Pharmacological Management Of Opioid Use Disorders

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SUBSTANCE USE DISORDERS

- Substance use disorders are most effectively treated when approached as a chronic disease, similar to diabetes
  - Can be managed but not cured
  - Treatment goal is "recovery"

FRAME OF REFERENCE: CHRONIC DISEASE

- Addiction: continued use despite adverse consequences
- Physical dependence: signs and symptoms experienced upon the abrupt discontinuation of a substance (withdrawal)
- "Dependence" eliminated from DSM-5

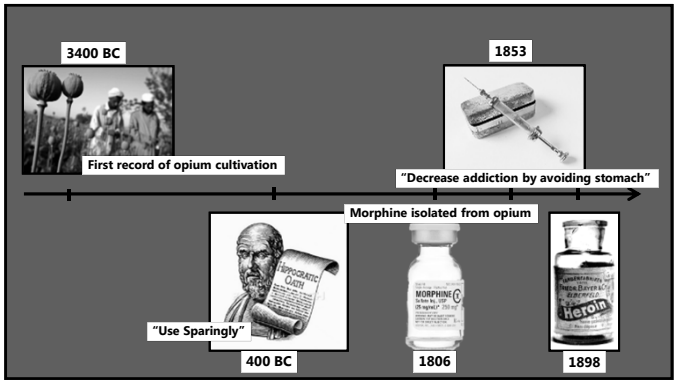
ADDICTION Vs. PHYSICAL DEPENDENCE

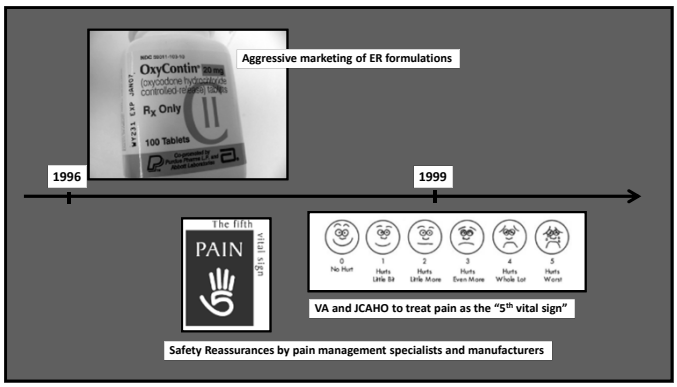
OUTLINE

- Historical Background
- Current context
- Psychopharmacology

OUTLINE

HISTORICAL BACKGROUND



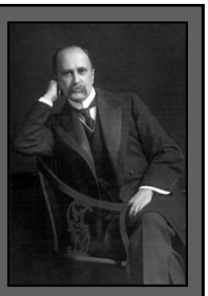


- 1870s – 80s: Overuse of hypodermic injection by physicians
- 1890's – 1910s: Change to more balanced prescribing patterns through education and pressure by reform-minded physicians and pharmacists

NEJM. David Courtwright, Preventing and Treating Narcotic Addiction

19TH C. OPIOID MEDICATION EPIDEMIC

"Man has an inborn craving for medication. Heroic dosing for several generations has given his tissues a thirst for drugs... It is really one of the most serious difficulties with which we have to contend. Even in minor ailments, which would yield to dieting or to simple home remedies, the doctor's visit is not thought to be complete without the prescription"



DR. WILLIAM OSLER'S OPINIONS

- 1914: Harrison Narcotic Act was intended to keep narcotic transactions within legitimate medical channels
  - Actually implemented by Treasury Department in a way that interfered with treatment of addiction

CRIMINALIZATION OF OPIOID ADDICTION AND TREATMENT

- 1919: Supreme court supported enforcement
  - The treatment of opioid addiction is "outside the realm of legitimate medical interest"
    -Webb et al vs. United States

CRIMINALIZATION OF OPIOID ADDICTION AND TREATMENT

- Controlled Substances Act (1970) is successor to Harrison Act
  - Enforced by Drug Enforcement Administration (DEA) which has ultimate authority (versus FDA) for determining medication schedule (I to IV)

