

METHADONE TREATMENT IN THE U.S.A

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**Developed and studied in the U.S.
and elsewhere**

**Allowed but more tightly regulated
than anywhere else**

Scientifically proven

Politically controversial

Hypothesis (1963–1964)

Heroin (opiate) addiction is a disease – a “metabolic disease” – of the brain with resultant behaviors of “drug hunger” and drug self-administration, despite negative consequences to self and others. Heroin addiction is not simply a criminal behavior or due alone to antisocial personality or some other personality disorder.

Functional State (Heroin)



Goals and Rationale for Specific Pharmacotherapy for an Addiction

- 1. Prevent withdrawal symptoms**
- 2. Reduce drug craving**
- 3. Normalize any physiological functions disrupted by drug use**
- 4. Target treatment agent to specific site of action, receptor, or physiological system affected or deranged by drug of abuse**

Characteristics of an Effective Pharmacotherapeutic Agent for Treatment of an Addictive Disease

- **Orally effective**
- **Slow onset of action**
- **Long duration of action**
- **Slow offset of action**

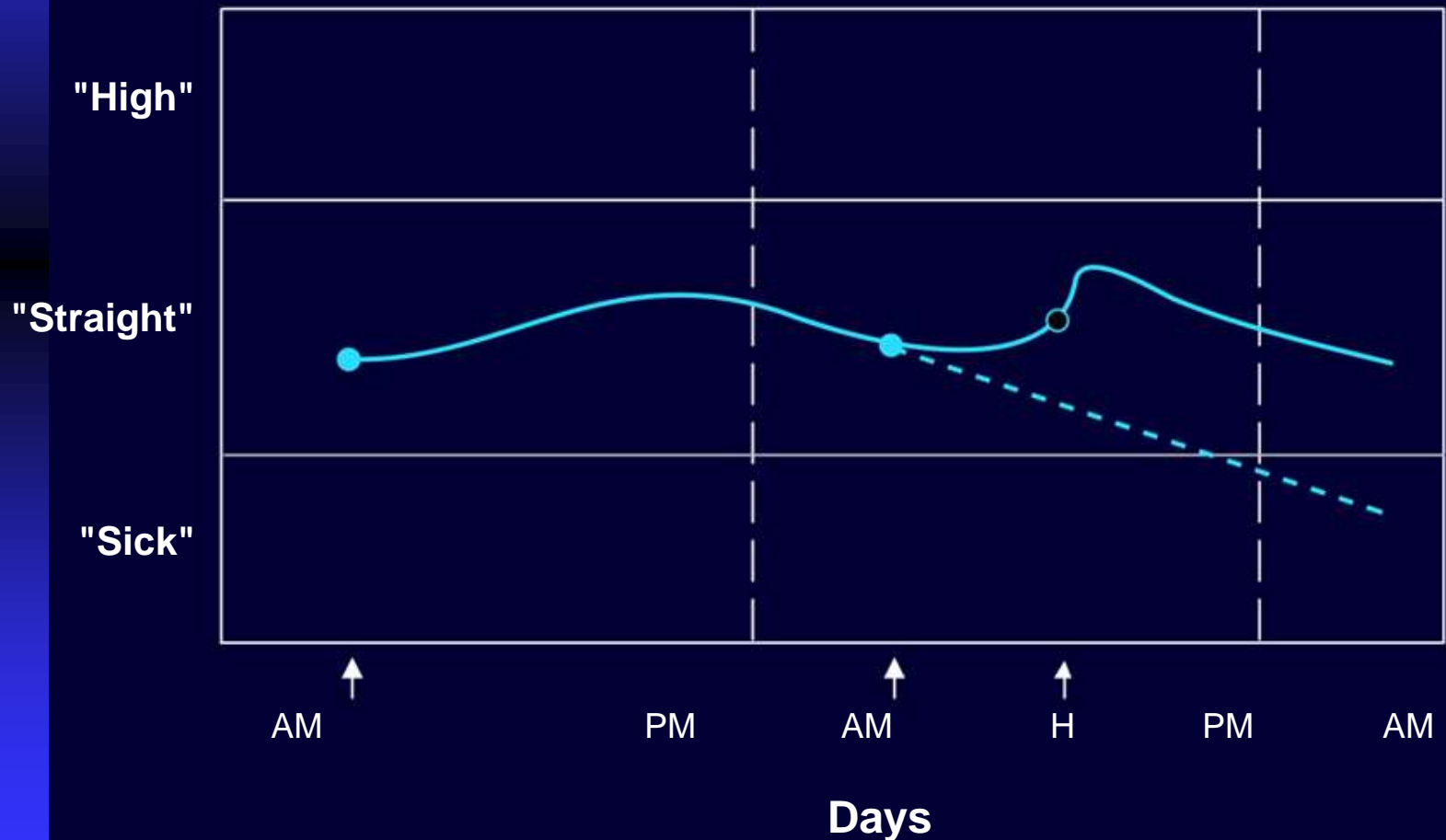
Heroin versus Methadone*

	<u>Heroin</u>	<u>Methadone</u>
Route of administration	intravenous	oral
Onset of action	immediate	30 minutes
Duration of action	3–6 hrs	24–36 hrs
Euphoria	first 1–2 hrs	none
Withdrawal symptoms	after 3–4 hrs	after 24 hrs

* effects of high dosages in tolerant individuals

Long-Acting Methadone Administered on a Chronic Basis in Humans - 1964 Study

Functional State (Methadone)



Plasma Methadone Levels in an Individual Maintained on 100 mg/day



Opioid Agonist Pharmacokinetics: Heroin Versus Methadone

Compound	Systemic Bioavailability After Oral Administration	Apparent Plasma Terminal Half-life ($t_{1/2\beta}$)	Major route of Biotransformation
Heroin	Limited (<30%)	3 m (30 m for active 6-acetyl-morphine metabolite) (4-6 for active morphine metabolite)	Successive deacetylation and morphine glucuronidation
