

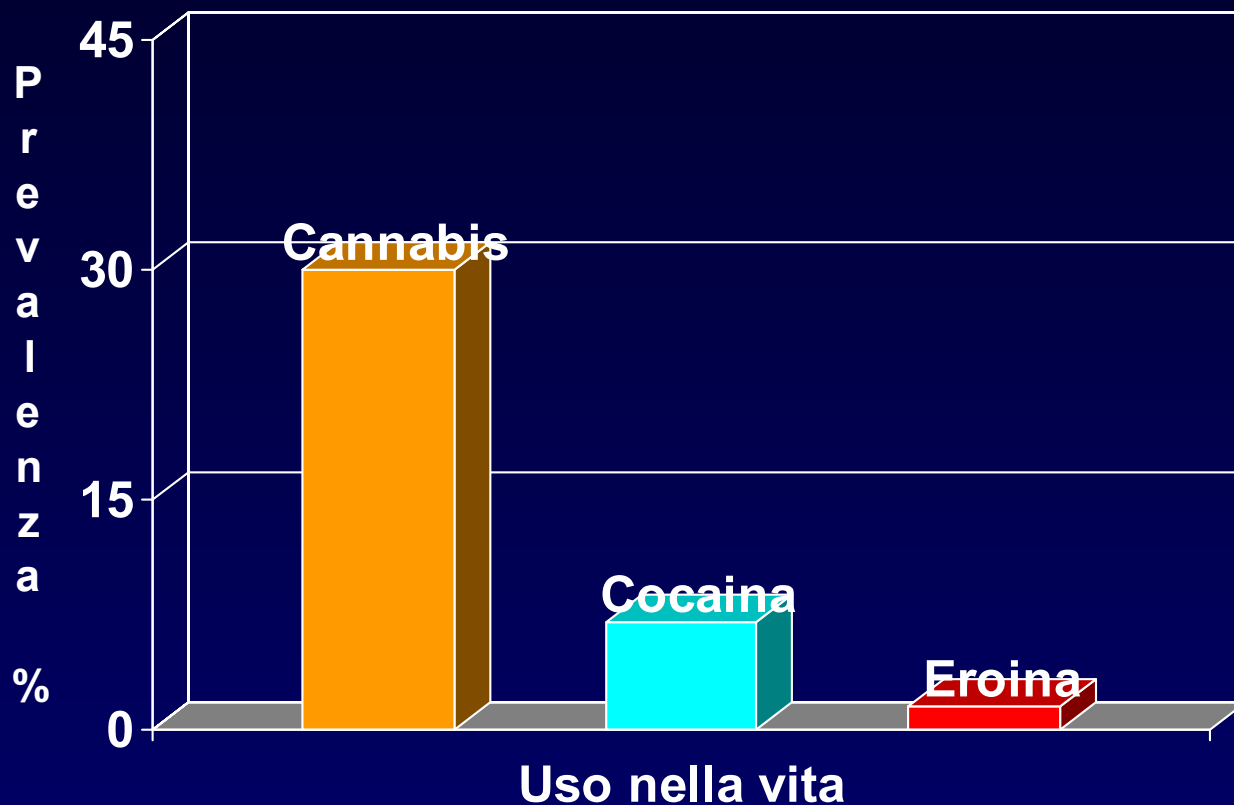
# **Stato dell'arte dei trattamenti contributo di VEdeTTE**

