Methadone Maintenance Treatment

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Background and Disclosures

- Board Certified in Psychiatry and Addiction Medicine
- Medical Director for Opioid Treatment Program in NE Tennessee
- No disclosures

Learning Objectives

- Awareness of regulations for methadone programs
- Pharmacology of methadone:
  - Unique properties for medication treatment for opioid use disorder
- System of methadone:
  - Unique aspects of treatment that differ from buprenorphine

Stigma…

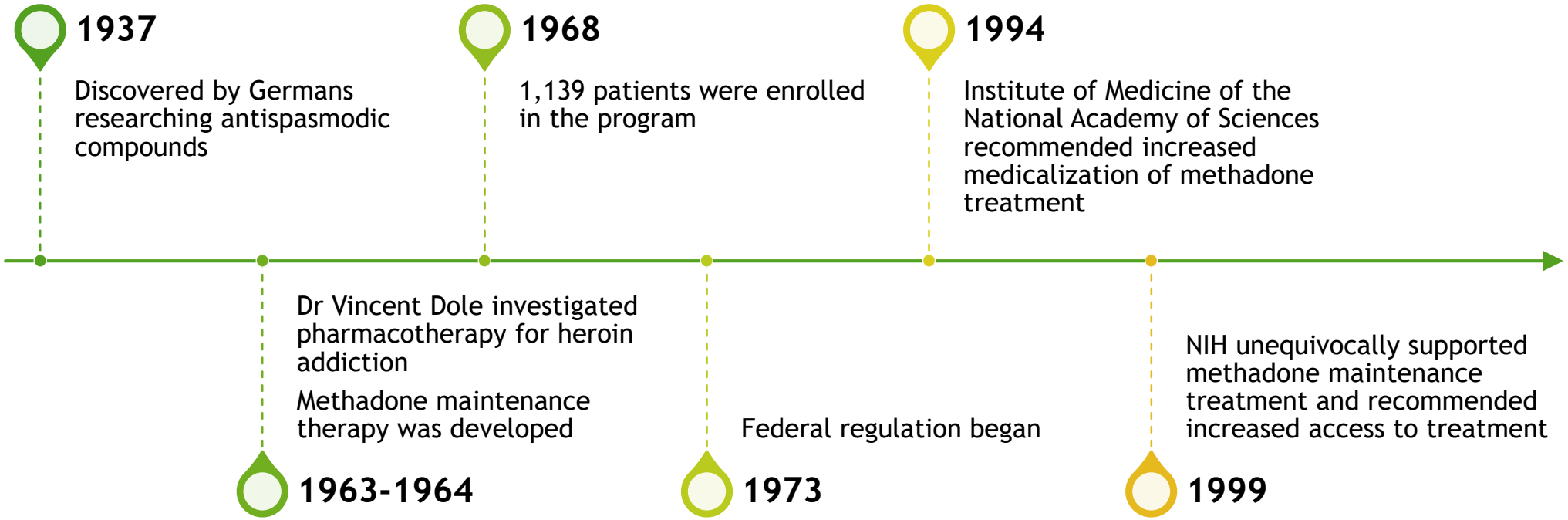
Anyone who questions the need for a treatment like this…

All it would take is a half day in my office and they would understand.

Outline

- Brief history
- Regulations and Federal Guidelines
- Pharmacology
- Admission criteria and discharge considerations
- Benzodiazepine usage while on methadone treatment
- Comparison of methadone and buprenorphine

History

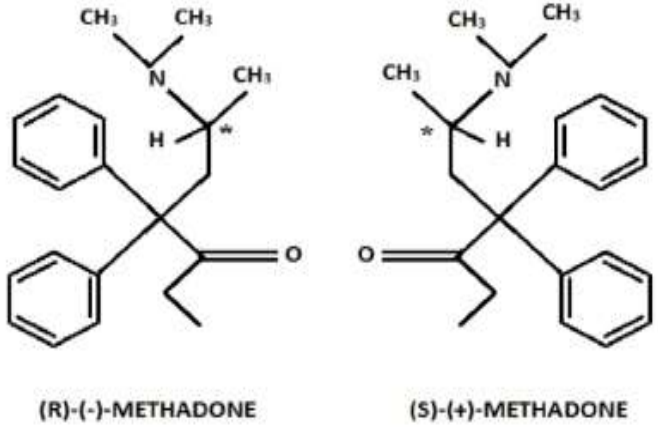

1937
Discovered by Germans researching antispasmodic compounds
1963-1964
Dr Vincent Dole investigated pharmacotherapy for heroin addiction
Methadone maintenance therapy was developed
1968
1,139 patients were enrolled in the program
1973
Federal regulation began
1994
Institute of Medicine of the National Academy of Sciences recommended increased medicalization of methadone treatment
1999
NIH unequivocally supported methadone maintenance treatment and recommended increased access to treatment

