Best Practices for Treatment of Opioid Use Disorder

David R. Gastfriend MD

Scientific Advisor, Treatment Research Institute

Chief Architect, CONTINUUM™,
American Society of Addiction Medicine

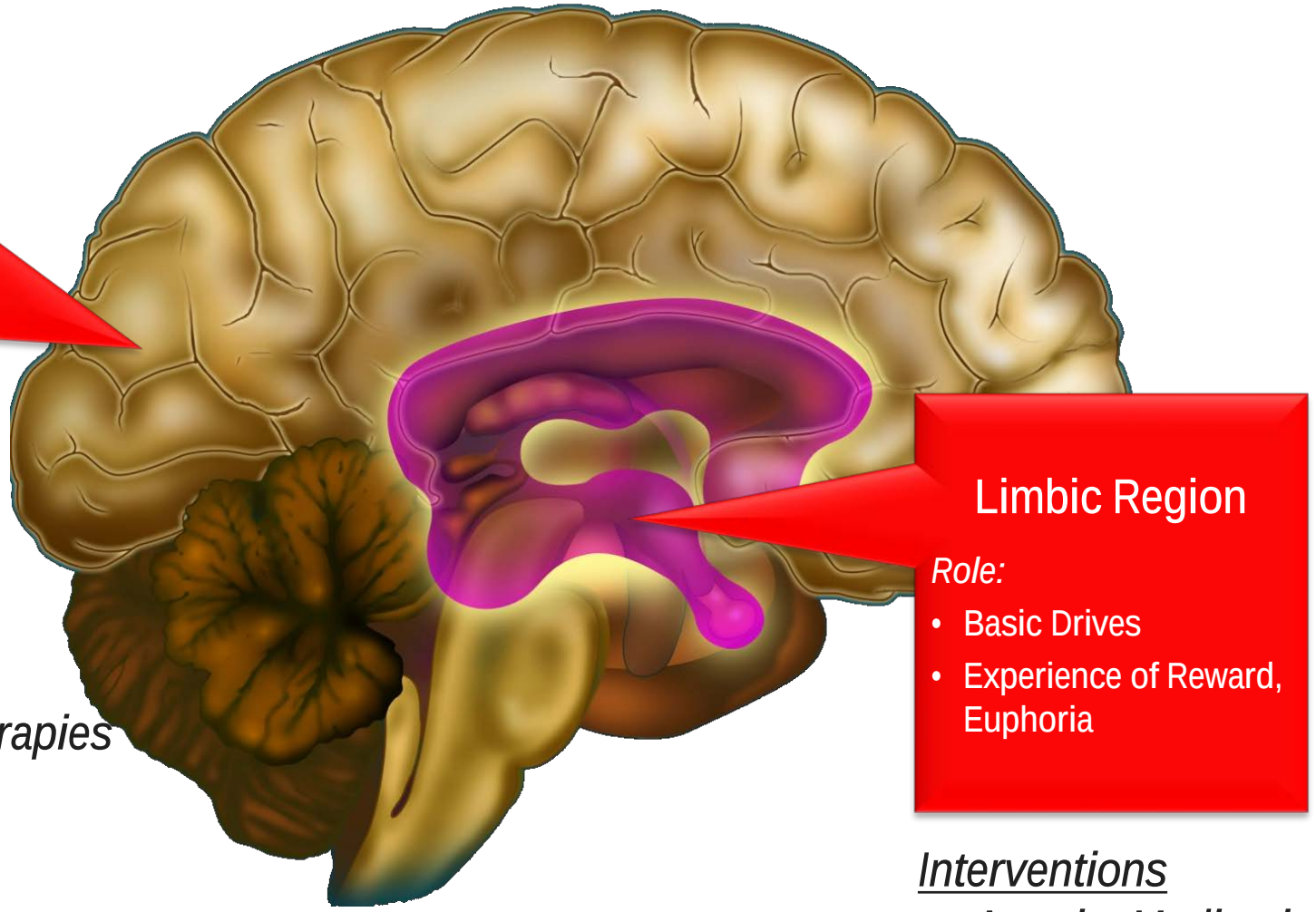
Chief Medical Officer, DynamiCare Health, Inc.

Disclosures:

- *Consultant: Alkermes, BioCorRx, Florida Alcohol & Drug Abuse Association, Indivior, Kaleo, Purdue Pharma, Rand Corp*
- *Royalty recipient: American Society of Addiction Medicine*
- *Shareholder: Alkermes, Inc.*


2007
WORLD
abc NEWS
with
Charles Gibson

Brain Structure: Two Regions – Cortex & Limbic



Cortex

Role:

- Decision making
- Thinking
- Reasoning
- Learning

Interventions

- *Psychosocial Therapies*
- *12 Step Programs*
- *Monitoring*

Limbic Region

Role:

- Basic Drives
- Experience of Reward, Euphoria

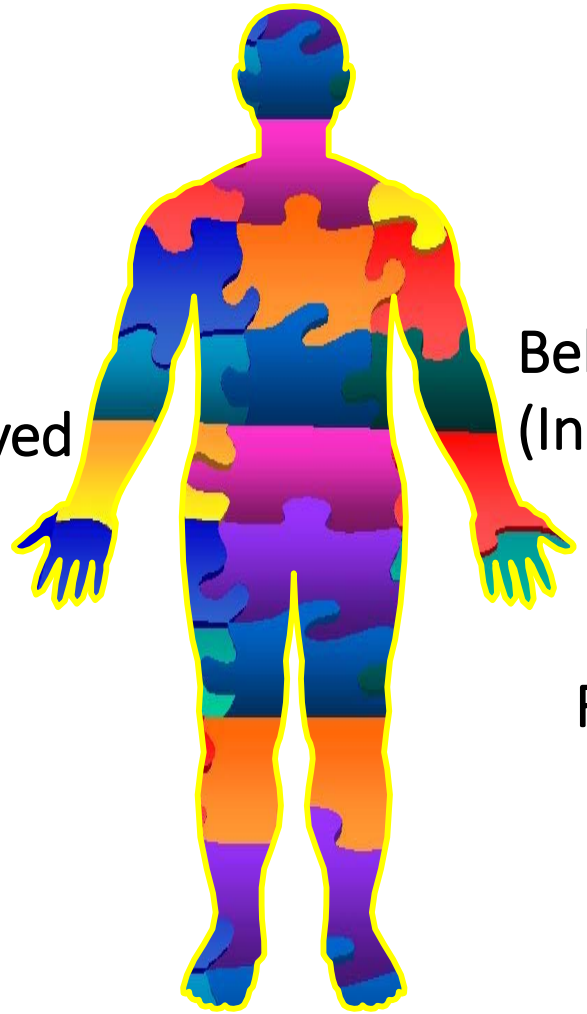
Interventions

- *Agonist Medications*
- *Antagonist Medications*

NIDA Drugs, Brains, and Behavior – The Science of Addiction Website. Available at: http://www.nida.nih.gov/scienceofaddiction/brain.html. Accessed June 1,2011.
Fowler JS et al. Sci Pract Perspect. 2007;3:4-16.

A Biopsychosocial Disorder: Treatment + Chemistry

Medications (*All* FDA-approved Agents)



Behavioral Therapies (Including Contingency Management)

Medical Detoxification Services

Recovery Support Services

Sanctions: measured, prompt, scientifically sound

NIDA

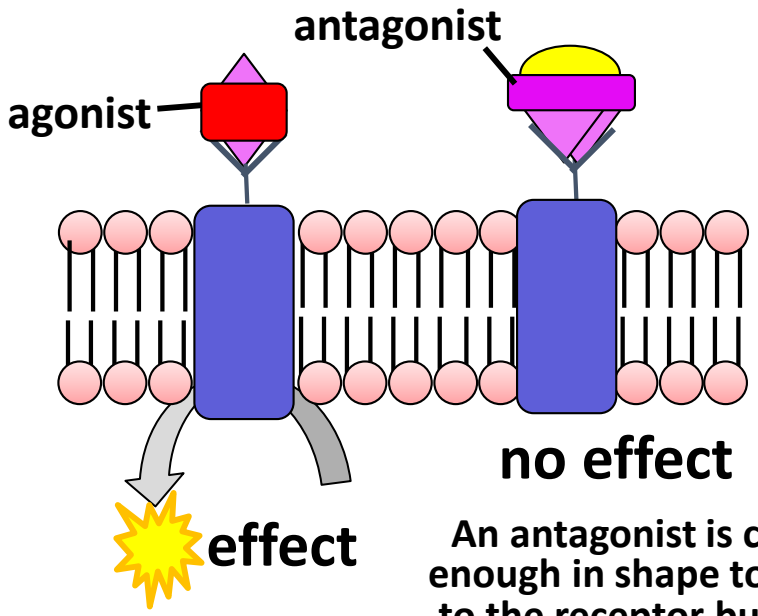
The Phases of Treatment

- Medical Detoxification – to manage withdrawal
- Post-Withdrawal Anti-Craving Medication – stabilizing brain chemistry
- Counseling – for the real *work* of recovery
  - Accept the disease
  - Know one's vulnerabilities
  - Anticipate risk factors
  - Insulate from re-encountering the drug of abuse, even under stress
  - Master new coping behaviors
  - Construct healthy relationships
  - Find purpose in life/spiritual grounding