Pier Paolo Pani

Medicina Tossicodipendenze

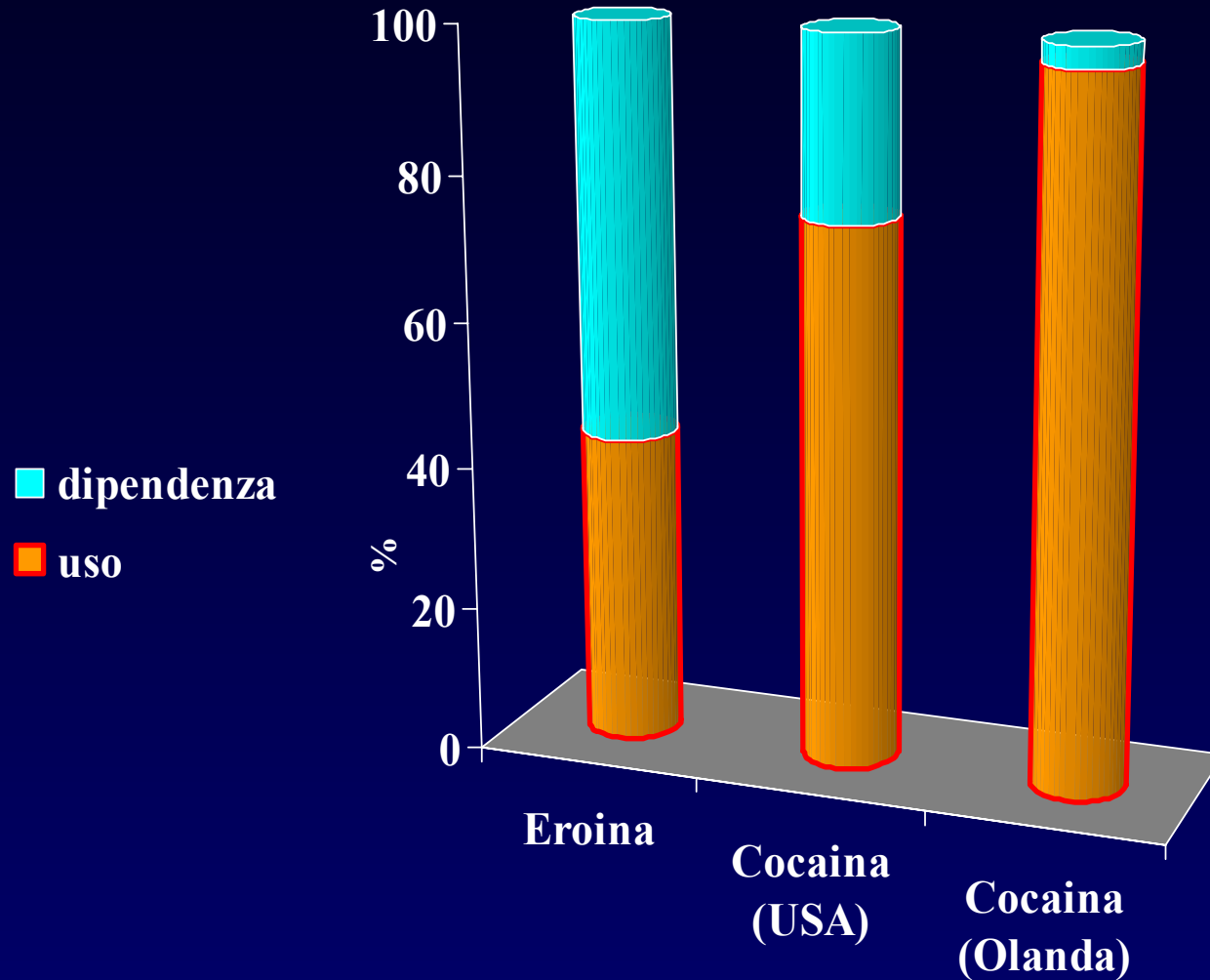
Ser.T. AUSL 8, Cagliari

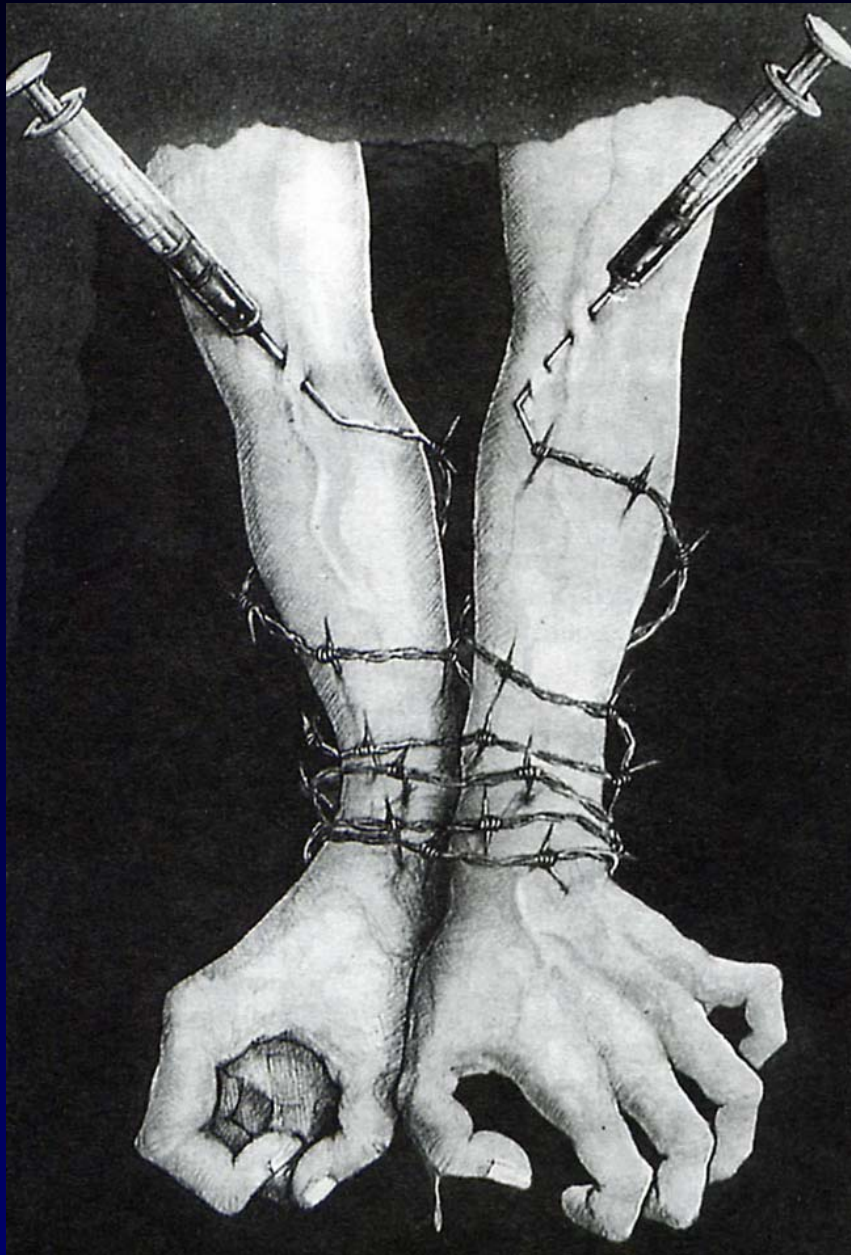
# PREVALENZA USO DI DROGHE NELLA POPOLAZIONE GENERALE (USO NELLA VITA ITALIA 2004)



# DIPENDENZA: PREVALENZA FRA I CONSUMATORI

Cohen, 1990; NSDUH, 2003.