Regulations

- Most opioid treatment programs open Sunday through Saturday
- Take Homes – earned with appropriate drug screens
  - First TH at 30 days
  - Second TH at 90 days
  - Weekly TH at 270 days
- Daily dosing continues for all who use illicit substances, alcohol, THC
- See SAMHSA Tip 43, 63, others
- Tennessee: Chapter 0940-05-42

Mechanism of Action

- Methadone is typically a racemic mixture of the R-methadone and S-methadone enantiomers.
  - R-methadone primarily a μ-opioid receptor agonist
  - S-methadone primarily an NMDA receptor antagonist
  - Minor receptor affinities:
    - Delta and kappa opioid receptors
    - Serotonin reuptake
    - Norepinephrine reuptake
- Methadone suppresses the respiratory drive
  - Methadone toxicity and death primarily result from respiratory depression



Pharmacokinetics

- Methadone has a mean elimination half life of about 22 hours, however it has a high degree of variability: from 4 hours to 91 hours*
- Methadone begins to induce the CYP system within 2-3 weeks of use
  - Primarily metabolized by CYP3A4, but also CYP2D6 and CYP1A2
- Individual differences in:
  - GI absorption
  - Liver metabolism
  - Protein carriers in the blood
  - Opioid receptor polymorphism
  - Opioid tolerance

** Hum Psychopharmacol Clin Exp 2004; 19: 565–576.*

Dosage

- Typical starting dose 20 mg – 30 mg (Regulations: no more than 40 mg first day)
- Dosing is observed by nurses to ensure patient safety
- Maintenance dose highly individualized
  - Typical maintenance dose at our clinic might be around 70 mg daily, however the range is as low as 20 mg daily and as high as 260 mg daily at our facility
  - Other clinics outside Tennessee much higher daily doses
  - Tennessee requires serum levels for dose greater than 120 mg;
    Peak and trough serum levels help determine fast metabolizers
- Because methadone has a long half-life, there is a risk of the medication building up to toxic levels. Tip 63 recommends:
  - Increase of 5 mg per 5 days by some experts, others 5 mg-10 mg every 3-4 days
- Dose should not be used as a positive or negative behavioral tool

Assessing Appropriate Dose is Complex

- Patients often say things like, “I was going to a clinic in another state, where they had me on 160 mg. At that dose I just sat around all the time, took a lot of naps. I think some of the people who come here just want more so that they can get the ‘nods.’ I’d prefer to keep my dose much lower, like probably 60 mg or so. I’m more functional at that dose.”
- Many people seek more for pain reasons, others for psychological reasons
- Often patients report insomnia due to overnight withdrawal symptoms
- COWS can be easily manipulated

- As patients get older, I inform them that for medical reasons (fall risk, aging heart, COPD) it is generally advisable to gradually decrease their dose.

Starting Methadone

- A person must have an opioid use disorder and have had this condition for the past 12 months
  - Exceptions can be made for people released from a controlled setting such as jail
- Medical comorbidities must be considered:
  - Prolonged QT
  - Respiratory issues (e.g. COPD, sleep apnea)
  - Sedating medications
  - Age-related concerns, including risk of falls

Stopping Methadone

- "When it comes to methadone, the greatest risk of death is on starting it and on stopping it."
- Patients discharged from methadone maintenance treatment have consistently worse outcomes than those continuing treatment
- Consensus panel recommends involuntary discharge be avoided if possible*
- Some patients stabilize and manage to come off completely, but for most it is a life-long treatment

**SAMHSA Tip 43*

Risks of Sedatives: Benzodiazepines and Alcohol

- Sedatives enhance the respiratory-depressant effects of methadone
- Outcomes are worse for patients who use benzodiazepines
- Clinical challenge: UDS benzodiazepine+, but how much?
- The treatment approach varies; there does not appear to be consensus
  - Federal guidelines stipulate that patients who use benzodiazepines should not be prohibited from methadone maintenance treatment
  - Some clinics have a zero-tolerance policy, and others appear permissive
- "Patients who are abusing benzodiazepines usually need detoxification and more intensive treatment interventions if they are to safely remain in MAT."*

**SAMHSA Tip 43*

A Comment on Recommended ASAM Level of Care

- Locally in Tennessee, there is no residential program to send patients to where they will be maintained on methadone.
  - (Acute psychiatric hospitalization locally does provide methadone.)
- Some programs provide a buprenorphine-managed detoxification, however this is not tolerated by all patients and is not recommended for high MMT dose
- Most patients who are forced to be abstinent (at a residential program) will not stay in treatment
- Practically speaking the result is that at an OTP in Tennessee, you generally are the highest level of care available.