Methadone	Essentially Complete (>70%)	24 h (48 h for active l-enantiomer)	N-demethylation

“Blending”– 1969-1973 (to 2002)

Early Formal Linkage Between Academic Centers and Community-Based Treatment Programs

- 1969 Initiation of special research-based methadone maintenance treatment program for youthful (16 to 21 yo) long-term heroin addicts (more than 3 years of multiple, daily self-administrations of heroin) *(Dole, Nyswander, and Kreek, later joined by Millman and Khuri at the Rockefeller Hospital)*
- 1971 Relocation of this “Adolescent Development Program” as a community-based treatment facility, with ties to Cornell-New York Hospital and continuing ties to Rockefeller University *(ADP headed by Drs. R. Millman and E. Khuri)*
- 1973 Creation of a second, separate community-based methadone maintenance treatment facility, the “Adult Clinic”, for adult long-term heroin addicts, also with ties both to Cornell-New York Hospital and to the Rockefeller University *(AC headed by Dr. Aaron Wells)*

Methadone Maintenance Treatment for Opiate (Heroin) Addiction

Number of patients in treatment: 179,000

Efficacy in “good” treatment programs using adequate doses:

Voluntary retention in treatment (*1 year or more*) 60 – 80%

Continuing use of illicit heroin 5 – 20%

Actions of methadone treatment:

- Prevents withdrawal symptoms and “drug hunger”
- Blocks euphoric effects of short-acting narcotics
- Allows normalization of disrupted physiology

Mechanism of action: Long-acting narcotic provides steady levels of opioid at specific mu receptor sites (*methadone found to be a full mu opioid receptor agonist which internalizes like endorphins and which also has modest NMDA receptor complex antagonism*)

Issues #1

- Controversy about dose
- Dole & Nyswander recommended 80-120 mg
- Some studies showed 40-50 did as well as 80
- Later studies confirmed Dole & Nyswander's original dose

McLellan et al study:

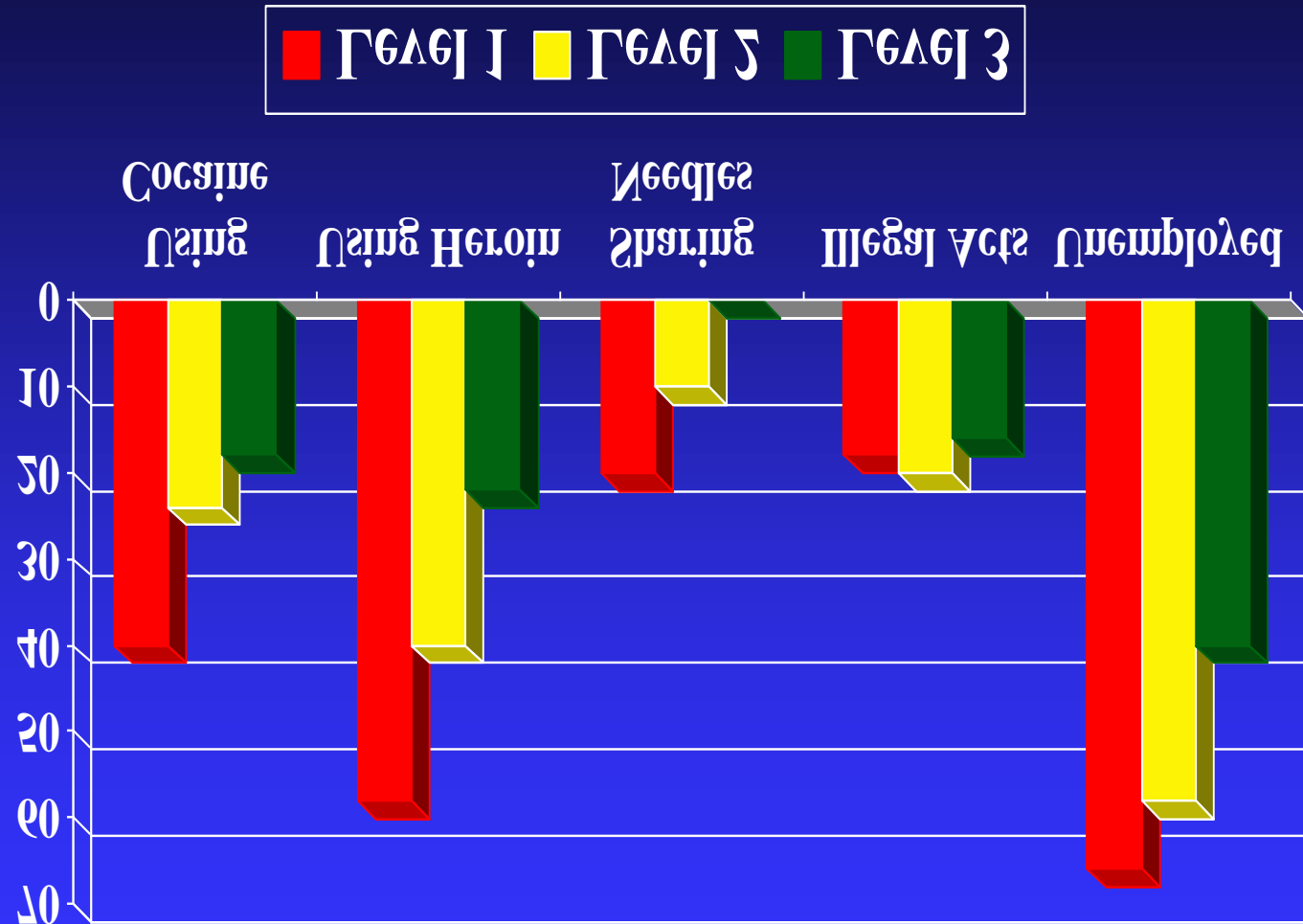
- More services associated with better outcomes**