# Addiction

**A chronic but  
treatable condition**

But “relapses” are common --  
like some medical problems!

Drug Addiction, like prostitution and like liquor, is not a police problem; it never has been and never can be solved by policemen. It is first and last a medical problem, and if there is a solution it will be discovered not by policemen, but by scientific and competently trained medical experts whose sole objective will be the reduction and possible eradication of this devastating appetite. There should be intelligent treatment of incurables in outpatient clinics, hospitalization of those not too far gone to respond to therapeutic measures, and application of the prophylactic principles which medicine applies to all scourges of mankind.

August Vollmer, Police Administrator, 1936

Per grazia ricevuta. Uno straordinario viaggio nei Santuari italiani «specializzati» - 1) La Vergine dei tossicodipendenti

# I DROGATI LA SUPPLICANO: TU PUOI FARE IL MIRACOLO

Sant'Anastasia (Napoli). Nella piccola cappella con per un momento il volto della Madonna si stringe a sé il suo arduo Gesù spinto appreso e commosso. Su, verso una Madonna bella ed aggraziata, ha lentamente tesi e proiettati, opera un potere sconosciuto al 1400.

**Da 13 anni, la Madonna dell'Arco di Sant'Anastasia, vicino a Napoli, è meta di un pellegrinaggio fra i più toccanti: quello dei giovani schiavi dell'eroina - Dal 1400 a oggi: storia di un culto che in Campania sta per superare quello di San Gennaro**

di SERGIO DE GREGORIO

«Una moltitudine di miracoli ha voluto testimoniare con la grandine e la devozione. Molti di questi prodotti di ringraziamiento sono sconosciuti. Accanto a un discepolo alla loro del miracolo infatti ci sono ancora altre ancora speranze di

sangue e lacrime emossioni. Non disposti, bensì veri. Perché la Madonna dell'Arco è la protettrice dei tossicodipendenti. È a lei che si rivolgono tutti giovani schiavi della droga per chiedere la grazia di uscire da quell'inferno. Cominciamo con il

Santuario della Madonna dell'Arco a Sant'Anastasia, periferia orientale di Napoli, il nostro viaggio a puntare attraverso i Santuari più particolari d'Italia. Luoghi di culto che hanno una loro specificità, nel senso che il culto o la Madonna che dà sen-

za il nome protegge in particolare modo una certa categoria di persone. Lungi dallo spirito nei quali cercano conforto anime disperate, nel tentativo di trovare speranza e pace.

Davanti all'immagine della Madonna dell'Arco è impigliato un giovane emiliano, nei ventisei anni. Ha le braccia strette con le mani in evidenza, lo sguardo perso. Un tossicodipendente, il mio migliore amico e venuto qui e ce l'ha fatto, racconta. «Devo farcela anch'io. Poco più in là c'è una donna stata a casa mia. Pregho per il figlio, che si liberi dall'eroina. Poi c'è un ra-



gazzo che dall'eroina è riuscito a liberarsi. «Grazie a Lei», dice indicando il volto della Madonna dell'Arco. «Prima per continuare a tener duro deve venire qui ogni giorno. Adesso è Lei la mia droga...», conclude sorridendo. «E poi qui mi sento in pace, come a casa mia. C'è tanta serenità, tranquillità».

Sembra tavollette «per grazia ricevuta» ricoperte il santuario. Un collezionista di sempre, oli e acquerelli, dipinti su carta, vetro e legno, che raccontano cinque secoli di grazie e disgrazie. Perché è solo da tredici anni che la Madonna dell'Arco protegge in special modo i drogati. Ma sono cinque secoli che la miracoli in pellegrini bisognosi che a lei si rivolgono.

«In un arco indefinito, collocato fra l'inizio e la metà del Quattrocento scorso», ci racconta padre Damiano Ikona, priore del Santuario e della maggiore comunità del Mezzogiorno, «un giocatore di pallamaglio, forse indispertito per l'ennesima partita persa, scagliò la sua palla di legno sul volto della Madonna, dispetta-»

● *continuazione da pag. 111*



# OPIOID ADDICTION: GENERAL STATEMENT

- Any treatment (methadone maintenance, therapeutic community, drug-free treatment) is better than nothing.
- The effects of treatment tend to be less evident after leaving the program.