Pharmacotherapy for Opioid Use Disorder: Goals

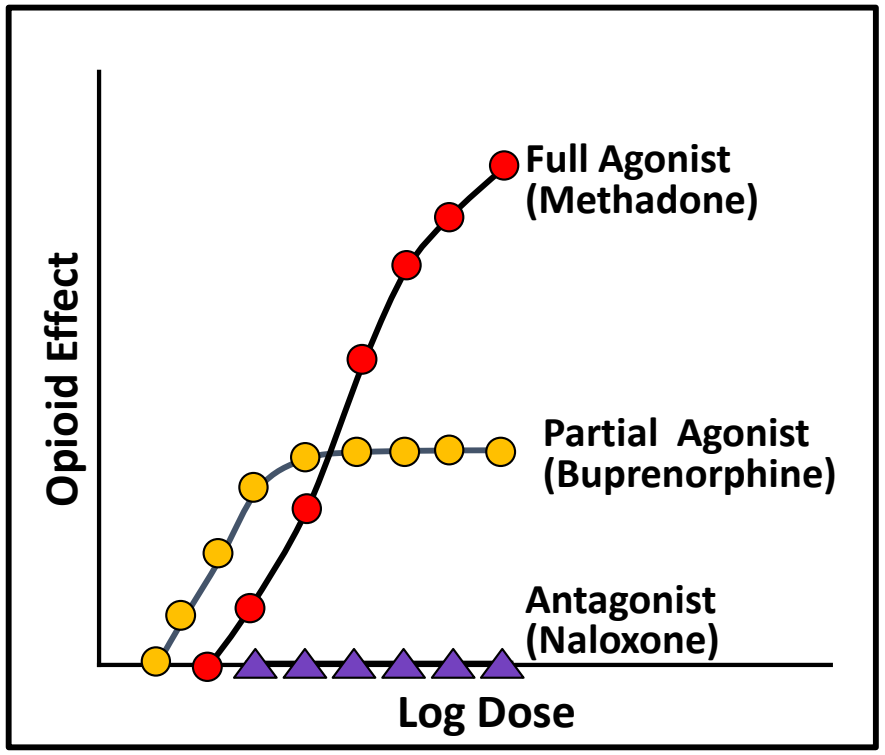
- Detoxification: detox without continued meds dominates; *inadequate care*
- Early recovery protection: Death upon prison release = 12-100x general population
- Anti-craving: stabilize urges/impulses to use to permit counseling to take hold
- Stress Response Normalization: OUD disrupts ACTH/Cortisol
- Extinction: of both positive and negative cue response
- Biological Stabilization: Eating, diurnal cycle, sexual function, self-care / activities of daily living / treatment retention, general healthcare, relationship bonding
- NOT Recovery: Disease acceptance, coping skills, rehab, spirituality

Full and Partial Agonists vs. Antagonists



An agonist has an active site of similar shape to the endogenous ligand binding to the receptor and producing the same effect

An antagonist is close enough in shape to bind to the receptor but not close enough to produce an effect. It also takes up receptor space and so prevents the endogenous ligand from binding



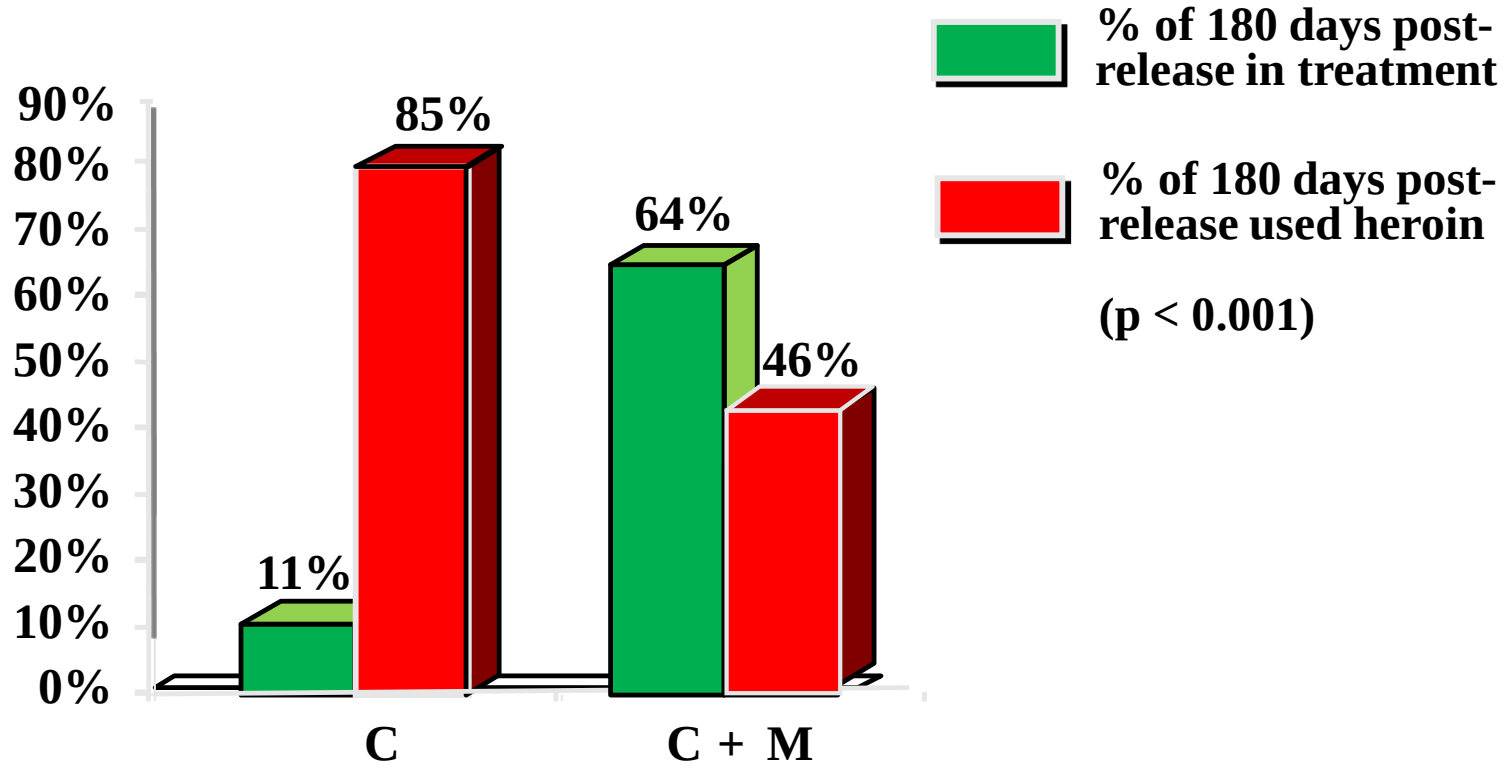
Agonist vs. Antagonists For Opioid Use Disorder

	AGONIST Pharmacotherapy		ANTAGONIST Pharmacotherapy
	Methadone (full)	***Buprenorphine (partial)***	***Oral Naltrexone, Extended-Release Naltrexone***
FDA Scheduling- Abuse Liability	**CII**	**CIII**	*none*
Maintenance of physiological opioid dependence	✓	✓	*no*
Potential for tolerance development	✓	✓	*no*
Compatible with ongoing illicit opioid use	✓	✓	*no*
Diversion issues	✓	✓	*no*
Requires Opioid Detoxification	*no*	*no*	✓
Risk of Opioid Withdrawal - Initiation	*no*	✓	✓✓
Risk of Opioid Withdrawal - Discontinuation	✓	✓	*no*
Pain Management Issues	✓	✓	✓✓

Note: No prospective head to head clinical studies have been conducted

MMT: Impact on Treatment & Heroin Use

During the 6 Mos. Post-release From Prison ± MMT (N=141)

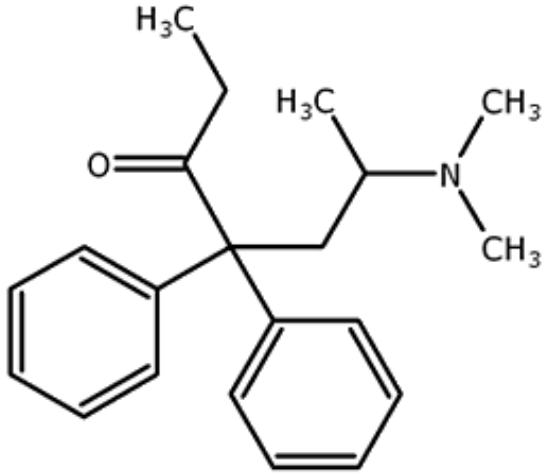


C = Counseling Only (N=70)
C+M = Counseling & Methadone Started in Prison (N=71)

Gordon, MS et al., Addiction 103:1333-1342, 2008.

Methadone:

- Full Mu-opioid agonist, slow onset & long duration (23 hrs)
- Extensive research shows benefit of treatment initiation
- Widely used in harm reduction: Anti-HIV & -HepC
- Start at 20-40 mg; titrating up until no craving or illicit use
- Average dose 80-100 mg daily
- Only in ~1,600 certified programs, per federal law
- Lipophilic; fat accumulation prolongs withdrawal
- Must be used as a long-term treatment
- Cardiac risk: Prolongs QTc
  with risk of Torsades de Pointes

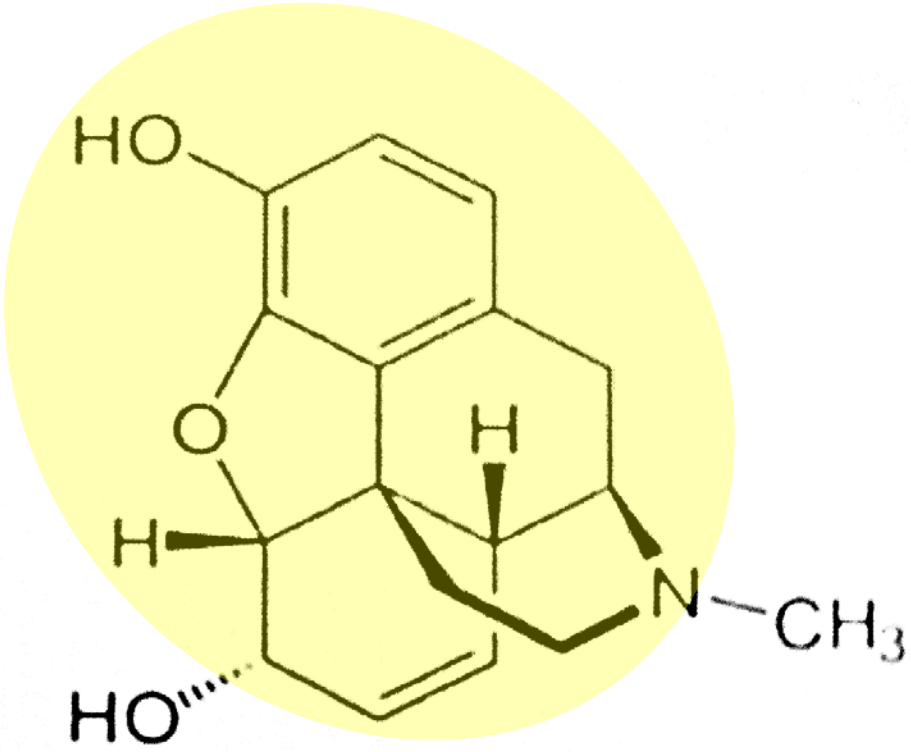


Methadone: For Whom?

