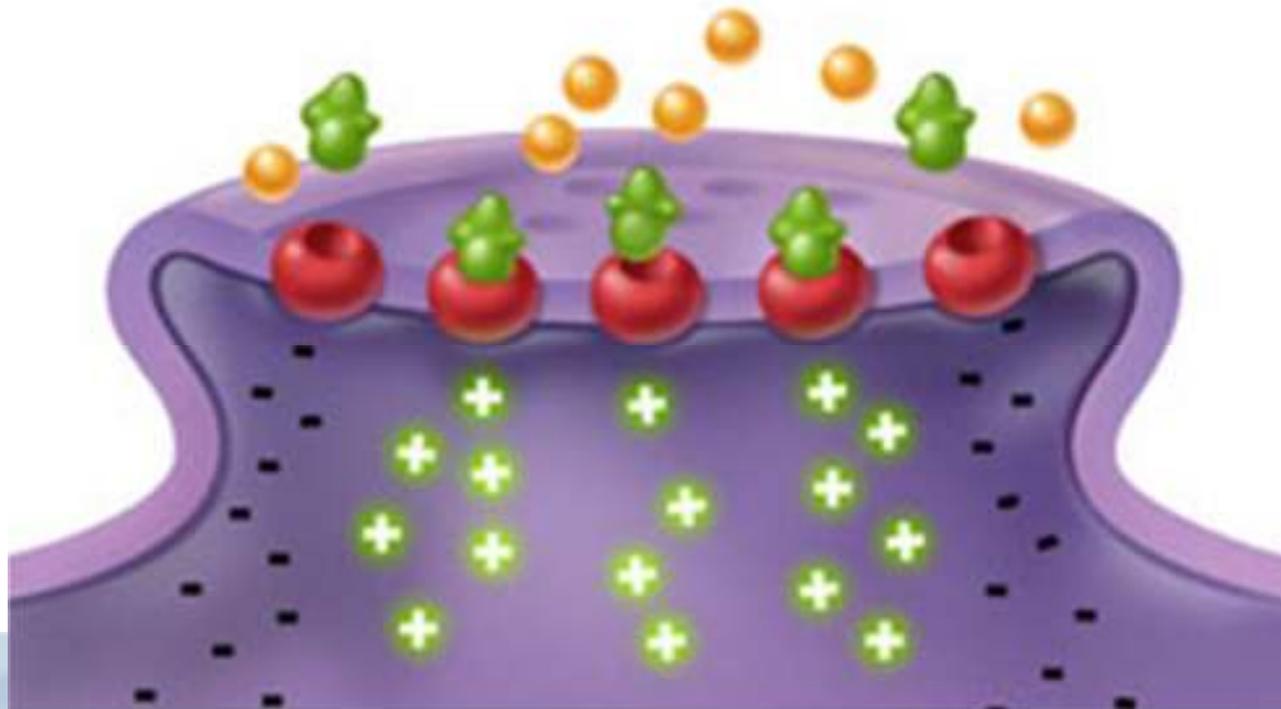


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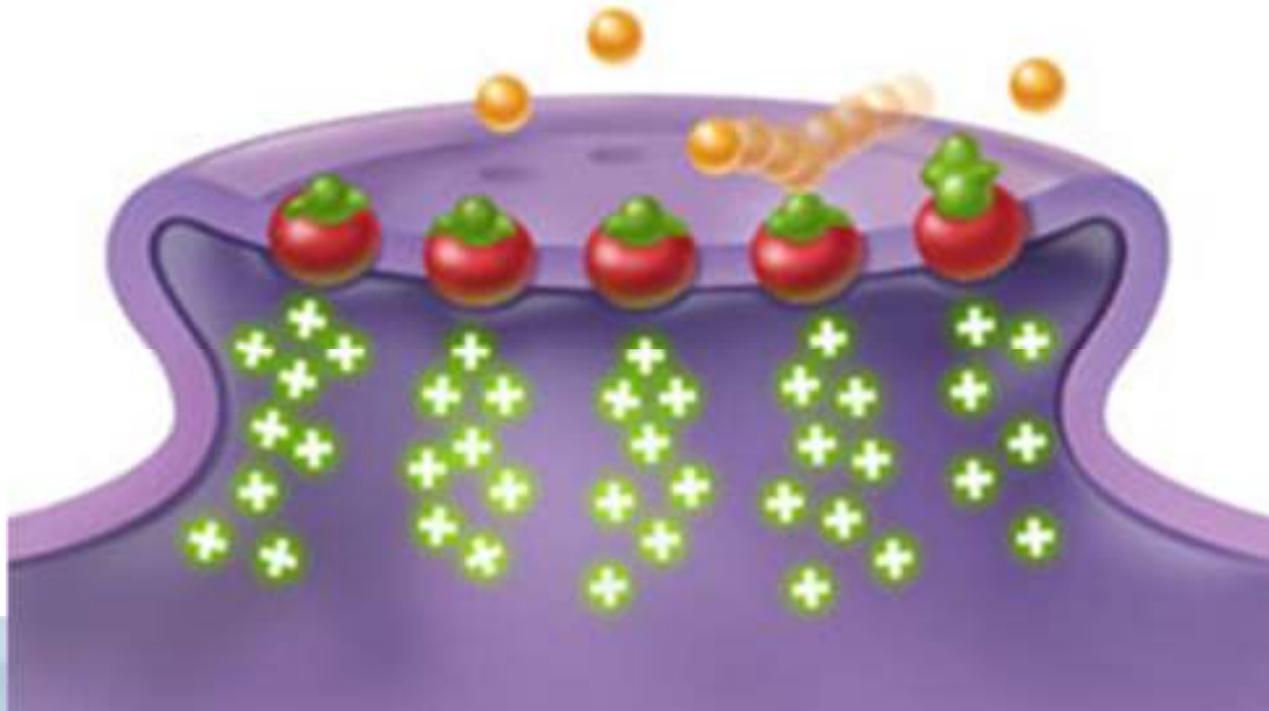


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Mechanism of Action



Mechanism of Action



Function at Receptor: Partial Opioid Agonists

***Mu
receptor***

Partial agonist binding ...

- ① Potent- activates at lower levels***
- ② Partial- safer, less abuse potential***
- ③ Kappa antagonist- less reinforcing***
- ④ High Affinity- displaces full agonists***

Rationale for Treatment

- ❖ Safety allows for Office Based Treatment and OBT lowers barrier to treatment
 - more providers
 - use of insurance
 - less stigma



Rationale for Treatment

- ❖ Long duration of action breaks repeat dosing habit
- ❖ Less opiate side effects- nausea, constipation, sexual dysfunction
- ❖ Less neonatal abstinence syndrome
- ❖ Less severe withdrawal symptoms if stopped
- ❖ Increased patient satisfaction



Effectiveness of Buprenorphine

- ❖ Abstinence rate and treatment retention are nearly equal to Methadone in studies up to 24 months.
- ❖ Efficacy approximately 50% with doses to 8mg; increases to 75% with doses to 16mg.
- ❖ Increasing dose increases effectiveness
- ❖ These two factors enable Office Based Treatment



Diversion and Abuse of Buprenorphine

- ❖ Known on the street as Bupe, Subs, Subbies, and Orange Guys
- ❖ Law enforcement authorities are reporting an increase in seizures of buprenorphine together with other controlled prescription drugs
- ❖ The estimated number of buprenorphine drug items analyzed by state and local forensic law enforcement labs in the U.S. has increased from 21 in 2003 to 8,172 in 2009
- ❖ Buprenorphine has been smuggled into state prisons
- ❖ The number of emergency department visits related to the nonmedical use of buprenorphine has increased from 4,440 in 2006 to 14,266 in 2009.
- ❖ Injecting and snorting

Non-pharmacologic Treatments

- ❖ Medical Treatment Team
- ❖ Substance Abuse Counselor Team
- ❖ Community Support Group Team



Medical Treatment Team

- ❖ Staff- Administrative, nursing, pharmacist and provider
- ❖ Physical Space and equipment- Exam room and instant UDS and ETOH testing.
- ❖ Finances- like a regular office visit.