CRIMINALIZATION OF OPIOID ADDICTION AND TREATMENT

CURRENT CONTEXT

KOLMAC

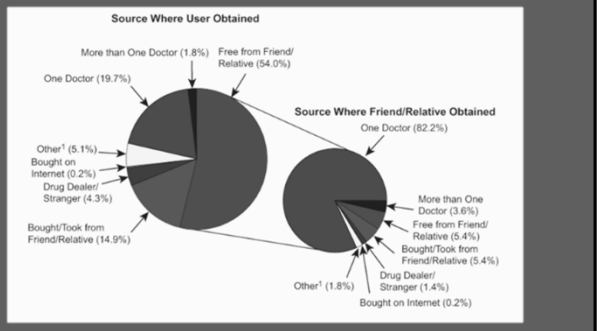
Sheppard Pratt

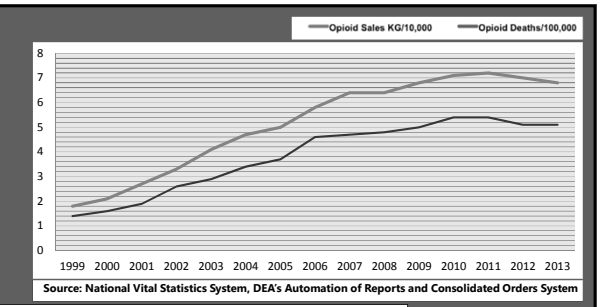
- Wave 1: Overprescribing of opioids
  - Established market for opioid use outside of inner cities
- Wave 2: Heroin
  - Shift due to cost from increased tolerance
- Wave 3: Fentanyl
  - Added to heroin to increase potency

CURRENT OPIOID EPIDEMIC: 3 WAVES

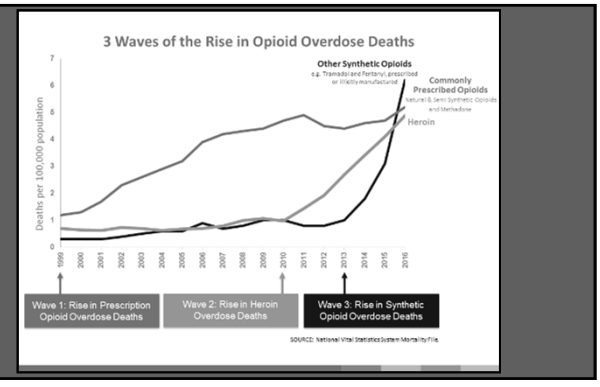
- 1990s to present: Overprescribing of opioids
  - Increased attention to pain management- well intentioned
  - Not accompanied by education of physicians
  - Exploited by pharmaceutical companies
    - Purdue Pharmaceuticals, OxyContin

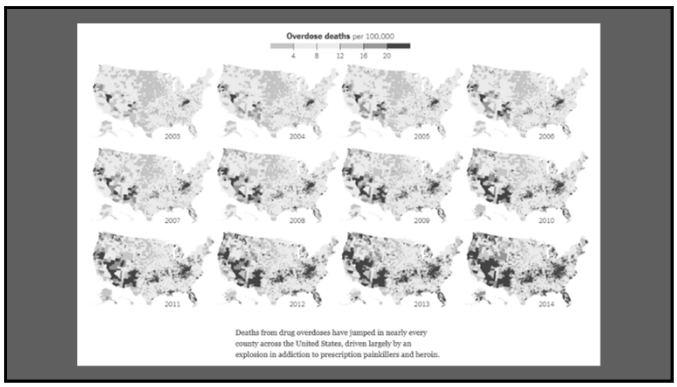
CURRENT OPIOID EPIDEMIC: 1990 to PRESENT

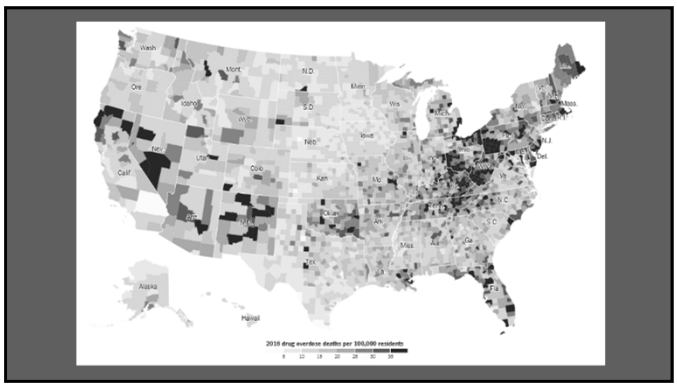




CURRENT OPIOID EPIDEMIC: 1999-2013







PSYCHOPHARMACOLOGY

- Full agonist: attaches to opioid receptor and fully activates it
  - Opium, morphine, codeine, oxycodone (OxyContin, Percocet), hydrocodone (Vicodin), methadone