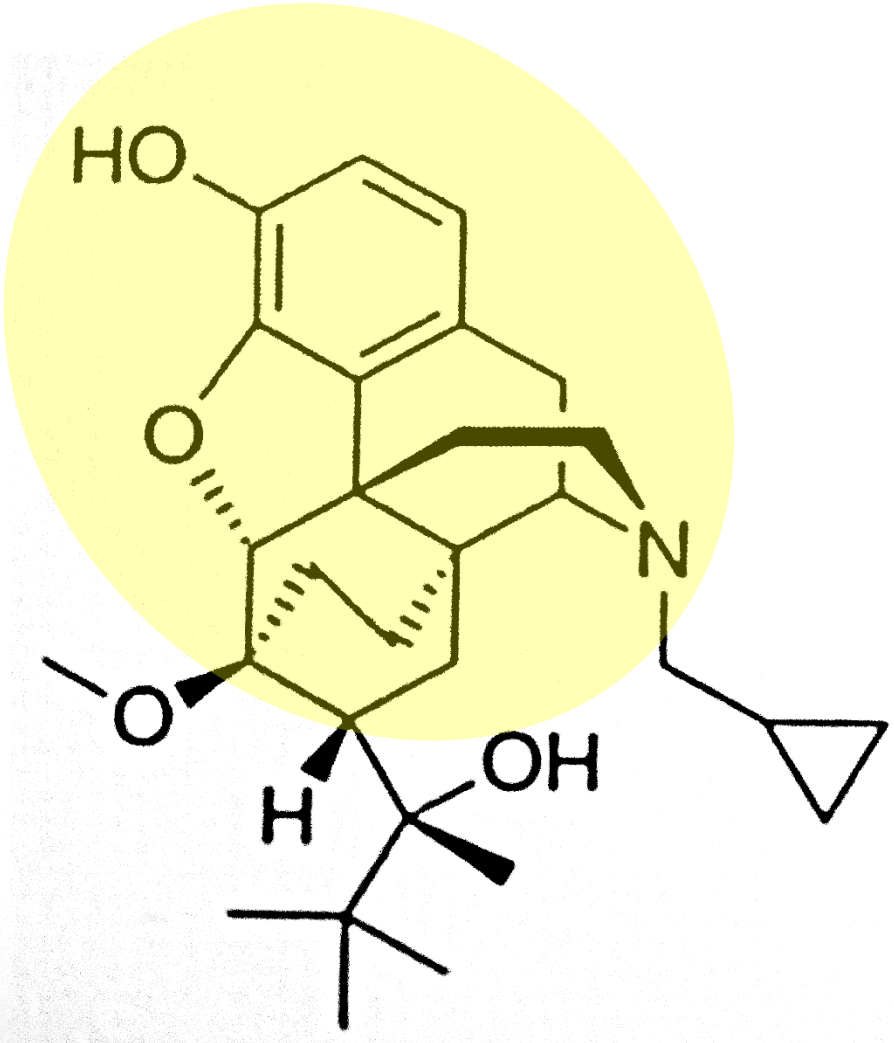
- Long history with chaotic lifestyle, psych illness, BZ use
- IV route of drug administration; high tolerance
- Needs close, daily supervision
- May have difficulty persisting with treatment
- High risk for diverting medication
- May benefit from take-home contingency management
- Wants to continue some subjective sense of opioid dependence
- Has chronic pain problems & needs/expects opioids
- Pregnant or planning to become pregnant
- Is prepared for long-term or even lifelong dosing

Methadone & Buprenorphine Molecules

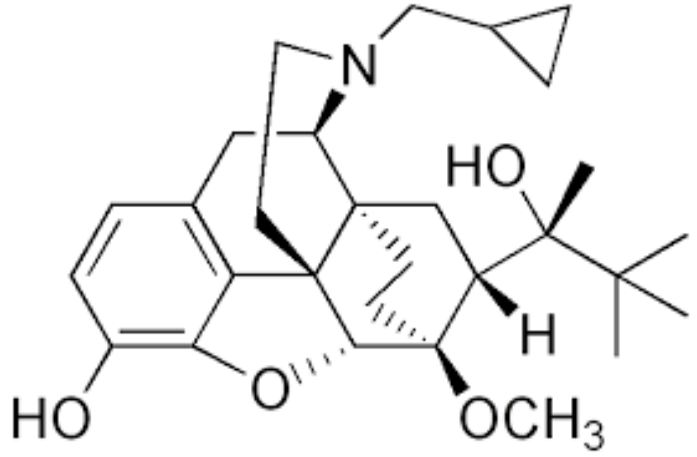
Methadone



Buprenorphine



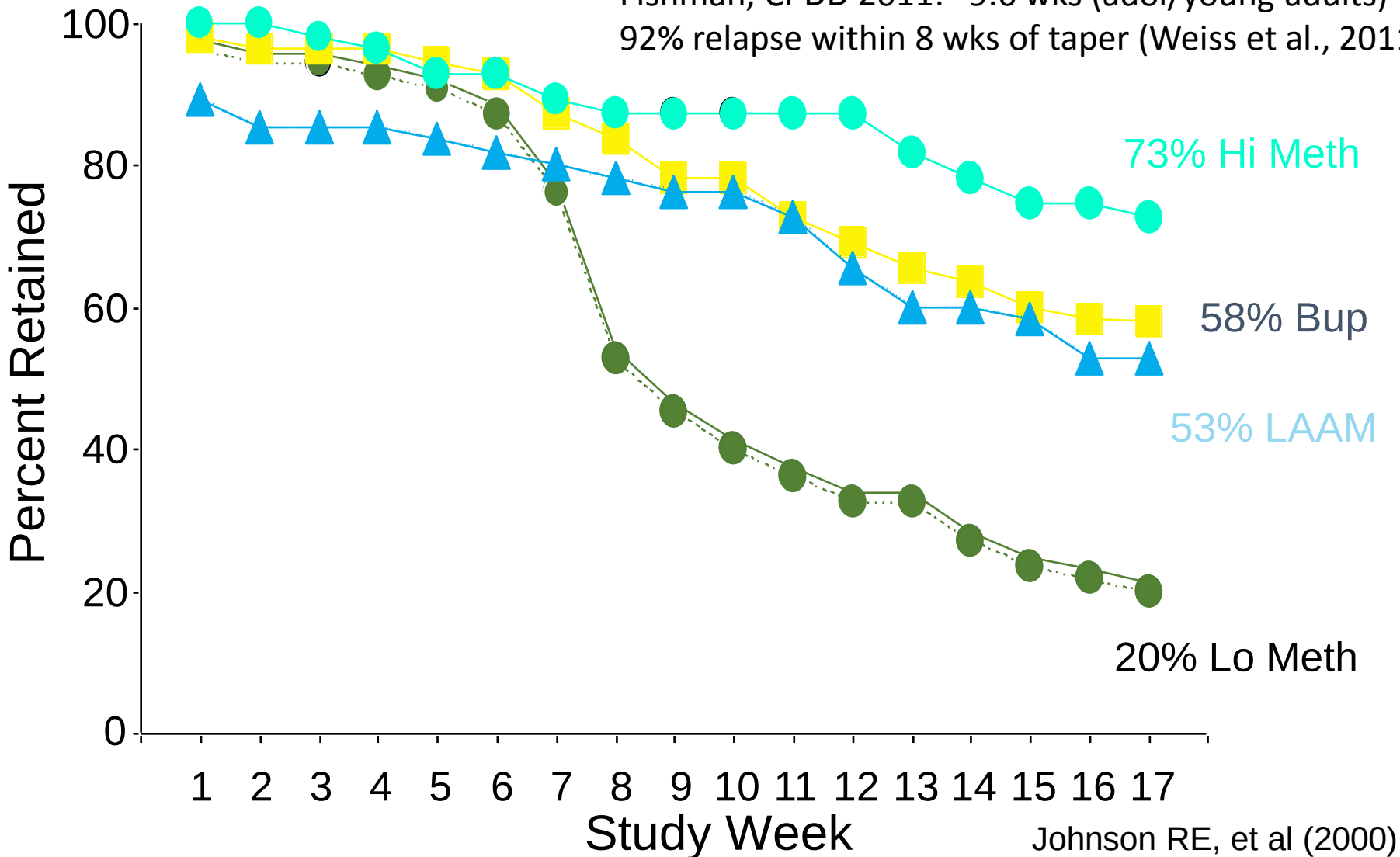
Buprenorphine



- Partial agonist: ceiling effect, less OD
- Opioid activity: ~half of methadone's
- Start patient in mild withdrawal (avoids provoking withdrawal)
- Slow onset, long-duration: helps reduce reinforcement
- Extensive research shows benefit of treatment initiation
- Prescribed daily, weekly or monthly in outpatient care
- Has greatly expanded access to care, but more is needed
- DEA Schedule C-III, requiring federal waiver, 100 patient limit
- Approved for opioid addiction (2002) as Subutex; now more commonly used as Suboxone (with naloxone in a 4:1 ratio)
- Generics (Zubsolv), film (Bunavail) & implant (Probuphine) approved

Agonists: Treatment Retention

Mean retention on BUP:
Yser, Addiction 2014: 66 days
Baser, AJMC, 2011: 69 days
Fishman, CPDD 2011: 9.6 wks (adol/young adults)
92% relapse within 8 wks of taper (Weiss et al., 2011)



Johnson RE, et al (2000)

Buprenorphine: For Whom?