# Myths about the treatment of addiction

Charles P O'Brien, A Thomas McLellan

The Lancet 1996; 347: 237-40

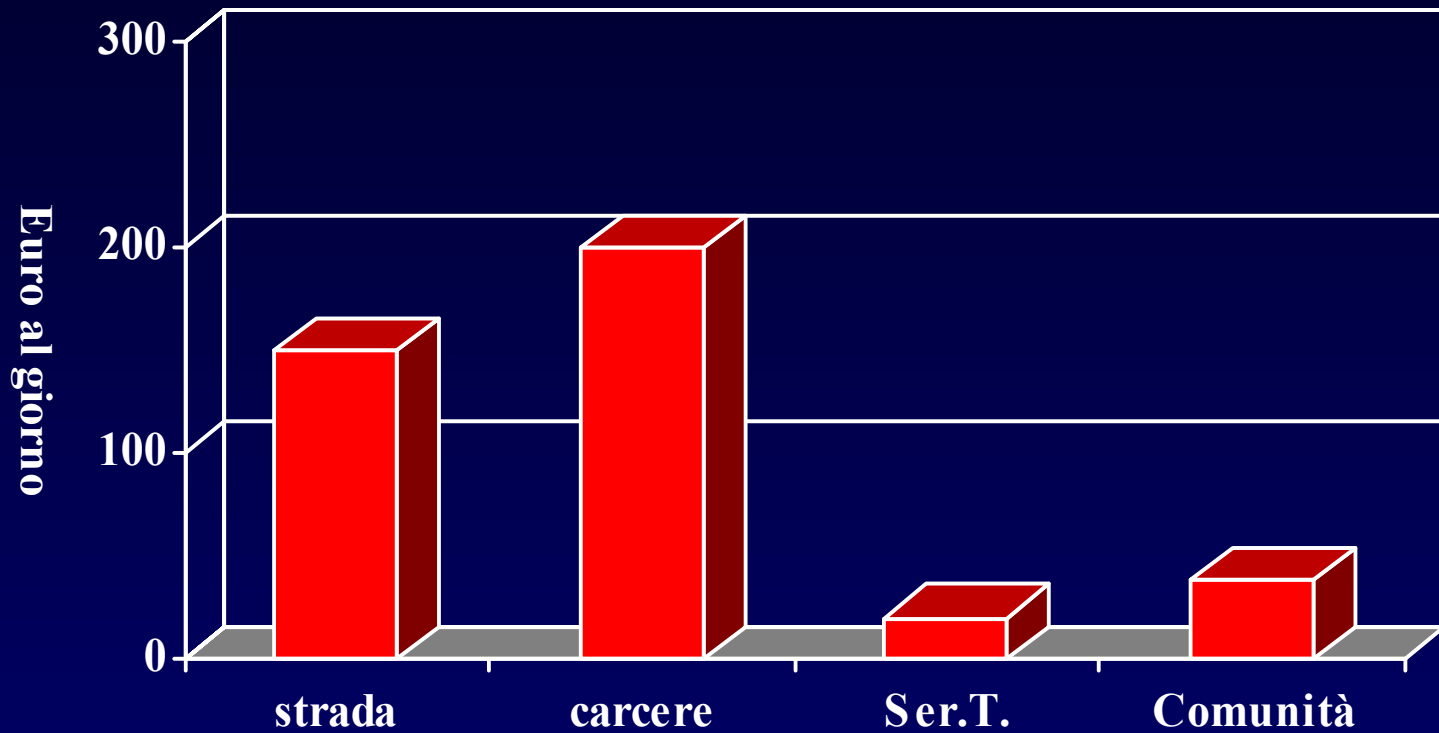
	Compliance and relapse
<b>IDDM</b>	
Medication regimen	<50%
Diet and foot care	<30%
Relapse*	30-50%
<b>Hypertension†</b>	
Medication regimen	<30%
Diet	<30%
Relapse*	50-60%
<b>Asthma</b>	
Medication regimen	<30%
Relapse*	60-80%

Disorder	Success rate (%)*
Alcoholism <sup>8</sup>	50 (40-70)
Opioid dependence <sup>9</sup>	60 (50-80)
Cocaine dependence <sup>10</sup>	55 (50-60)
Nicotine dependence <sup>11</sup>	30 (20-40)

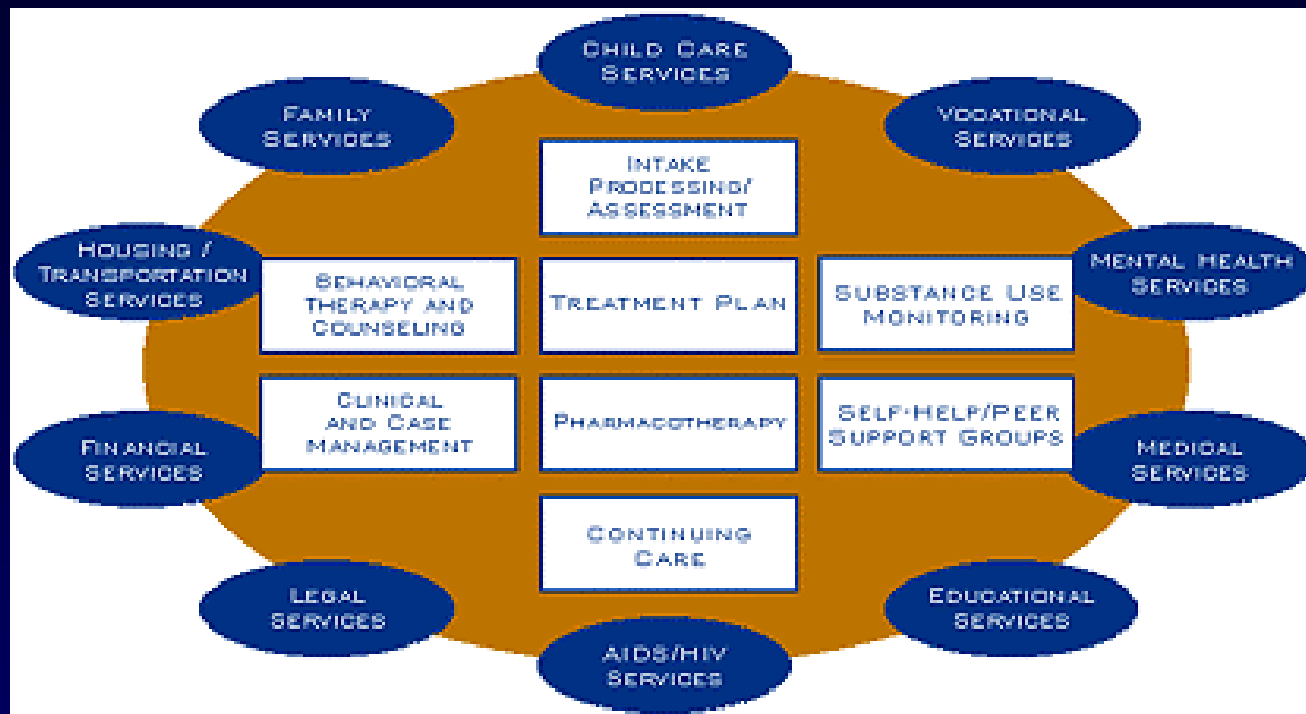
\*Follow-up 6 mo. Data are median (range).