Substance Abuse Counselor Team

- ❖ Certified Substance Abuse Counselors
 - Refer, contract or hire
 - Group and individual appointments
- ❖ Recovery Coaches
 - From inside or outside the program



Community Support Group Team

- ❖ NA, AA, Celebrate Recovery, Pastors
 - Flexibility vs Effectiveness
- ❖ PO, Day Reporting, Other SS Programs
- ❖ Hotlines, Sponsors



Treatment Tools- Initial

- ❖ Summary of program structure, expectations and consequences
- ❖ Initial drug history and lab screening
- ❖ COWS- Clinical Opioid Withdrawal Scale
- ❖ Controlled substance agreement
- ❖ Instruction on how buprenorphine works



Treatment Tools- Routine

❖ Chart system to address complicating factors

- Medical- Hepatitis C, sleep hygiene, elective surgery, pregnancy, chronic pain, etc...
- Psychosocial- counseling, life changes
- Psychiatric
 - Mood disorders
 - Anxiety disorders



Treatment Tools- Routine

- ❖ Remember it is a disease and relationship is with the drug, not you.
- ❖ Monitor more closely
 - Increase frequency of visits, pill counts
- ❖ Intervention
 - Individual visits, journal, community service
- ❖ Discharge- three strikes



Treatment Tools- Routine

- ❖ Annual lab screening (TSH, CBC, CMP)
- ❖ Urine Drug Testing (every visit)
- ❖ Breath Alcohol Testing (every visit)
- ❖ Prescription Monitoring Programs (every 3 months)
- ❖ Pill Counts (every 3 months at random)
- ❖ Support Session proof and confirmation (every visit)
- ❖ Document behavior during groups (every visit)



Methadone vs. Buprenorphine

- ❖ Both considered comparable in various outcomes
- ❖ Systematic reviews suggest methadone is superior in retaining patients
- ❖ Limitations of trials comparing the agents
 - Dose of buprenorphine used often ≤ 8 mg
 - Induction protocols varied -rapid induction more effective (Kamien et al, 2008)
 - Incongruities in trial design

Methadone vs. Buprenorphine

- ❖ When administered at higher doses, buprenorphine (9.2 ± 3.4 mg) is as effective as methadone (81.5 ± 35.4 mg) at retaining patients in treatment (Gerra et al, 2004)
- ❖ A meta-analysis comparing the agents in achieving negative urine sample found the effect size favored methadone (West et al, 2000)
- ❖ Reinforcing and subjective effects of IV methadone (5, 10, 20 mg) and buprenorphine (0.5, 2, 8 mg) are similar (Comer et al, 2005)
- ❖ Analgesia of buprenorphine is superior to methadone (Stimmel, 2005)

Methadone vs. Buprenorphine

- ❖ Existing data suggest that cost-effectiveness of each medication is comparable
- ❖ Mental clarity associated with buprenorphine may be greater than with methadone (Rapeli et al, 2007)
- ❖ Withdrawal of symptoms after cessation of therapy are less severe with buprenorphine than methadone (George et al, 2007; Reed et al, 2007)
- ❖ Buprenorphine associated with lower overdose risk than methadone (Bell et al, 2009)

Pain Management in Patients in ODT

❖ For patients on methadone:

- Continue maintenance treatment without interruption
- Use non-opioid agents for acute pain management
- Provide adequate individualized doses of opioid agonists, titrated to desired analgesic or functional effect
- Give opioids on a fixed schedule rather than prn
- Multiple daily doses of methadone may be required for analgesia

❖ Long-term use of methadone and buprenorphine is associated with hyperalgesia syndrome

❖ Do not use mixed agonists-antagonists in patients maintained on methadone → withdrawal

Cost and Utilization Outcomes of ODTs (Baser et al., 2011)

- ❖ Retrospective claims database analysis evaluating healthcare costs associated with treatment of opioid dependence with medications (buprenorphine, methadone and naltrexone) vs. no medication
 - Medication associated with fewer inpatient admissions of all types
 - Total healthcare costs 29% lower for patients who were medicated
 - Total healthcare costs for oral and extended-release naltrexone similar with buprenorphine, methadone had highest healthcare costs among medications

Cost and Utilization Outcomes of ODTs (Baser et al., 2011)

D. Total Cost per Patient (inpatient + outpatient + pharmacy costs):
Instrumental Variable Matched Outcomes 6 Months After Index Date



NTX indicates naltrexone; XR-NTX, extended-release injectable naltrexone.