MMT vs. BUP RCT (N=1,267)
Retention: MMT ≥80 mg/d = 80% vs. BUP 30-32 mg/d = 60%
Drug Use: Lower for BUP vs. MMT

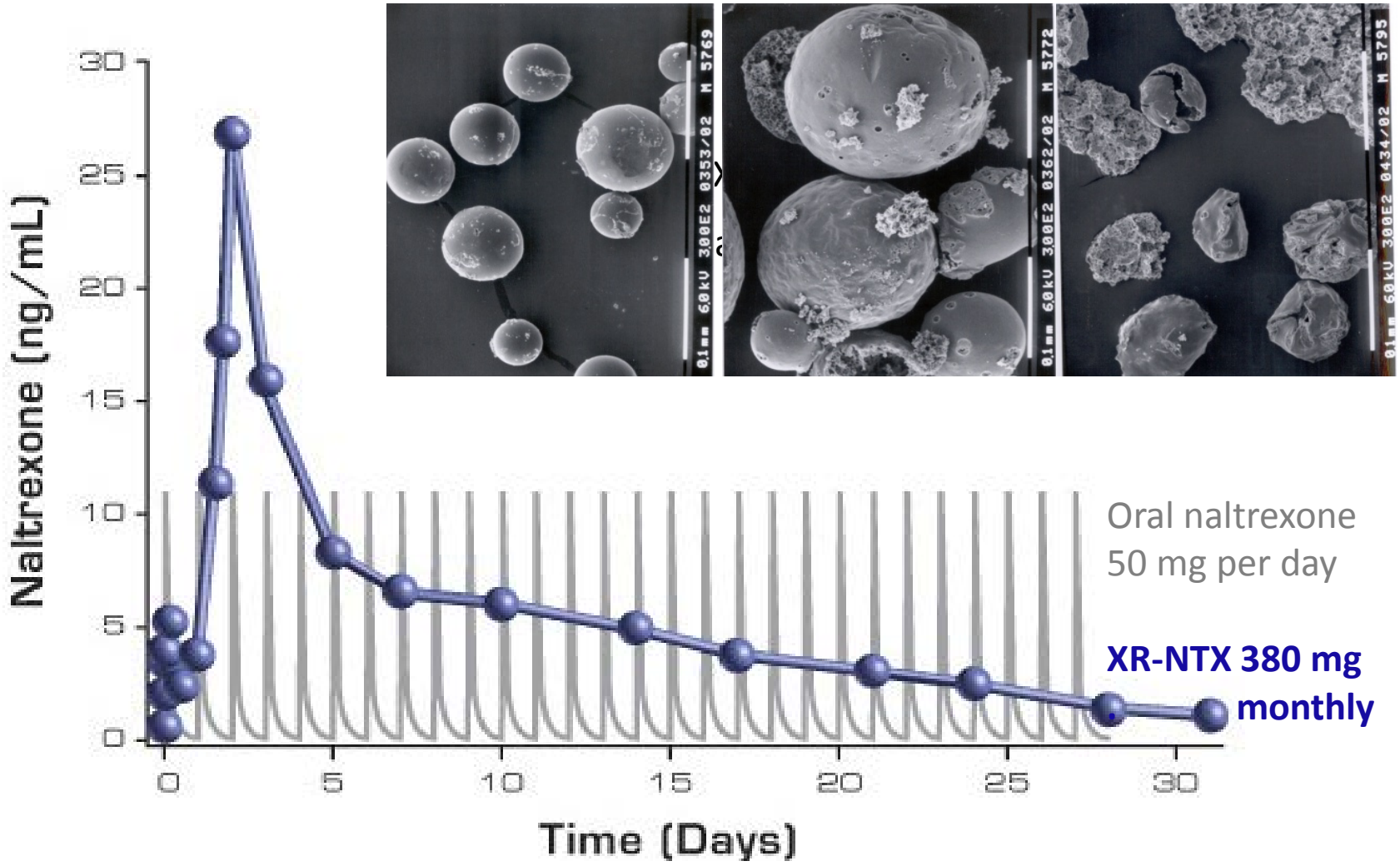
- Able to maintain a treatment plan without the daily supportive contacts/structure of a clinic
- Has structure in daily life (e.g., employed)
- Has a strong sober support system
- Has adequate stress management skills
- Pregnant women
- Patient with cardiac concerns (no QT prolongation)
- Wants less subjective sense of opioid dependence than with methadone

Extended-Release Naltrexone (XR-NTX)

- Oral NTX not better than placebo; XR-NTX: efficacy for retention & relapse
- Opioid antagonism (full competitive blockade) for 1 month
- Patient must be opioid-free 7-10 days (unless rapidly detoxed)
- Detox causes loss of tolerance, so patient must be cautioned
- Buttock muscle injection can cause injection site reactions;
  also nausea, “naltrexone flu”, toothache
- Hepatic safety: no Boxed Warning; Chronic HepC & HIV - OK
- No withdrawal upon treatment completion
- Not a controlled substance; no street value
- Treatment of choice for opioid + alcohol dependence

XR-NTX Pharmacokinetics

Mean Steady-State Naltrexone Concentration



*Predicted concentrations based on rapid achievement of steady state and literature evidence

1. Dean RL. *Front Biosci.* 2005;10:643-55.
2. Dunbar JL et al. *Alcohol Clin Exp Res.* 2006 Mar;30(3):480-90.

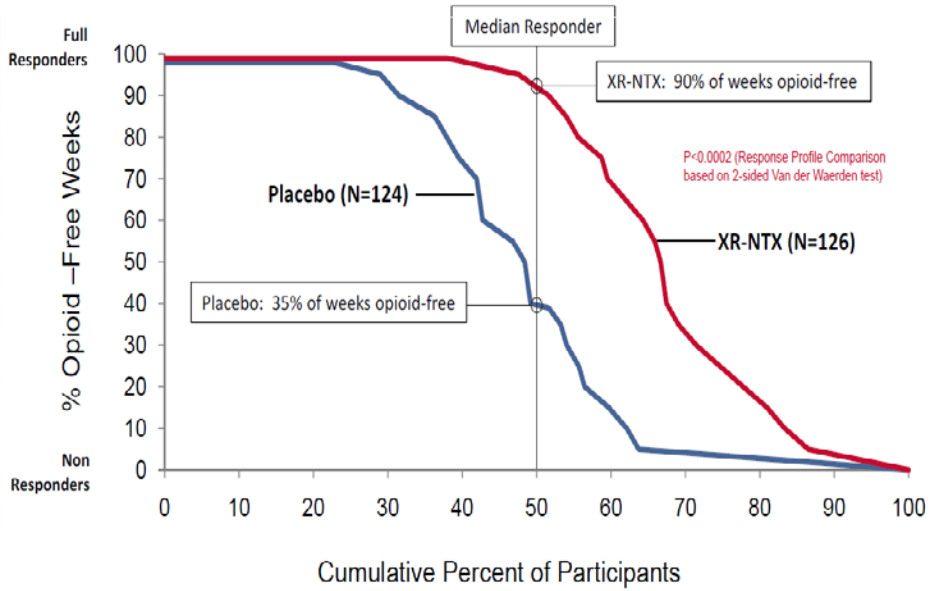
Plasma concentrations do not necessarily correlate with clinical efficacy.

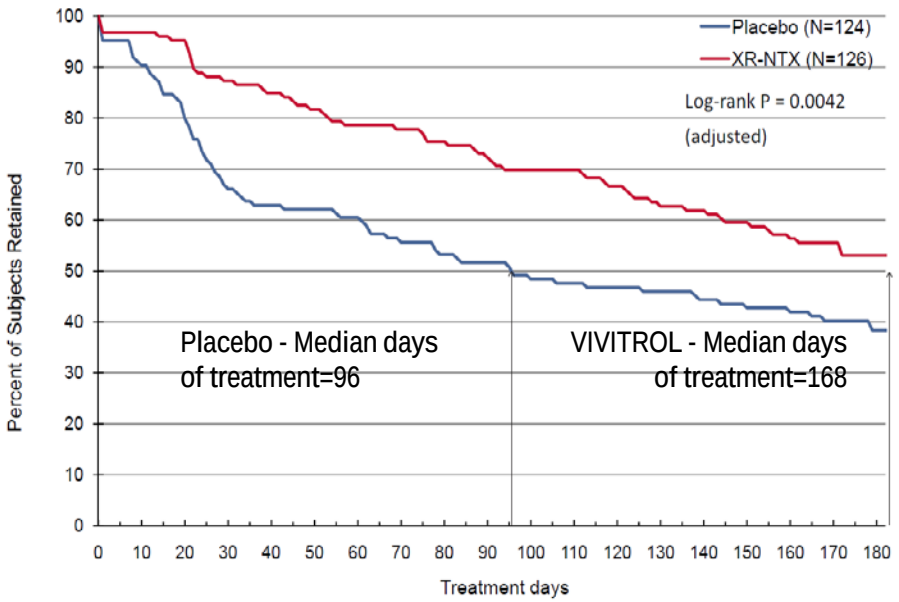
XR-NTX RCT: Abstinence, Retention, Craving

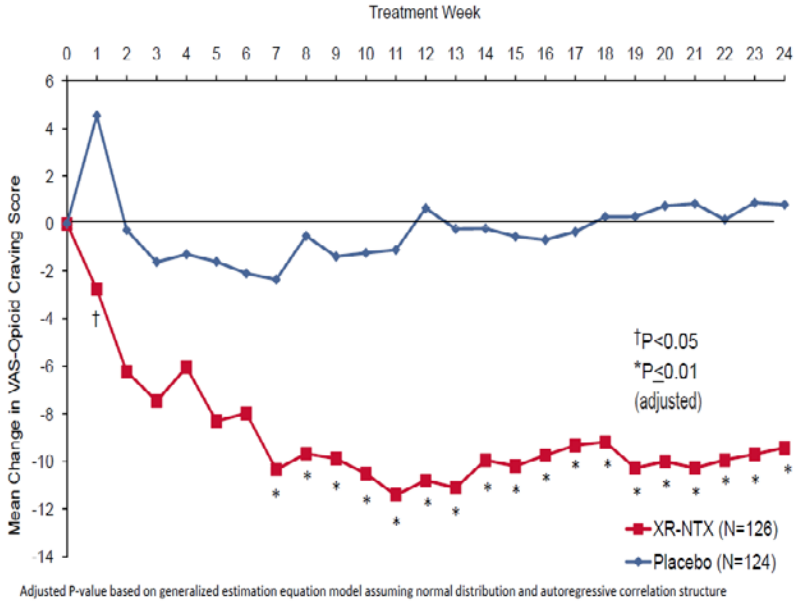
	XR-NTX (n=126)	Placebo (n=124)
Age (years)	29·4 (4·8)	29·7 (3·6)
Men	113 (90%)	107 (86%)
White	124 (98%)	124 (100%)
Duration of opioid dependence (years)	9·1 (4·5)	10·0 (3·9)
Days of pre-study inpatient detoxification	18 (9)	18 (7)
Opioid craving scale	18 (23)	22 (24)
HIV serology positive	51 (40%)	52 (42%)
Hepatitis C positive	111 (88%)	117 (94%)

Data are mean (SD) or number (%). XR-NTX=extended-release naltrexone.