SOME BASIC TERMS

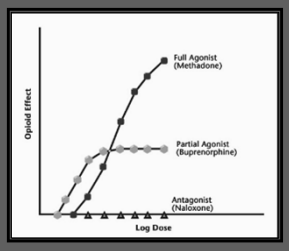
- Antagonist: attaches to opioid receptor and blocks it instead of activating it
  - Naltrexone (Revia, Vivitrol)

SOME BASIC TERMS

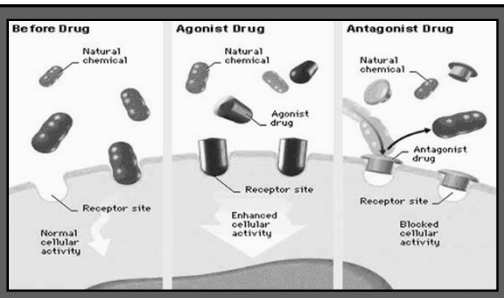
- Partial agonist: attaches to opioid receptor, partially activates and blocks it
  - Buprenorphine (Suboxone, Subutex)

SOME BASIC TERMS

- Affinity for receptor determines which agent is displaced from receptor



SOME BASIC TERMS



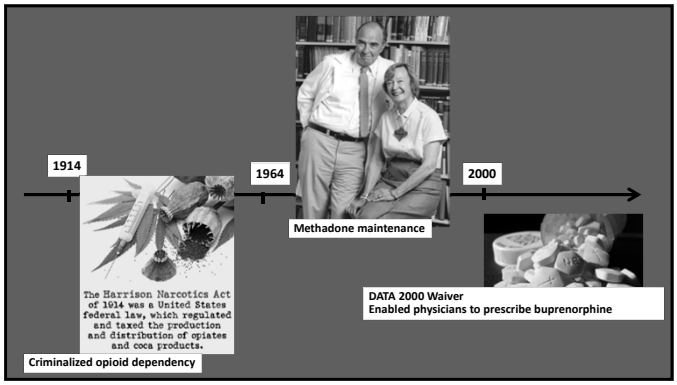
SOME BASIC TERMS

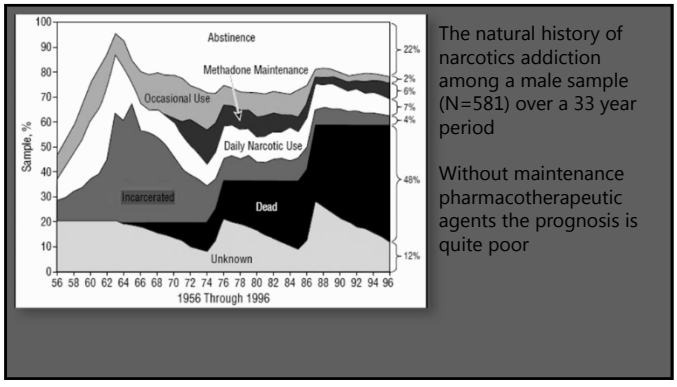
- Blocking effect
  - If antagonist is attached to the receptor site, agonist will have no effect
- Precipitated withdrawal
  - If agonist is attached to receptor site, antagonist will displace it and trigger the abrupt onset of severe withdrawal symptoms

IMPORTANCE OF SEQUENCE

- Compared to alcohol use disorders: greater reliance on relapse prevention medications for better outcomes
- High relapse rates when medications are discontinued
  - 5 year standard for recovery does not hold

HOW LONG TO STAY ON MEDICATIONS?





The natural history of narcotics addiction among a male sample (N=581) over a 33 year period

Without maintenance pharmacotherapeutic agents the prognosis is quite poor

- Non-agonist medication
  - Withdrawal management: non-specific supportive medication
  - Ongoing recovery support: opioid antagonist

TWO STRATEGIES

- Agonist medication
  - Withdrawal management: full or partial opioid agonist
  - Ongoing recovery support: opioid agonist

TWO STRATEGIES

- Alpha-2 adrenergic agonists are the cornerstone
  - Reduce adrenergic hyperactivity in upregulated locus coeruleus
  - Agents

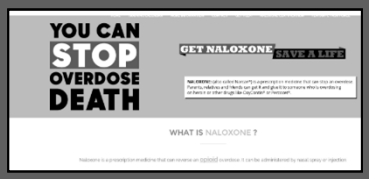
    Clonidine most common
    Guanfacine has less hypotension and sedation
    Lofexidine is newest addition