Table 1: Success rates for addictive disorders

# COSTO DELLA TOSSICODIPENDENZA



# Components of Comprehensive Drug Addiction Treatment



# ***DARP***

## **Drug Abuse Reporting Program** First National Evaluation of Treatment Effectiveness

**Funded by the  
National  
Institute on  
Drug Abuse**



**1969-73**

35 Cities

139 Programs

~44,000 Patients

All treatment types

Follow-ups: 1,3,6,12 Yrs

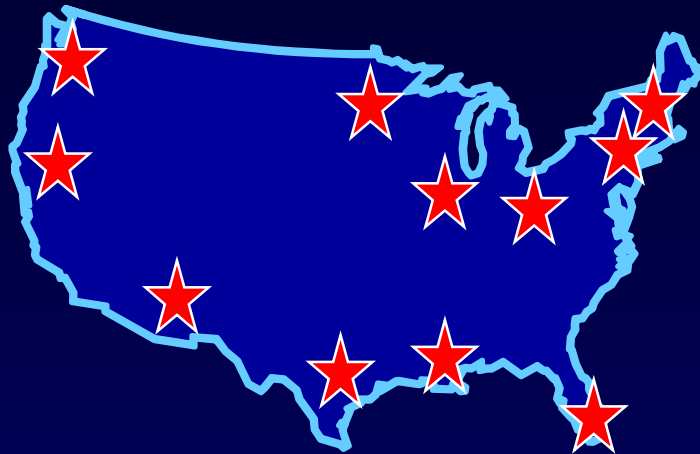
Sells, Simpson, Demaree, & Joe  
*6 books & 150 papers published (funded 1970-1990)*

# ***DATOS***

## Drug Abuse Treatment Outcome Studies

Third National Evaluation of Treatment Effectiveness

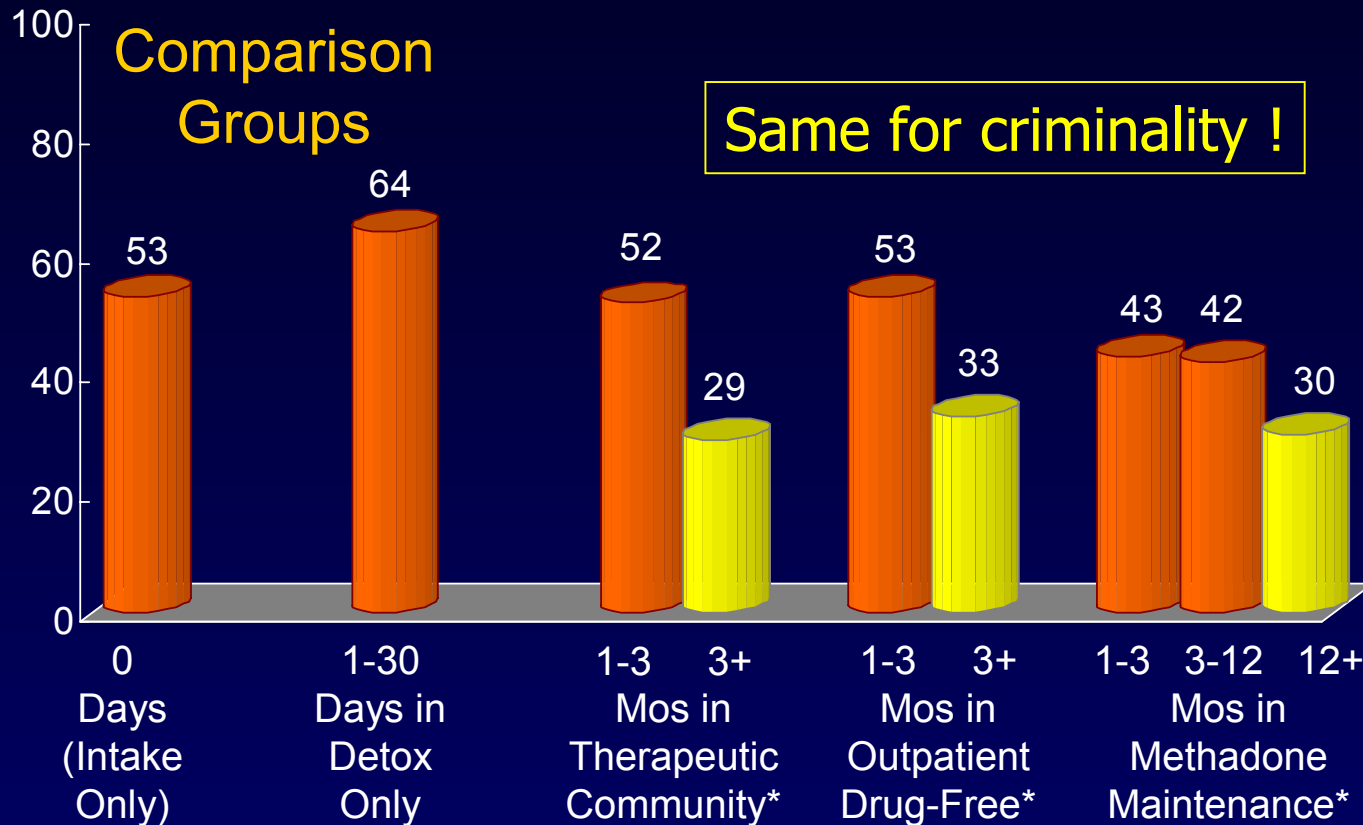
**Funded by the  
National  
Institute on  
Drug Abuse**