Table 1: Demographics and baseline clinical characteristics







Krupitsky E et al. *Lancet*. 2011:1506-13

XR-NTX: For Whom?

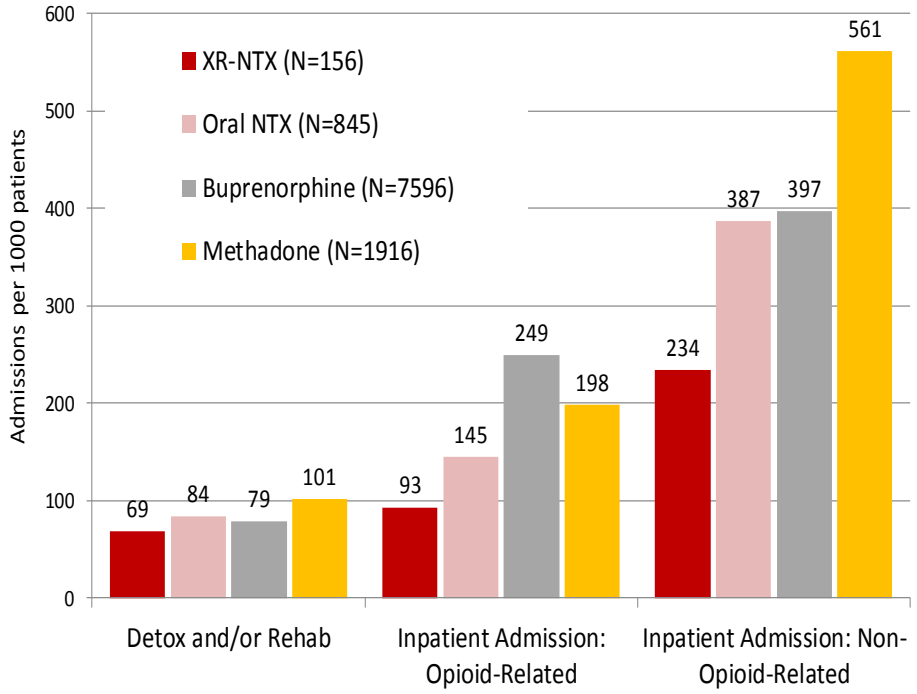
- Motivated to undergo detox & be opioid-free
- Preparing to leave rehab or jail/prison opioid-free
- Monitored by judges, professional boards, employers, schools or sports teams that may not allow agonist treatment
- Structure & social supports in place (BUT, chronicity/severity can be mild or severe)
- Rejects agonist treatment or has failed agonist treatment
- Succeeded with agonist treatment & wants to conclude it
- Wants shorter-term medication that can be easily concluded
- Late adolescent/emerging adult with shorter duration addiction
- Has both opioid and alcohol dependence

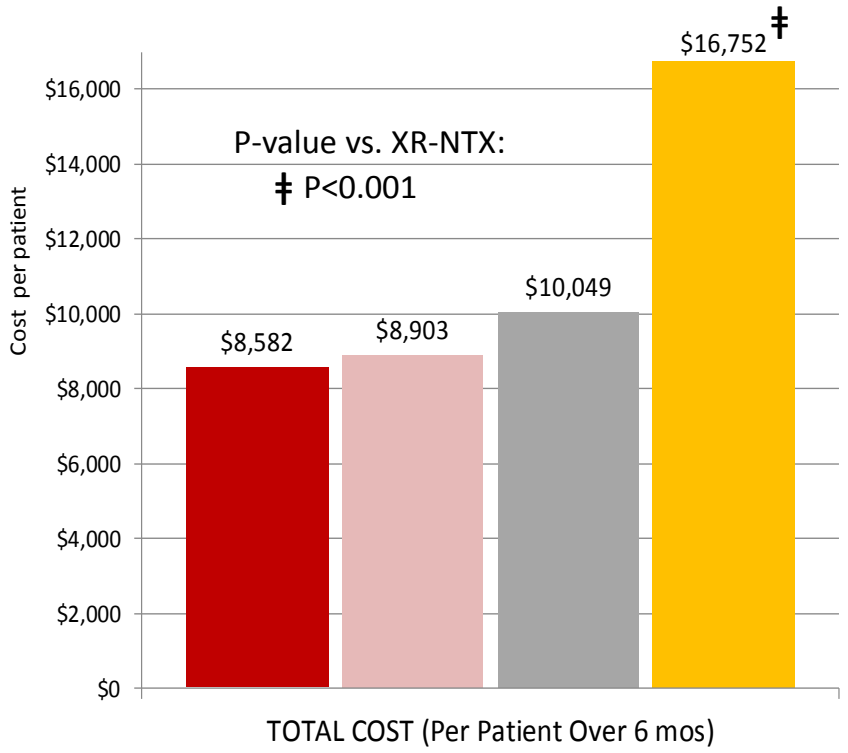
Healthcare Costs with OUD Pharmacotherapies

- MMT, direct = $ 1/day
- MMT, overall = $10-20/day

BUP = $ 4-$30/day
XR-NTX = $20-40/day

6-mo retrospective insurance cost study: all meds + inpt + outpt services (N=10,413) casemix controlled with with instrumental variable analysis