Comparison – Pharmacologic Properties

Methadone

- Full agonist medication
  - No risk precipitated withdrawal
  - No ceiling effect: higher dose means more effect
- High variability in metabolism
  - Regularly report withdrawal symptoms, people take their dose first thing when they wake up
  - COWS score elevated
  - Swings in blood pressure

Buprenorphine

- Partial agonist
  - High risk precipitated withdrawal
  - Ceiling effect: little difference above 16 mg per day
- Low variability in metabolism
  - Once stabilized, very few complaints about withdrawal symptoms
  - COWS score usually 0 or 1
  - Fewer complaints about dose not lasting

Tolerability

Methadone

- Medical comorbidities pose greater risk
- Better-tolerated than buprenorphine (patients “like it”)
- More likely effective for people who use very large quantities of opioids**

Buprenorphine

- Better overall safety profile
- More frequent complaints about headaches, GI side effects
- Some patients significantly fear precipitated withdrawal
- Less likely effective for people who use large quantities of opioids**

***Evidence for this is not strong – general impression*

When Chronic Pain is a Factor

Methadone

- When dosed for pain (e.g. palliative setting), often given three times daily
- However MMT is given once per day for most; fast metabolizers may be approved for twice-daily dosing
- Because methadone has no ceiling effect, it is more attractive to people with a high pain burden

Buprenorphine

- Patients usually have take-homes and can split their dose; three times daily dosing for pain can be easily done
- The analgesic effect of buprenorphine is not as potent as methadone

Program Differences

Methadone

- Daily dosing until take homes are earned
  - A form of behavioral activation
- "The pig is more committed"