**1991-93**  
11 Cities  
96 Programs  
~10,000 Patients  
All treatment types  
Follow-up: 1 & 5 Yrs

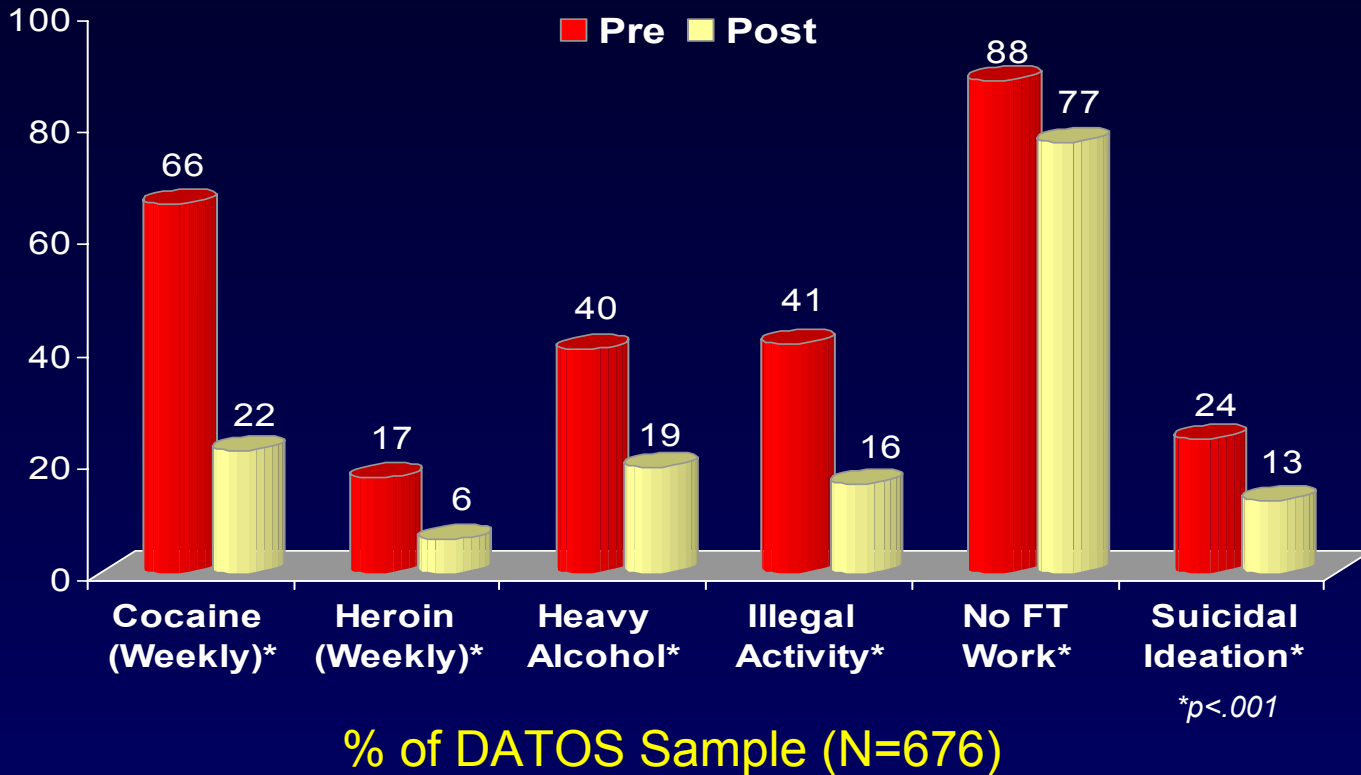
**60 Studies Published (or In Press) –**  
*Psychology of Addictive Behaviors* (Dec 97)  
*Drug and Alcohol Dependence* (Dec 99)  
*Archives of General Psychiatry* (June 99; In press)  
*Journal of Adolescent Research* (In press)