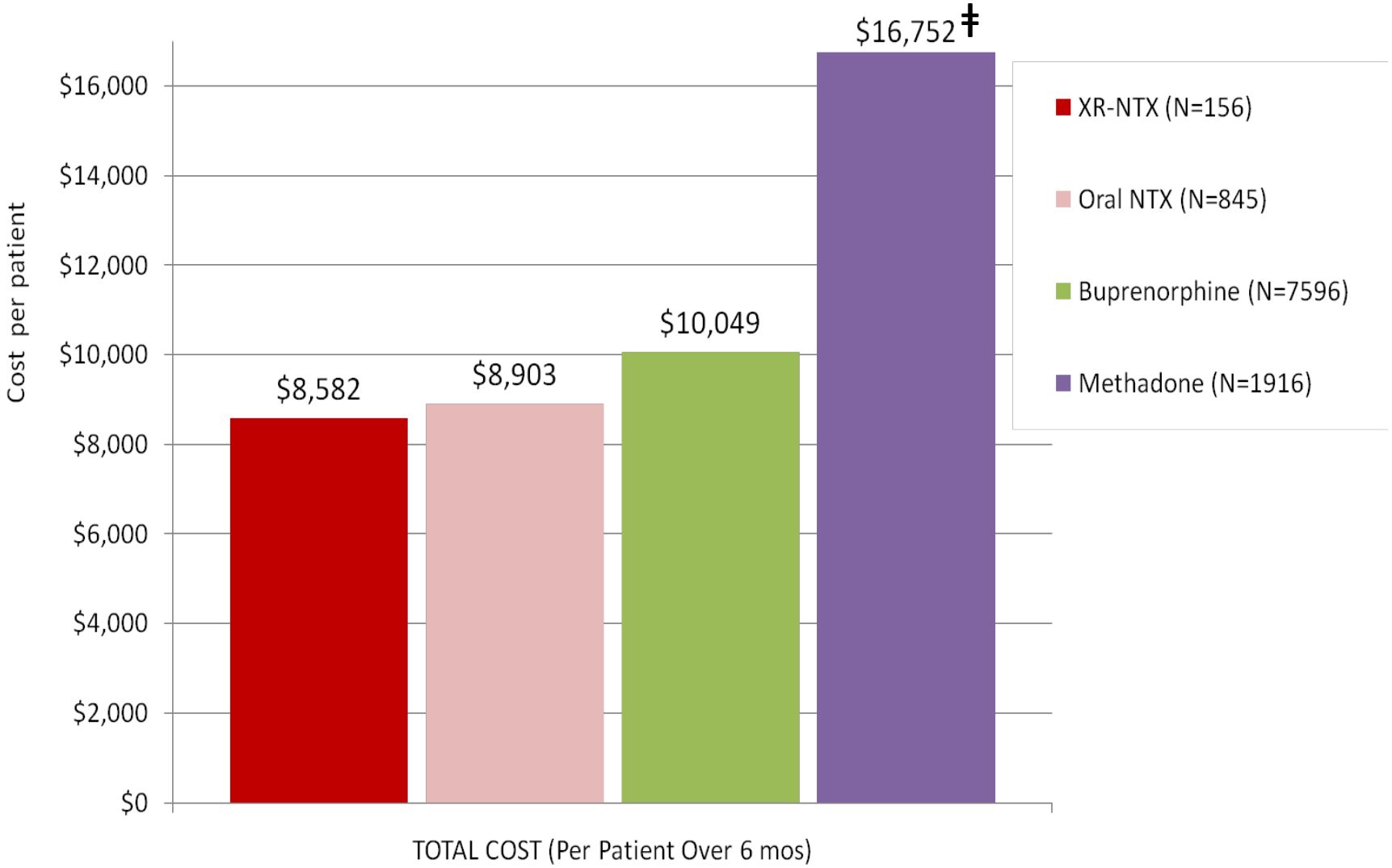




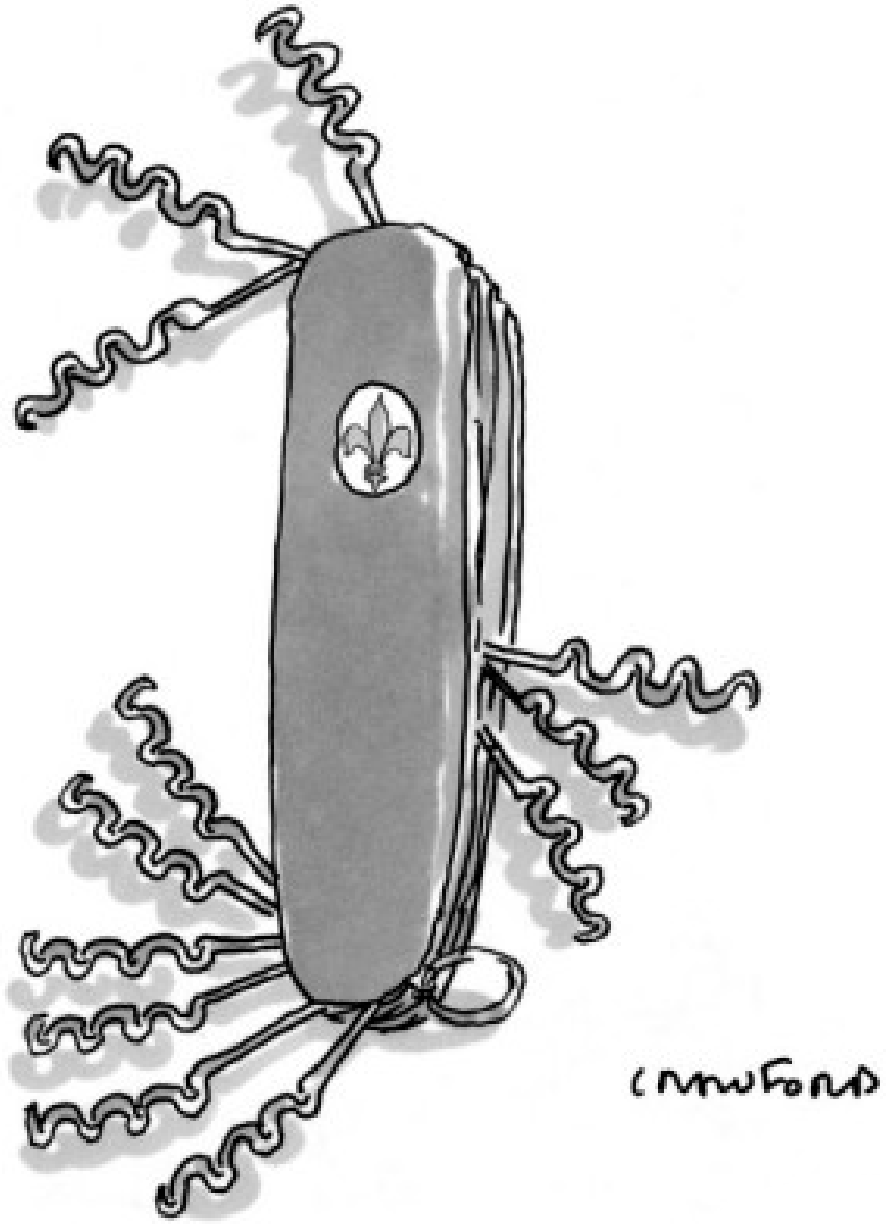
(Baser O , Chalk M, Fiellin DA, Gastfriend DR. AJMC 17: S235-S246, 2011)

6-Mo TOTAL Healthcare Costs

(Inpatient + Outpatient + Pharmacy)



P-value vs. XR-NTX: ‡ P<0.001



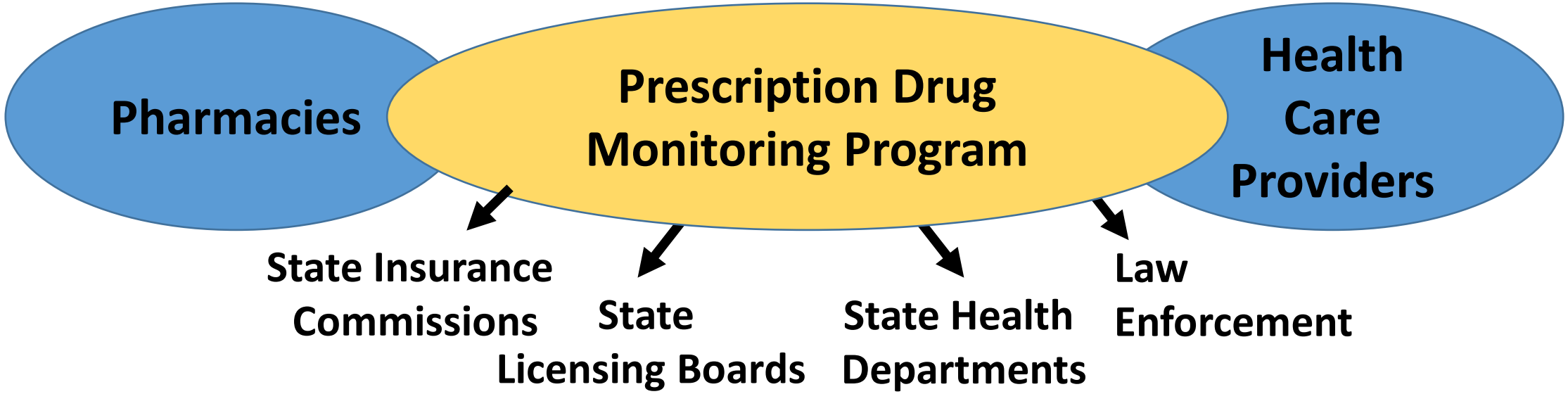
FRENCH ARMY KNIFE

Conclusions: MAT in Opioid Dependence

- Opioid dependence: chronic, requires long-term meds + counseling
- Goals: save lives, stabilize behavior, establish social function
- Agonists & antagonists are superior to counseling alone
- All FDA-approved agents are appropriate 1st-line approaches
- Programs should provide ALL options, & DESEGREGATE care
- Low initial costs can become high costs longer-term, and high initial costs can result in lower costs longer-term. Therefore, cost should NOT be a consideration in clinical care.
- Patient choice may be the BEST basis for drug selection.
- If one agent is unsuccessful, try the other options!

Overdose: Prevent, Educate, Monitor, Reverse

- Mandate Training: <1% of U.S. MDs train in addiction medicine
- Develop better abuse-deterrent opioid medicines
- Prescription Drug Monitoring Programs: Need a nationwide system



- Naloxone: Can cut U.S. opioid overdose deaths in half

Overdose Risks & Solutions

- Accidental poisonings: leading cause of accidental death (>MVA)
- ≤61% of accidental poisonings are attributed to opioids
- Nonfatal opioid OD occurs 3-7 times more than fatal OD
- ODs account for >6000 ED visits per day (SAMHSA, 2013)
- Opioid Risks: Rx opioids, Heroin, Illicit Fentanyl, BZs, ETOH, Stimulants switching pain meds, COPD, Sleep Apnea
- Check the state PDMP: Prescription Drug Monitoring Program
- Address Predispositions: History, family Hx,
  re-entry from controlled environment…

Overdose Risks & Solutions

- Teach safe use: “IF you’re going to use, use a “Test Shot” & always use with others.”
- Naloxone and CPR <u>for all opioid users</u>
  - From injection to death: *1-3 hours to reverse an OD*
  - San Francisco DPH (2003-09) 1,942 trained w/naloxone; 24% took a refill
  - 11% used for an OD. In 399 cases, 89% reversed. <1% serious adverse effects.
  - 911: has Good Samaritan assurances
  - Provide Naloxone to: users, families, 1st responders/providers, bars/clubs
  - Train patients/families in Rescue Breathing

Can Treatment Work for All With Addiction?

EDITORIAL

Editorials represent the opinions of the authors and JAMA and not those of the American Medical Association.

Physician Substance Abuse and Recovery

What Does It Mean for Physicians—and Everyone Else?

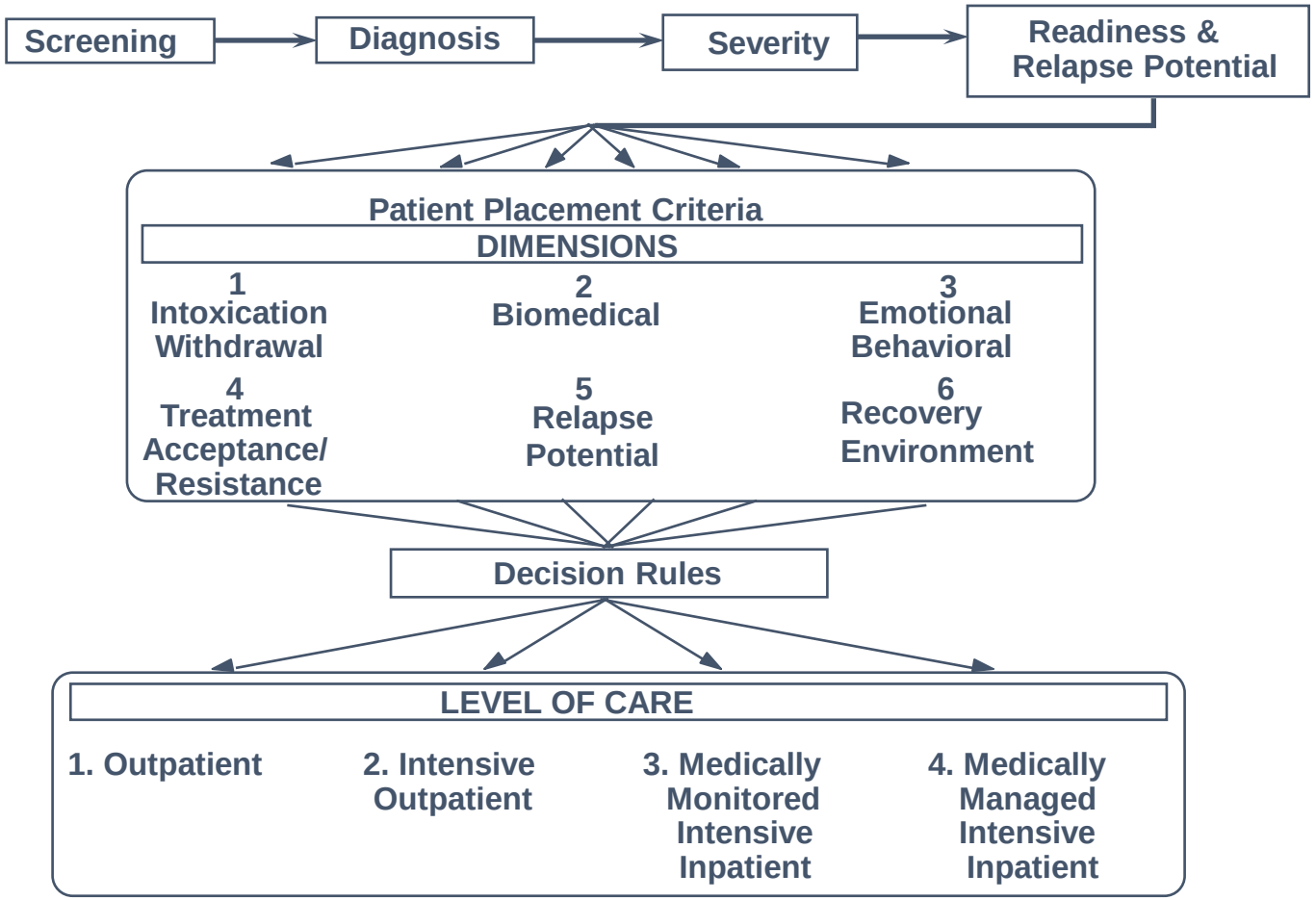
David R. Gastfriend, MD

THE 10% TO 15% PREVALENCE OF SUBSTANCE USE DISorders among physicians is similar to that in the general population,[1,2] but the quality and intensity of treatment given to physicians may far exceed that available to other individuals with these disorders.[3-5] Recognition of the impaired physician began to emerge only in the 1970s[6] and has led to the development of physician health programs (PHPs). These are now mature models, available in many states, usually through medical societies, as an alternative to monitoring by state government boards of registration in medicine.[7] In many cases, physicians who voluntarily contract with a PHP may remain anonymous[8] to the state medical board and the National Practitioner Data Bank, a feature designed to promote early intervention in the disease process, ie, before patients are harmed. Many PHPs now offer services to other health professionals also. Treatment in these programs is probably the most compre-

See also p 1453.