Levels of Treatment in Methadone Maintenance Programs

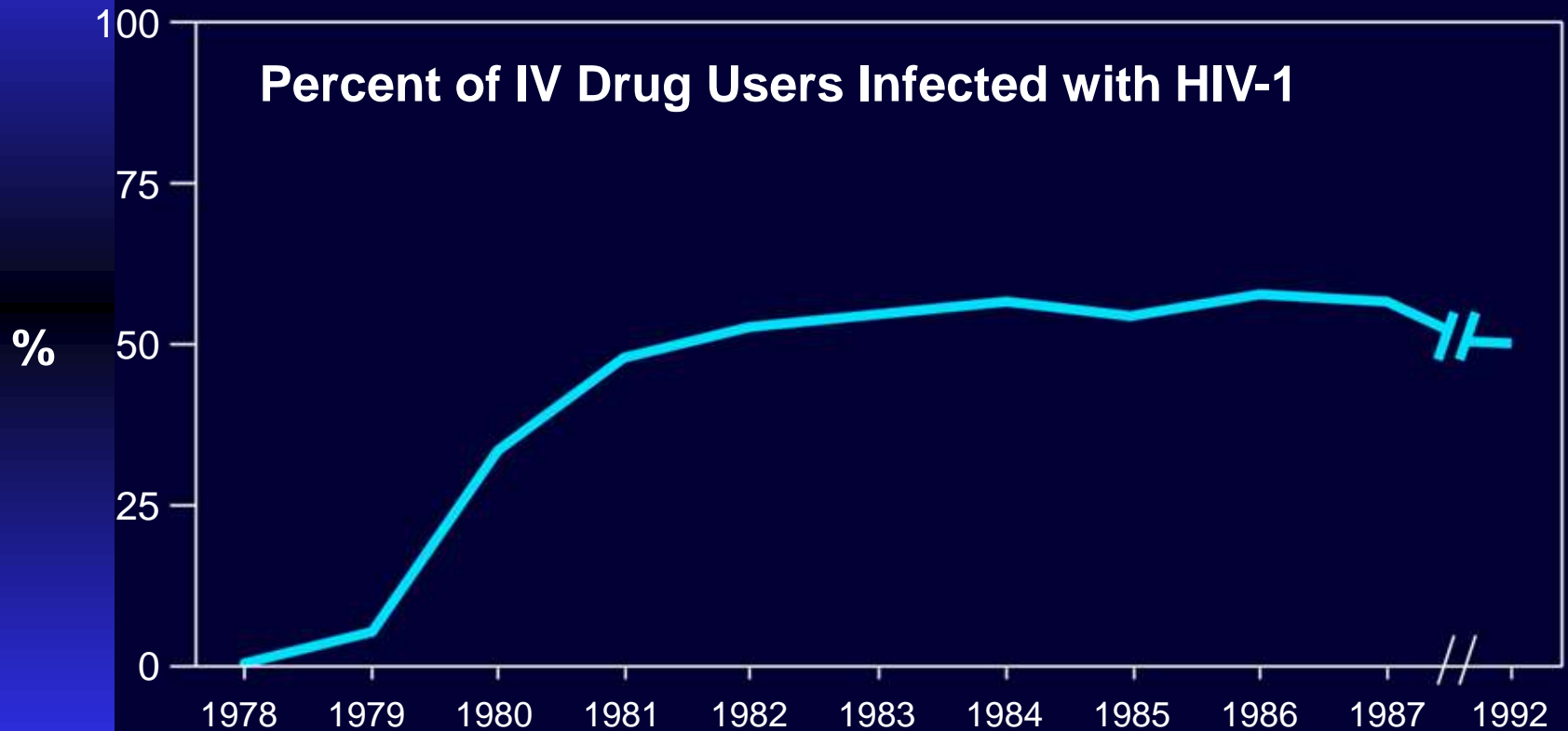
Random Assignment 6 Months

	Level 1 *	Level 2	Level 3
	(n=29)	(n=34)	(n=36)
<u>Methadone:</u>	> 60mg	>60mg	>60mg
<u>Urine/Breath:</u>	weekly	weekly	weekly
<u>Counseling:</u>	Emergency	Emergency Regular	Emergency Regular Employment FamTherapy Psych Care
*does not include 13 patients not completing treatment			

Methadone Levels Study



Identification of HIV-1 Infection and Changing Prevalence in Drug Users New York City: 1978 – 1992; 1983 - 1984 Study



Prevalence of HIV-1 (AIDS Virus) Infection in Intravenous Drug Users New York City: 1983 - 1984 Study: Protective Effect of Methadone Maintenance Treatment

50 – 60% Untreated, street heroin addicts:
Positive for HIV-1 antibody

9% Methadone maintained since <1978
(beginning of AIDS epidemic):
less than 10% positive for HIV-1 antibody