P vs XR-NTX:

^a*p* < .05.

^b*p* < .01.

^c*p* < .001.

Extended-release Naltrexone

- ❖ FDA approved for opiate dependence in September 2010
- ❖ Administered by depot injection monthly
- ❖ 250 patients with opioid dependence were recruited from 13 sites in Russia and were randomized to 24 weeks of treatment (Krupitsky et al, 2011)
 - 380 mg of extended-release naltrexone by intramuscular injection (n = 126) or placebo injection (n = 124), every 4 weeks.
 - Patients had been detoxed off opioids for at least a week and received biweekly individual drug counseling.
- ❖ After 24 weeks, the median percentage of opioid-free urine screens was 90% among patients taking extended-release naltrexone, compared with 35% among patients taking placebo ($P < 0.0002$)
- ❖ COST: \$1100.00 per dose

Pregnancy



Pregnancy

- ❖ Mothers' reluctance to engage in treatment may be due to fear of stigmatization and hostility
- ❖ Substance abusing women (Jansson et al, 2009)
 - 76% physical abuse, 73% emotional abuse, 40% sexual abuse
 - 75-90% mood disorders
- ❖ Abrupt withdrawal can cause miscarriage, stillbirth or premature labor
- ❖ Opioid dependent women and their neonates have poor outcomes without treatment

Pregnancy: Methadone Treatment

- ❖ 30+ year track record of success
- ❖ Higher and/or split doses often needed in 3rd trimester
- ❖ Neonatal abstinence syndrome common within 72 hrs
 - Hyperirritability
 - GI dysfunction
 - Respiratory distress
 - Yawning, sneezing
 - Fever
 - Uncoordinated suck reflex
 - Generally treated with oral morphine or methadone
- ❖ Traditionally considered standard of careBUT.....

Pregnancy: Buprenorphine Treatment

- ❖ MOTHER Trial (Jones et al, 2010)
- ❖ Double-blind, double-dummy, flexible-dosing, randomized, controlled study in which buprenorphine and methadone were compared for care of 175 pregnant women with opioid dependency at eight international sites
- ❖ Primary outcomes were the number of neonates requiring treatment for NAS, the peak NAS score, the total amount of morphine needed to treat NAS, the length of the hospital stay for neonates, and neonatal head circumference

Pregnancy: Buprenorphine Treatment

- ❖ Treatment was discontinued by 16 of the 89 women in the methadone group (18%) and 28 of the 86 women in the buprenorphine group (33%)
- ❖ Neonates whose mothers were treated with buprenorphine required significantly less morphine (mean dose, 1.1 mg vs. 10.4 mg; $P < 0.0091$), had a significantly shorter hospital stay (10.0 days vs. 17.5 days, $P < 0.0091$), and had a significantly shorter duration of treatment for the neonatal abstinence syndrome (4.1 days vs. 9.9 days, $P < 0.003125$)
- ❖ No significant differences between groups in other primary or secondary outcomes or in the rates of maternal or neonatal adverse events

Breastfeeding

- ❖ Less than 3% of maternal daily dosage of methadone is found in breast milk
- ❖ Mothers are encouraged to breastfeed; amount of methadone in milk is enough to suppress withdrawal
- ❖ Breastfeeding reduces hospital stay by 50%
- ❖ At 6 weeks, mothers continuing methadone are advised to either reduce their own methadone dose or wean the infant slowly to formula
- ❖ Breastfeeding is encouraged in patients on buprenorphine, less than 1% (dose/kg) is transferred into breast milk



QUESTIONS?

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