Author Affiliations: Addiction Research Program, Department of Psychiatry, Massachusetts General Hospital, and Department of Psychiatry, Harvard Medical School, Boston, Mass. Dr Gastfriend is now vice president of medical affairs, Alkermes Inc, Cambridge, Mass.
Corresponding Author: David R. Gastfriend, MD, Alkermes Inc, 64 Sidney St, Cambridge, MA 02139 (david.gastfriend@alkermes.com).

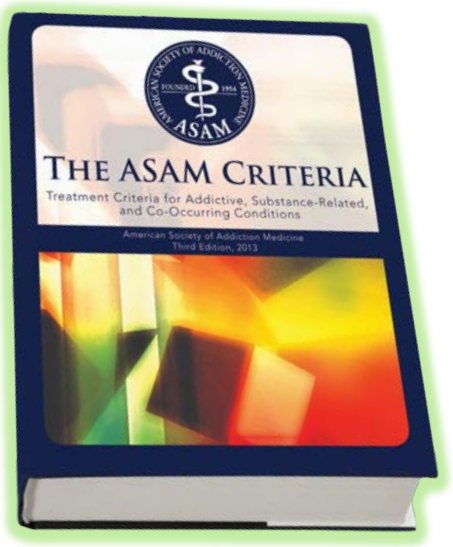
The ASAM Criteria for Treatment Matching



ASAM
American Society of Addiction Medicine

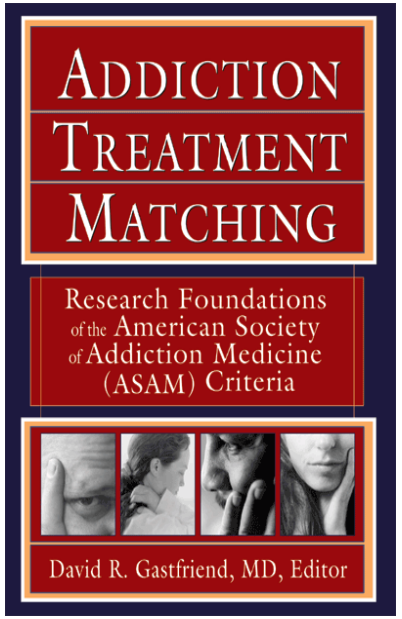
ASAM Text: Hundreds of Decision Rules

To place patients in the least intensive & restrictive care that meets the patient's multi-dimensional needs and affords optimal treatment outcome



www.ASAMcriteria.org

www.haworthpress.com

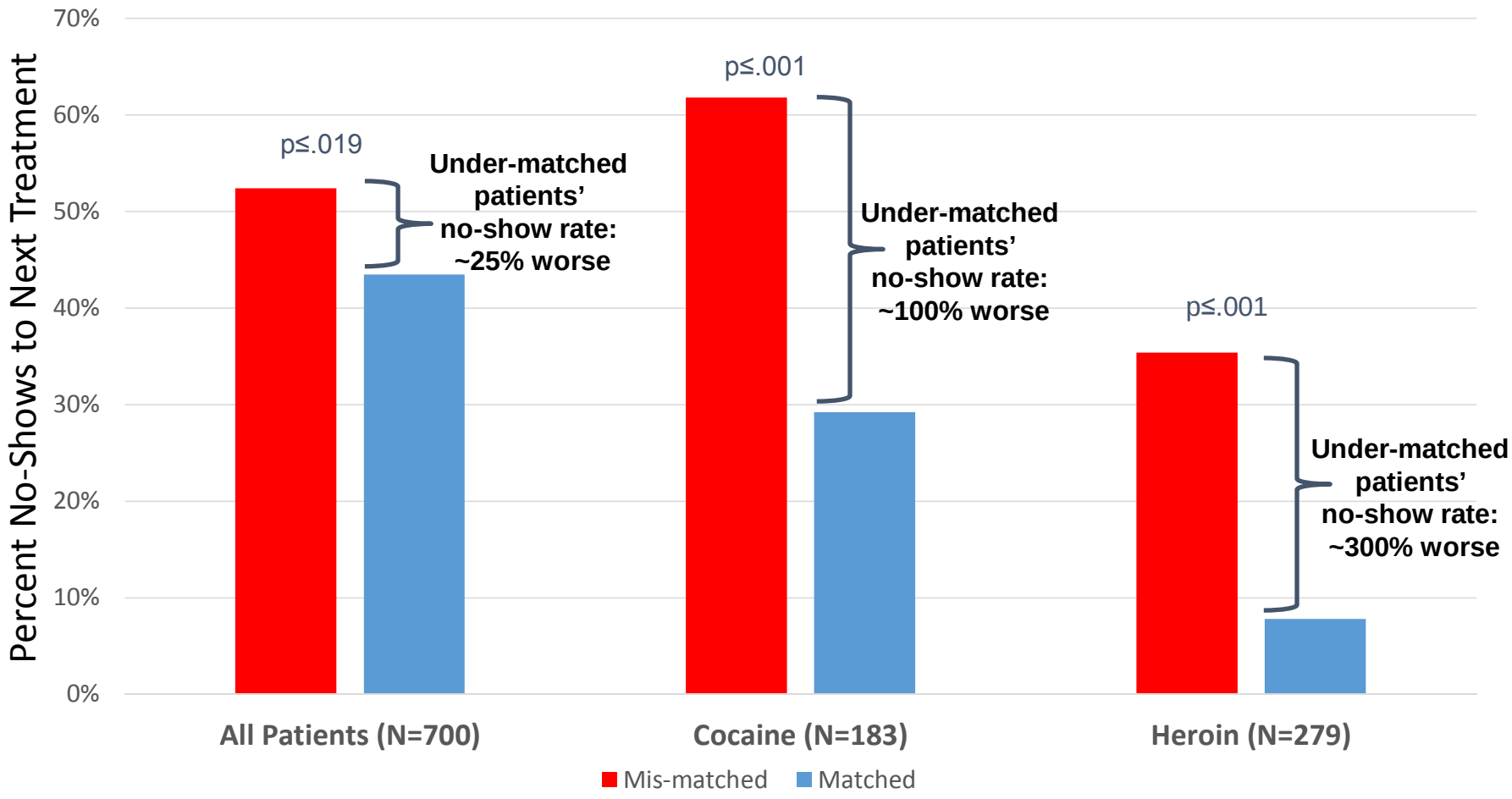


ASAM PLACEMENT CRITERIA

LEVELS OF OF CARE	1. OUTPT	2. INTENSIVE OUTPT	3. MED MON INPT	4. MED MGD INPT
CRITERIA				
Intoxication/ Withdrawal	no risk	minimal	some risk medical	severe risk 24-hr acute
Medical Complications	no risk	manageable	monitoring required	med. care required
Psych/Behav Complications	no risk	mild severity	moderate	24-hr psych. & addiction Tx required
Readiness For Change	cooperative	cooperative but requires structure	high resist., needs 24-hr motivating	
Relapse Potential	maintains abstinence	more symptoms, needs close monitoring	unable to control use in outpt care	
Recovery Environment	supportive	less support, w/ structure can cope	danger to recovery, logistical incapacity for outpt	

Under-Matching Worsens No Show to Treatment

From Inpatient Detox to Either Residential Rehab or Day Treatment:
All patients, High Frequency Cocaine Users and Heroin Users



"Nobody ever asks 'How's Waldo?'"

ASAM•CS

Section	% Complete
Used Substances	100%
Alcohol Use	18.2%
CIWA Sedative and Alcohol Scale	0%
Addiction Treatment History	80%

1809808

Religion: Protestant Ethnicity: Caucasian

Edit

"How strong is your desire to use any drug right now?"