NON-AGONIST WITHDRAWAL MANAGEMENT

- Supportive medications for other symptoms
  - Anxiety: phenobarbital
  - Insomnia: sedating antidepressants, quetiapine
  - Nausea: ondansetron

NON-AGONIST WITHDRAWAL MANAGEMENT

- Naloxone (Narcan)
- Short acting antagonist
- Two formulations
  - Parenteral
  - Nasal Spray



OVERDOSE REVERSAL: OPIOID ANTAGONIST

- Issues
  - Larger doses required to reverse "fentalogues"
  - Lack of follow up treatment

OVERDOSE REVERSAL: OPIOID ANTAGONIST

NALTREXONE FORMULATIONS

- Oral (Revia)
  - 24 hour effective duration
  - Extend to 72 hours by giving 150 mg
- Depot parenteral lasts 30 days (Vivitrol)
  - Large volume requires gluteal intramuscular injection

NALTREXONE INITIATION

- Must allow opioid washout period of several days before beginning oral
  - Length of washout depends on opioid being used
  - Some protocols use early administration of .5 mg to 1 mg doses prepared by compounding pharmacist
- Precede parenteral with one week of oral

NALTREXONE BENEFITS

- No psychoactive effect
  - Blocks psychoactive effect of opioid agonists
- Philosophical preference by some patients and corrections officials

- Black box warning for oral formulation for hepatic toxicity
  - Extremely rare at 50 mg dose
- Short term: initiation more difficult than with agonists

NALTREXONE ISSUES

- Long term: poor adherence
- Side effects:
  - Need to over-ride if emergency requires opioid analgesia
  - Oral: nausea
  - Parenteral: site injection pain

NALTREXONE ISSUES

- 1964: First used by Dole and Nyswander
  - Harassed until formal approval in 1971
- Dispensed, not prescribed, in highly regulated settings
  - Can be prescribed for pain
- Better long-term outcomes than abstinence programs

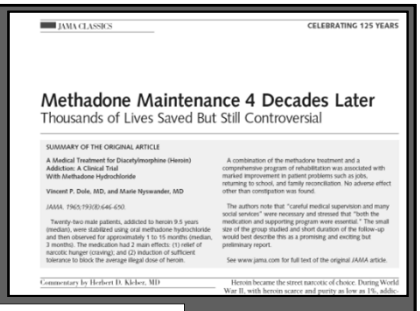
METHADONE

- Based on opioid's relation to stress response system
- Addictive use of opioids creates persistent disruption of hypothalamic-pituitary-adrenal axis
  - Abstinence: hyper-responsive
  - Heroin: hypo-responsive
  - Methadone: normal response

METHADONE THEORY

- Use low initial dose and increase slowly to prevent overdose by long acting metabolites
- Use high enough maintenance dose to block euphoric effect of other opioids
  - Usually 60 mg or higher
- Taper off slowly over several months (usually blind)

METHADONE KEYS


JAMA CLASSICS CELEBRATING 125 YEARS

Methadone Maintenance 4 Decades Later
Thousands of Lives Saved But Still Controversial

SUMMARY OF THE ORIGINAL ARTICLE

A Medical Treatment for Diacetylmorphine (Heroin) Addiction: A Clinical Trial With Methadone Hydrochloride

Vincent P. Dole, MD, and Marie Nyswander, MD

JAMA. 1965;193(8):646-650.

Twenty-two male patients, addicted to heroin 9.5 years (median), were stabilized using oral methadone hydrochloride and then observed for approximately 1 to 15 months (median, 3 months). The medication had 2 main effects: (1) relief of narcotic hunger (craving); and (2) induction of sufficient tolerance to block the average illegal dose of heroin.

A combination of the methadone treatment and a comprehensive program of rehabilitation was associated with marked improvement in patient problems such as jobs, returning to school, and family reconciliation. No adverse effect other than constipation was found.

The authors note that "careful medical supervision and many social services" were necessary and stressed that "both the medication and supporting program were essential." The small size of the group studied and short duration of the follow-up would best describe this as a promising and exciting but preliminary report.

See www.jama.com for full text of the original JAMA article.