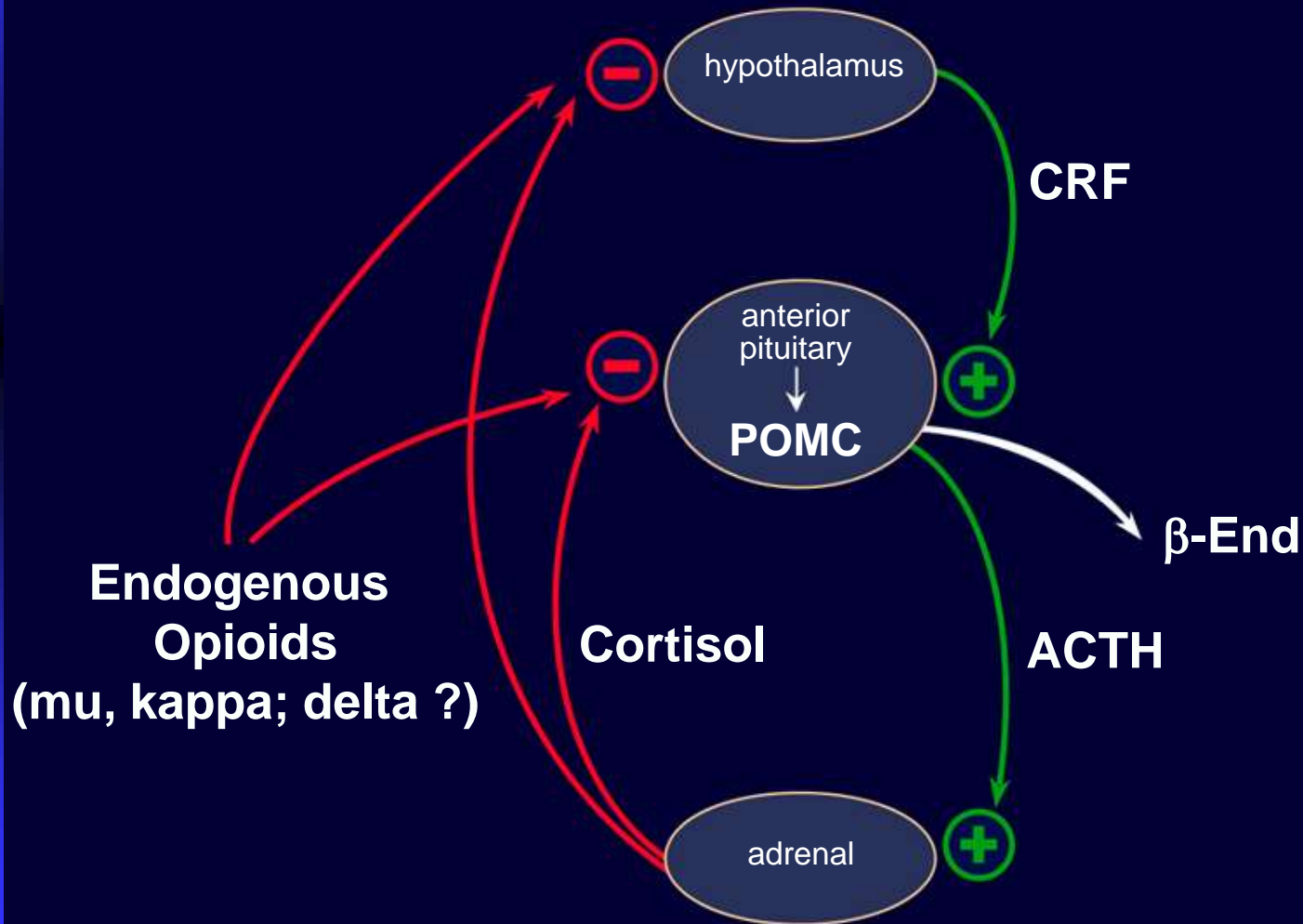
Hypothesis — Atypical Responsivity to Stressors: A Possible Etiology of Addictions

Atypical responsivity to stress and stressors may, in part, contribute to the persistence of, and relapse to self-administration of drugs of abuse and addictions.

Such atypical stress responsivity in some individuals may exist prior to use of addictive drugs on a genetic or acquired basis, and lead to the acquisition of drug addiction.

Genetic, environmental and direct drug effects may each contribute to this atypical stress responsivity.

Hypothalamic-Pituitary-Adrenal Axis and the Endogenous Opioid System Have Interrelated Roles in the Biology of Addictive Diseases



Neuroendocrine Effects of Opiates, Cocaine, and Alcohol in Humans: Hormones Involved in Stress Response

- Acute effects of opiates
- Chronic effects of short-acting opiates (e.g. heroin addiction)

Suppression of
HPA Axis

- Opiate withdrawal effects
- Opioid antagonist effects
- Cocaine effects
- Alcohol effects

Activation of
HPA Axis

- Chronic effects of long-acting opiate (e.g. methadone maintenance treatment)

Normalization of
HPA Axis

HPA – Hypothalamic-pituitary-adrenal axis (involved in stress response)

Many reviews

- **Institute of Medicine**
- **National Institutes of Health Consensus Conference**
- **Medical journals**
- **All recommend it**

In Spite of Extensive Data
Persistent Ambivalence!