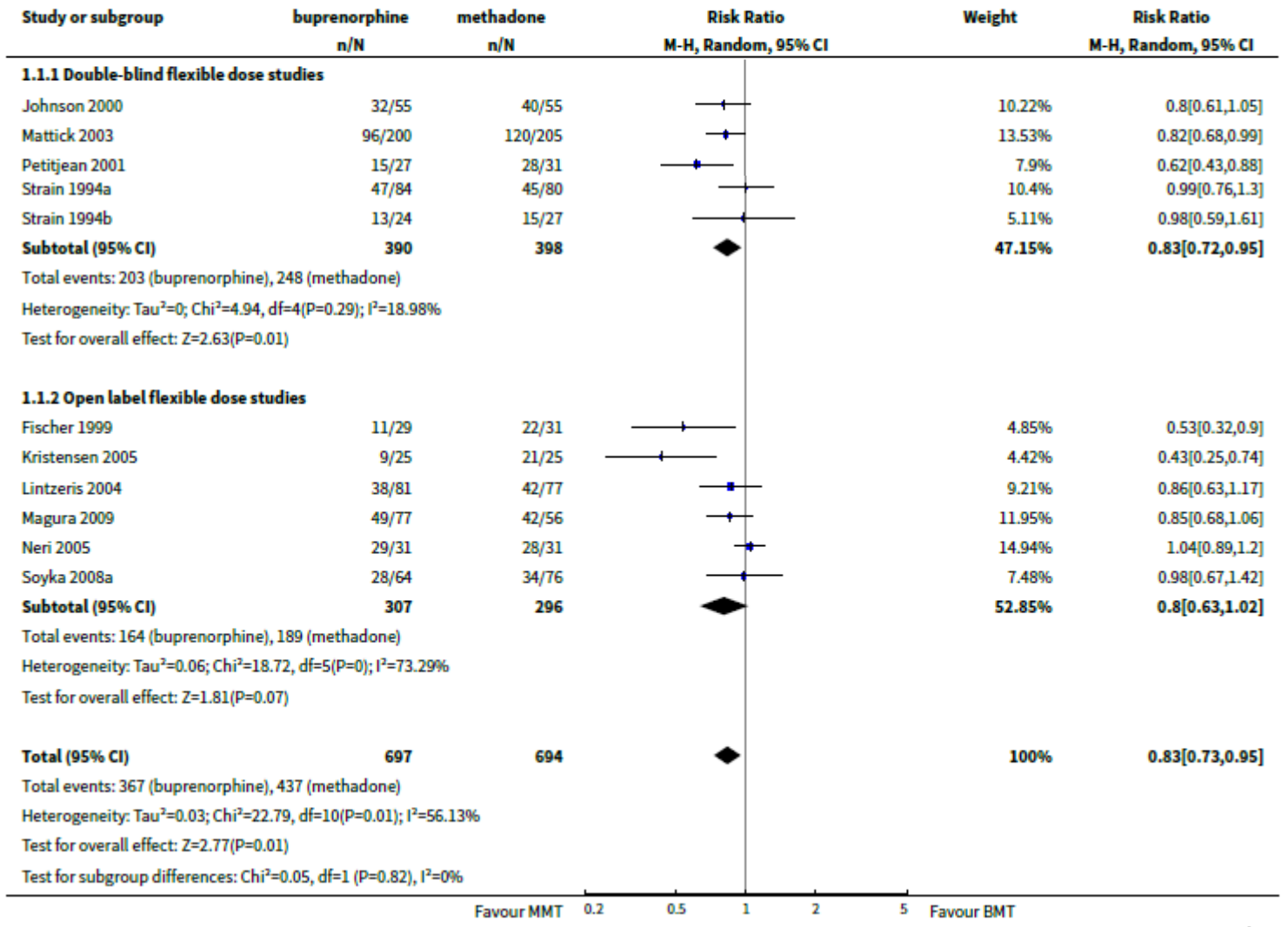
Buprenorphine

- Usually filled at a pharmacy; visit frequency ranges weekly to every 2 months
- "The chicken is less committed"
- Nearly all patients would prefer not to have to visit the clinic daily, however it clearly has therapeutic effects to do so.

Net Outcomes: Methadone and Buprenorphine

- 2014 Cochrane Review Methadone vs Buprenorphine
  - Methadone treatment retention was greater
  - No difference on:
    - Morphine-positive urines
    - Self-reported heroin use
    - Cocaine-positive urines
    - Benzodiazepine-positive urines
    - Criminal activity

Analysis 1.1. Comparison 1 Flexible-dose buprenorphine versus flexible-dose methadone, Outcome 1 Retention in treatment.



Study or subgroup	buprenorphine n/N	methadone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Double-blind flexible dose studies					
Johnson 2000	32/55	40/55		10.22%	0.8[0.61,1.05]
Mattick 2003	96/200	120/205		13.53%	0.82[0.68,0.99]
Petitjean 2001	15/27	28/31		7.9%	0.62[0.43,0.88]
Strain 1994a	47/84	45/80		10.4%	0.99[0.76,1.3]
Strain 1994b	13/24	15/27		5.11%	0.98[0.59,1.61]
Subtotal (95% CI)	**390**	**398**		**47.15%**	**0.83[0.72,0.95]**
Total events: 203 (buprenorphine), 248 (methadone)					
Heterogeneity: Tau^2=0; Chi^2=4.94, df=4(P=0.29); I^2=18.98%					
Test for overall effect: Z=2.63(P=0.01)					
1.1.2 Open label flexible dose studies					
Fischer 1999	11/29	22/31		4.85%	0.53[0.32,0.9]
Kristensen 2005	9/25	21/25		4.42%	0.43[0.25,0.74]
Lintzeris 2004	38/81	42/77		9.21%	0.86[0.63,1.17]
Magura 2009	49/77	42/56		11.95%	0.85[0.68,1.06]
Neri 2005	29/31	28/31		14.94%	1.04[0.89,1.2]
Soyka 2008a	28/64	34/76		7.48%	0.98[0.67,1.42]
Subtotal (95% CI)	**307**	**296**		**52.85%**	**0.8[0.63,1.02]**
Total events: 164 (buprenorphine), 189 (methadone)					
Heterogeneity: Tau^2=0.06; Chi^2=18.72, df=5(P=0); I^2=73.29%					
Test for overall effect: Z=1.81(P=0.07)					
Total (95% CI)	**697**	**694**		**100%**	**0.83[0.73,0.95]**
Total events: 367 (buprenorphine), 437 (methadone)					
Heterogeneity: Tau^2=0.03; Chi^2=22.79, df=10(P=0.01); I^2=56.13%					
Test for overall effect: Z=2.77(P=0.01)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.82), I^2=0%					

2014 Cochrane Review: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence (Review), Mattich et al

Trivia:

S-methadone is currently being studied for what clinical application?

… as an antidepressant.

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Questions?