Commentary by Herbert D. Kleber, MD

Heroin became the street narcotic of choice. During World War II, with heroin scarce and purity as low as 1%, addic-

METHADONE CONTROVERSIES

METHADONE CONTROVERSIES

- Originally intended as supportive medication for comprehensive treatment program
  - Psychosocial components reduced over time
- Stigmatized over time

METHADONE CONTROVERSIES

- In 1990, the Office of National Drug Control Policy stated clearly that methadone maintenance was both legitimate and an important part of the spectrum of drug abuse treatment

WHO Model List
of
Essential Medicines

18th list
(April 2013)
(Final Amendments – October 2013)

24.5 Medicines for disorders due to psychoactive substance use	
nicotine replacement therapy (NRT)	**Chewing gum:** 2 mg; 4 mg (as polacrilex). **Transdermal patch:** 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
Complementary List	
□ *methadone**	***Concentrate for oral liquid:*** *5 mg/ml; 10 mg/ml (hydrochloride).* ***Oral liquid:*** *5 mg/5 ml; 10 mg/5 ml (hydrochloride).* ** The square box is added to include buprenorphine. The medicines should only be used within an established support programme.*

- In October 2002, FDA approved two Schedule III opioid partial agonist buprenorphine formulations for opioid use disorder

BUPRENORPHINE

IMPACT OF BUPRENORPHINE

- Reduced deaths from overdose
  - France, 1995–2004: 79% reduction
  - Baltimore, 2002–2009: 61% reduction

From 225 → 87
Resurgence of overdose deaths in recent years with shift from pain pills to heroin and adulteration with fentanyl

BUPRENORPHINE REGULATIONS

- DATA 2000: law "carved a window" in Controlled Substances Act
  - Extended political process
- Buprenorphine is the only medication approved

BUPRENORPHINE REGULATIONS

- Prescriber must obtain "waiver"
  - 8 hour training, in person or online
  - Given a second DEA number starting with "X"

- Rare overdose
  - Ceiling effect on respiratory depression
- Blocks other opioids at lower dose
  - High affinity for receptor site
- Less sedation

BUPRENORPHINE Vs. METHADONE

- Less euphoria for most patients
  - Partial agonist
- Legal to prescribe in office based practice
  - For waivered physicians
- Pregnant opioid addicts: less severe neonatal abstinence syndrome

BUPRENORPHINE Vs. METHADONE

- Sublingual. mono vs. combo (with naloxone)
  - Combo preferred to reduce diversion
  - Greater incidence of nausea in combo

    Possibly related to GI absorption of naloxone
    Tip: spit out saliva after sublingual med dissolves

BUPRENORPHINE FORMULATIONS

BUPRENORPHINE FORMULATIONS

- Extended release
  - Implanted (Probuphine)
    - Requires surgical procedure
      Limited use
  - Subcutaneous (Sublocade)
    - Recently released, limited experience

BUPRENORPHINE PROTOCOL

- Mild withdrawal symptoms must be present to avoid precipitated withdrawal
  - Transition from methadone: reduce to 30 mg/day and wait 48 to 72 hours
  - Recent problems with heroin + "fentalogues"
    - Tramadol: up to 400 mg/day for 24 to 48 hours.

BUPRENORPHINE PROTOCOL

- 4 mg hourly until symptoms remit
  - Daily range- 8 to 24 mg
  - Lower initial dose (2 mg) when no recent use
- Can taper over 1 to 4 weeks but longer-term stabilization for months is preferable
  - High rate of relapse if use is short-term

- Eliminates withdrawal symptoms quickly
- Eliminates cravings
- Leaves them feeling "normal"

BUPRENORPHINE RESULTS

- Improved treatment results
  - Longer stays in treatment
  - Fewer relapses
  - Fewer overdoses

BUPRENORPHINE RESULTS

- Patients
  - Concern about getting off
- Patient families
  - Negative publicity

ADDRESSING RESISTANCE

- Addiction treatment community
  - "Not really clean"
  - Narcotics Anonymous: "Unable to work the 12 steps"

ADDRESSING RESISTANCE

- Buprenorphine the ideal medication for this co-occurring condition
- Legitimate pain syndrome does not require DEA "X waiver" for prescriber

ADDICTED PAIN PATIENT

- Must divide into 3 to 4 doses/day
  - Analgesic effect is shorter
- May require up to 32 mg/day
  - Ceiling effect for analgesia is higher
  - Insurance may not cover

ADDICTED PAIN PATIENT

- Recommendation is to maintain patient on agonist and treat neonatal abstinence syndrome (NAS) with morphine
  - NAS severity reduced by rooming in