0	1	2	3	4
Not at all	Slightly	Moderately	Considerably	Extremely

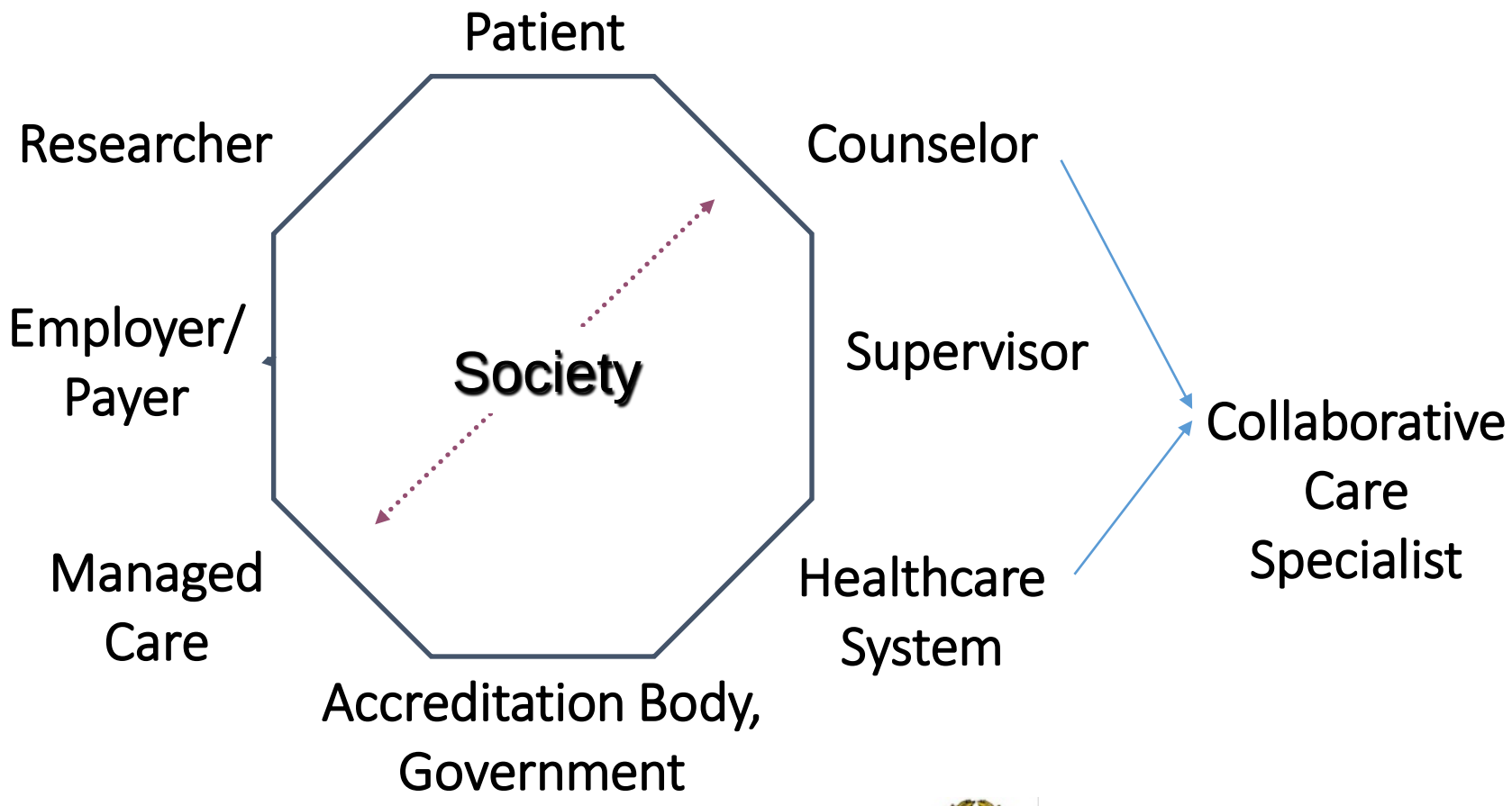
"Have your addiction symptoms increased recently? How...? (Ask about any items below not mentioned by the patient) Have you had more craving, risk behaviors, more frequent use, increased amount of substance or have you used a more rapid route of administration?"

- No; has been fully participating in all recommended treatments
- No; open to fully participating in any recommended treatments
- Passive or some hesitations
- Resists important components
- Rejecting or obstructs plan with many contingencies

"Do you feel you are likely to continue using or, if not using, that you are in danger of relapsing? How soon...? Do you feel at risk, even if you have had some treatment previously?"

"Do you have any concerns about pursuing treatment...? Would anything possibly hold you back, such as money, insurance, schedule, attending groups, having to take medicines, drug

Stakeholders in the Health IT Revolution

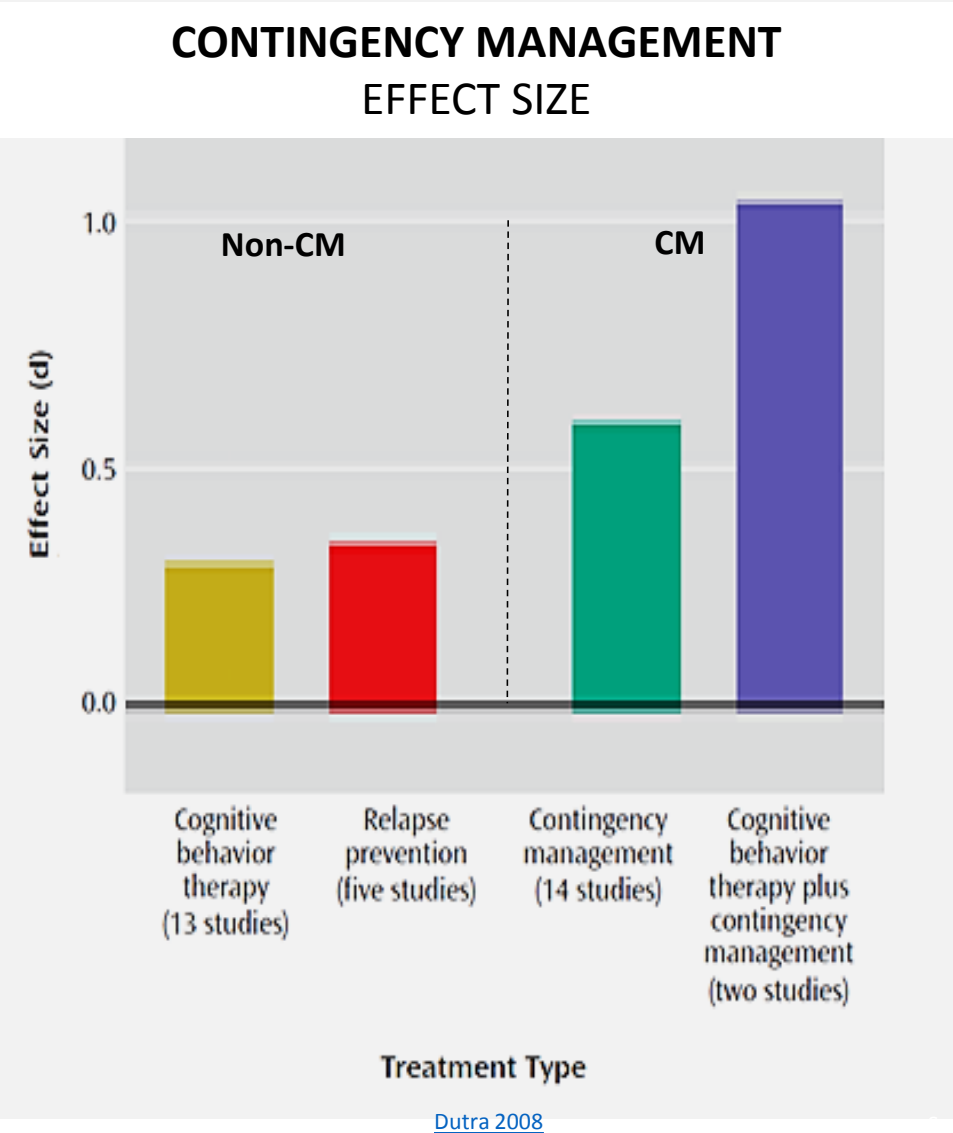


Psychosocial Therapy/Support

- **Psychosocial therapies dominate – without meds**
- **This stands in stark contrast to extensive research evidence favoring COMBINED care *with medication***

  - **Brief interventions**
  - **Motivational Enhancement Therapy**
  - **12-step programs**
  - **Cognitive-Behavioral Therapy**
  - **Cue exposure therapy**
  - **Behavioral Couples Therapy**
  - **Recovery Support Services: Coaches, Wrap-around services**
  - **Contingency Management: Incentives to restart reward system**

INCENTIVES WORK!



Dutra 2008

Incentives for addiction treatment, called Contingency Management (CM), are effective for all drugs, >40 RCT's, 5 meta-analyses

Yet over 90% of U.S. addiction treatment programs *do not use it!*

Barriers to adoption:

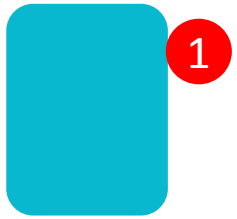
- **Cost of rewards**
- **Labor-intensive (drug testing & distributing rewards)**
- **Lack of training**
- **Cultural resistance**

Benishek 2014 Carroll 2014 Dutra 2008 Herbeck 2008

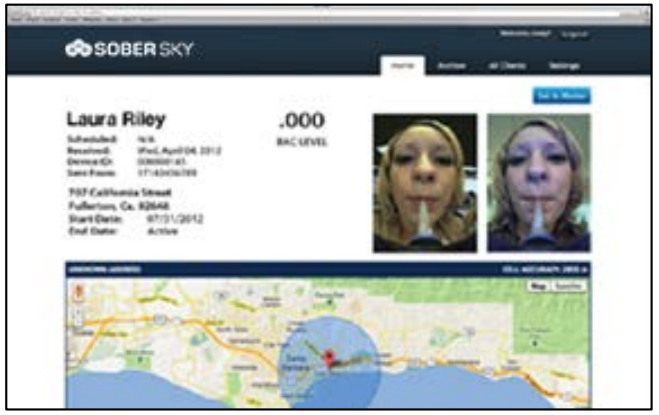
HOW TO MAKE INCENTIVES WORK

Crowdfunding campaign raises money for incentives

User receives smartphone app, debit card, and testing device



User gets "random" alerts for drug testing (via predictive analytics)



User performs drug test, smartphone app verifies it

Money is deposited

onto debit card!

Myths & Ethical Conundrums

- “Gold standard” = health, NOT necessarily abstinence
- MAT: “Medication-Assisted Treatment” – *stigma?*
  “Medication in Addiction Treatment”?
- Lifelong “Endorphin Deficiency”: little or no evidence
- MMT & OBOT “long term treatment” is not the norm
- Reinforcement: Critical & inadequately studied
- When MVAs peaked, U.S. mandated airbags, raising car costs by $1,000; OD deaths now surpass MVAs – what can we spend?
- Would we license autos that omit seat belts or headlights?
  Do we accredit hospitals for bypass surgery without cardiology?
- If med/surgical specialties report 5-year outcomes, should addiction treatment?
- Is it ethical to <u>mandate</u> treatment + pharmacotherapy in CJ? Is it ethical NOT to?


LASSIE!
GET HELP!!