# Daily Opioid Use: % in Year 1 After Discharge

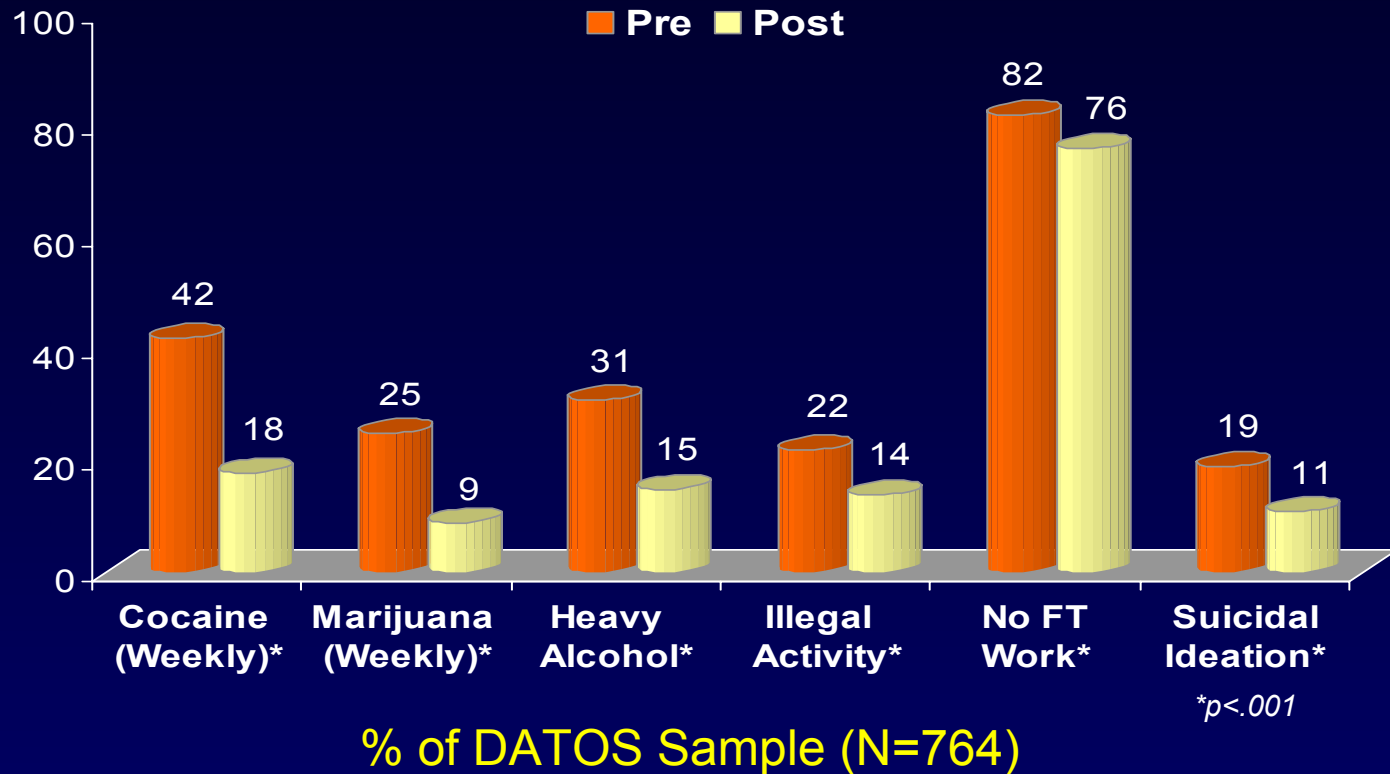


\*p<.01

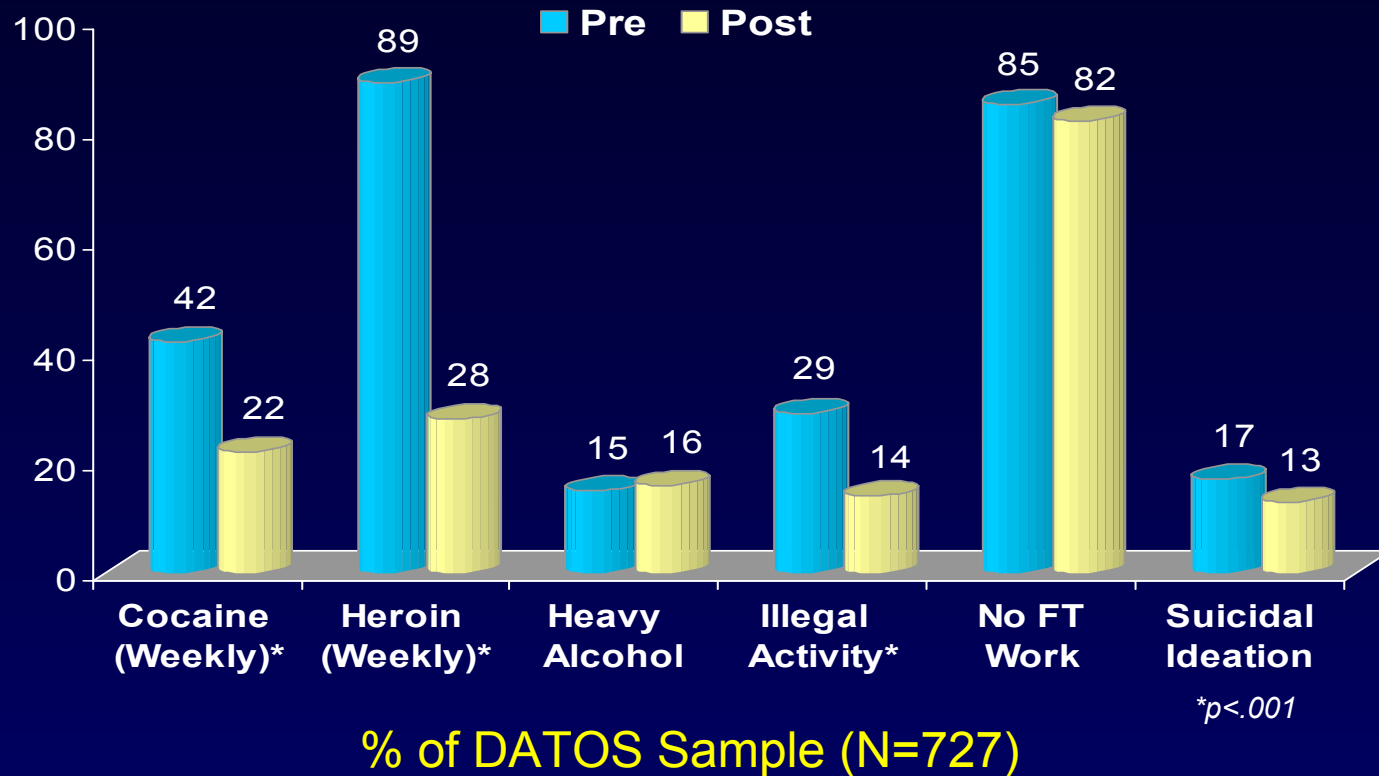
# Long-Term Residential (LTR) Treatment Changes from Before to After Treatment