Examples:

In August '98, the Mayor of New York gave a speech in which he said:

“Over a period of time, hopefully within the next two, three or four years, we will phase out and do away with methadone maintenance programs in the City of New York”.

**In later speech Mayor said that
maintenance is:**

**A “terrible perversion of drug
treatment”**

**He added that “for at least a very
large percentage of the people on
methadone you’re just sustaining
their dependence, you’re just
sustaining their addiction”**

**But, after much input from many
studies,**

**In October 1999, he supported
\$5 million in additional funding
to improve methadone programs
that are run by the City's Health
and Hospital Corporation**

The Addiction Free Treatment **Act of 1999**

**October 1998 three senators submitted a
resolution that:**

**“...the Federal Government should adopt a zero-
tolerance drug-free policy that has as its principal
objective the elimination of drug abuse and
addiction, including both methadone and
heroin...”**

**“...methadone is a synthetic opiate ...that results
in the transfer of addiction from one drug to
another drug....”.**

Addiction Free Treatment Act (cont)

“Heroin addicts and methadone addicts are unable to function as self-sufficient, productive members of society...”

Totally opposite the data!

**Many heroin addicts in criminal justice
system**

Growing interest in “drug courts”

But, judges rarely refer to methadone

**Prefer therapeutic communities, other
“drug-free” options**

Disconnect between data and political attitudes

Difficult to understand because:

- Courts and Congress have easy access to data**
- Many studies**
- IOM, NIH reviews**

Why are data ignored?

**U.S. tradition of personal responsibility
and self-reliance**

**Example: review of naltrexone grant, one
reviewer commented:**

**“medications should not be used in
treating addiction because they remove
personal responsibility”**

Other possible reasons :

Patients “brought it on themselves”

Undeserving of treatment

A moral, not medical issue

Patients can be difficult to manage

Angered many people

Punishment deserved

**(Even though punishment alone doesn't work
very well)**

Other possible reasons :

**Widespread impression that
treatment doesn't work**

**Because patients relapse after it
ends**

Reflects use of acute disease model

Things may be changing

Last NIDA director helped people see addiction as health problem

But with behavioral/criminal manifestations

Paper by McLellan, O'Brien, Kleber influential

- **Compared compliance & outcome of addiction rx with chronic diseases (diabetes, asthma, hypertension)**
 - **Compliance & outcomes similar**
 - **For many, addiction needs long-term treatment**

Implications of disease model:

- Supports treatment
- Reduction in severity without “cure” meaningful
- Reductions in HIV risk, overdose deaths, crime examples
- No clear consensus yet on these implications

Other positive developments: criminal justice studies

Inciardi:

Prisoners randomized to prison along

Prison + drug-free treatment

**Prison + drug-free treatment + treatment after
release**

Dose/response relationship

These studies not yet done with courts & methadone

Administrative Initiatives for Methadone Expansion:

**NIDA, SAMSA, recommend methadone
expansion**

**Oversight of programs shifted to health care
agencies**

“Medical maintenance” permitted

**Current administration says treatment needs
more emphasis**

Political Initiatives:

**Voters in Arizona, California
passed laws mandating more
treatment**

But, additional funds not provided

**Fear of backlash if funds not
provided**

Other funding problems

Managed care pressures for shorter, less expensive treatment

**Many cost savings outside medical system
(legal, social, lost employment)**

No single payer in U.S.

“Get those patients on somebody else’s budget!”

Result of Budget Pressures

“Dumbing down” of staff

Caseloads of 60-80 patients in some programs

General decrease in amount & quality of care

Administrative actions opposite research findings

Ambivalence continues (“the beat goes on”)

Buprenorphine/naloxone may be area for expansion

Funding seems more dependent on political/administrative decisions than data

Continuing pressure to reduce health care costs

Addiction treatment the first thing to cut

The implicit policy:

“When people say we have no policy on treating addiction, it’s not true.

We have a policy, it is that we should treat them, but not very well”

**Walter Ling
Professor, UCLA**

A question:

Is it possible to get political support for treating an unpopular group of patients, especially when we have many serious international issues?

We keep trying.