PREGNANCY AND OPIOID USE DISORDERS

- Methadone is still the standard of care but NAS can be severe
- Buprenorphine (mono): less severe NAS
  - Lower doses of morphine
  - Fewer days in NICU

PREGNANCY AND OPIOID USE DISORDERS

- Buprenorphine triggers precipitated withdrawal even when moderate withdrawal symptoms are present after 24 hours of abstinence

PROBLEM: FENTANYL ADULTERATED HEROIN

- Solution: "tramadol bridge"
  - Opioid agonist with lower receptor affinity than buprenorphine
  - Initially not scheduled, now Schedule IV
  - Dosing 50 mg/hour up to 400 mg/day
    - 150 to 200 mg most usual
  - Discontinue tramadol 12 hours before starting buprenorphine

PROBLEM: FENTANYL ADULTERATED HEROIN

We agree with your analysis that tramadol may be administered (but not prescribed) to a patient for the purpose of relieving acute withdrawal symptoms while arrangements are being made for referral for treatment (with Kolmac or another provider), assuming that the administration occurs under the following conditions:

> no more than one day's medication may be administered to the person or for the person's use at one time;
> such emergency treatment may be carried out for no more than 72 hours; and
> the 72-hour period cannot be renewed or extended. (21 C.F.R. § 1306.07(b)).

Based upon our understanding of the circumstances under which Kolmac physicians administer tramadol, we believe that the application of the 72-hour exception to registration in these circumstances is reasonable. We understand that Kolmac physicians: (1) utilize tramadol in emergency situations to relieve acute withdrawal symptoms, while making arrangements for placement in a maintenance/detoxification program; (2) administer no more than one day's medication to the person or for the person's use at one time; and (3) utilize this treatment for not more than 72 hours.

TRAMADOL: 72 HR CSA EXCEPTION

- Over one million patients now taking it
  - Compared to a quarter million on methadone
- Incorporation into traditional 12-Step based residential treatment program
  - Hazelden/ Betty Ford project

EXPANDED USE OF BUPRENORPHINE

- Increased patient limit to 275 for physicians who…
  - Have addiction certification
  - Have had waiver for the 100 patient limit for one year
  - Or practice in a qualified health setting (provide counseling and accept insurance)
- New: NPs and PAs allowed to prescribe

EXPANDED USE OF BUPRENORPHINE

- Street use for relief of withdrawal rather than euphoria
- Street price has fallen below price of heroin

DIVERSION OF BUPRENORPHINE

- Prior authorization now banned in Maryland
- Stabilization doses
  - Vary by individual tolerance and preference
  - 12 mg as "blocking dose"

ONGOING ISSUES WITH BUPRENORPHINE

- Co-morbid pain management
  - Chronic
  - Elective surgical procedures

ONGOING ISSUES WITH BUPRENORPHINE

- Discontinuing
  - When: task versus time based
  - How: protocols
  - Relationship to long term recovery

ONGOING ISSUES WITH BUPRENORPHINE

- "Safety sensitive" workers
  - Opioid addicted physicians in many states are not allowed to regain license to practice if taking buprenorphine

Disagreements about mild cognitive impairment

BUPRENORPHINE CONTROVERSIES

BUPRENORPHINE CONTROVERSIES

- Traditional residential rehabilitation programs
  - Most "Minnesota Model" programs do not offer buprenorphine to patients beyond detoxification

BUPRENORPHINE CONTROVERSIES

- Narcotics Anonymous
  - Some groups restrict participation of members on buprenorphine: welcome but not equal
  - Patients feel "caught in the middle" and tend either to discontinue buprenorphine earlier or avoid NA

BUPRENORPHINE: UNANSWERED QUESTIONS

- How long should a person stay on it?
- What about studies that suggest no benefit from increased therapy?
  - Role of therapy versus medication

- Full agonist: methadone
  - Pro: stabilizes opioid system, reduces pain
  - Con: access is limited, can be abused, overdoses, discontinuation

SUMMARY

- Partial Agonist: buprenorphine (Suboxone, Subutex)
  - Pro: stabilizes opioid system, reduces pain
  - Con: discontinuation

SUMMARY

- Antagonist: naltrexone (Revia), Vivitrol
  - Pro: no abuse, easy to discontinue
  - Con: no opioid system stabilization or pain reduction

SUMMARY


Sheppard Pratt
HEALTH SYSTEM
KOLMAC
Outpatient Recovery Centers
Leaders in addiction treatment since 1973