# Outpatient Drug-Free (ODF) Treatment Changes from Before to After Treatment



# Outpatient Methadone Treatment (OMT) Changes from Before to After Treatment



# METHADONE EFFECTIVENESS

- There is strong evidence from clinical trials that heroin-dependent individuals have much better outcomes in terms of illicit drug consumption and other criminal behavior when they are maintained on methadone than when they are not treated at all, when they are simply detoxified and released, or when methadone is tapered down and terminated arbitrarily.
- Methadone clinics have significantly higher retention rates among opioid-dependent populations than do other treatment modalities for similar patients.
- When assessed following discharge from methadone treatment, patients who stayed in treatment longer have better outcomes than patients who left earlier.
- Patients do much better, generally, when they are stabilized on higher rather than lower doses.

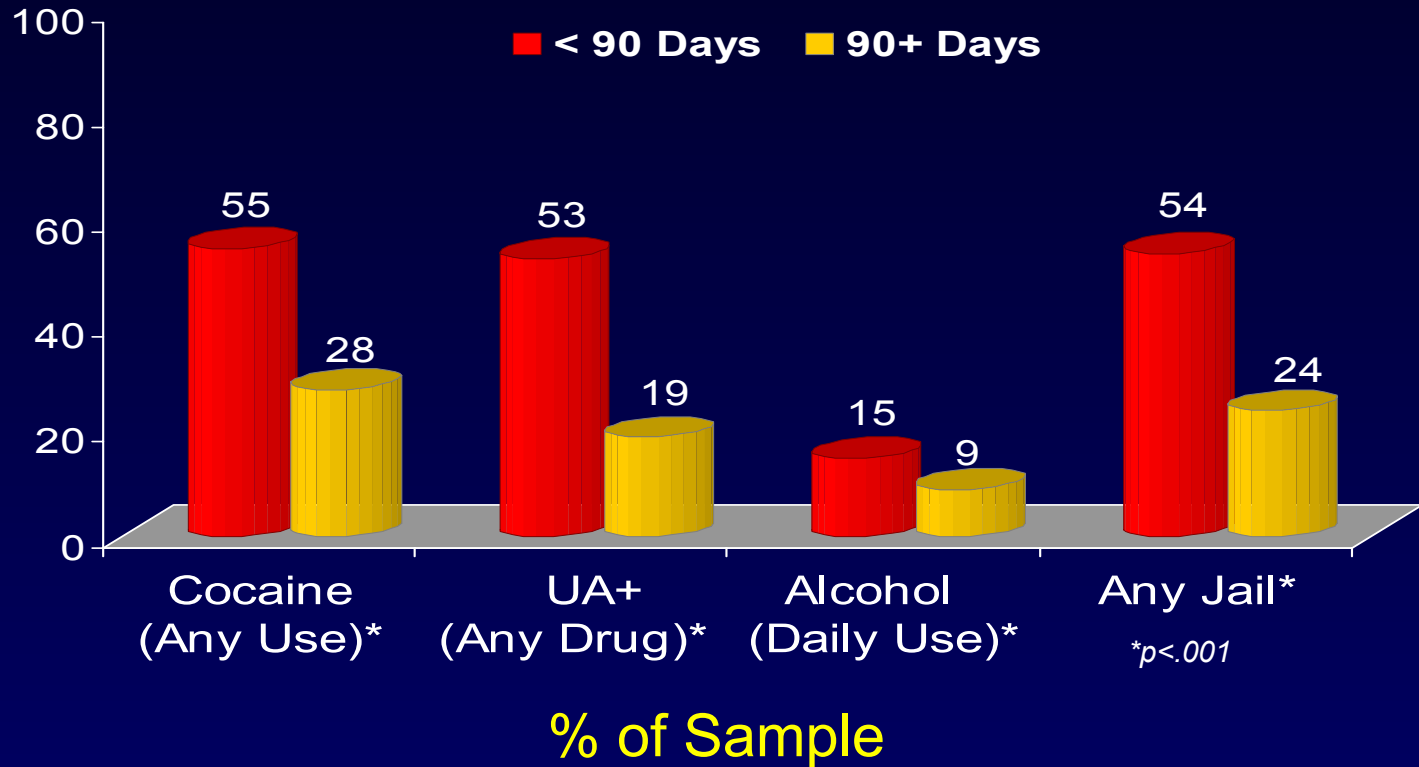
# THERAPEUTIC COMMUNITY EFFECTIVENESS

- TC patients end virtually all illicit drug taking and other criminal behavior while in residence.
- They perform better (in terms of reduced drug taking and other criminal activity and increased social productivity) after discharge than before admission.
- They also have better outcomes at follow-up than individuals who simply undergo detoxification or who contact but do not enter a TC program.
- The length of stay is the strongest predictor of outcomes at follow-up, with graduates having the best outcomes at that point.
- Attrition from TCs is typically high—above the rates for MM but below the rates for OPNM treatment.).

# L'OTTIMIZZAZIONE DEL TRATTAMENTO

- Ritenzione
- Dose dei farmaci agonisti
- integrazione e personalizzazione

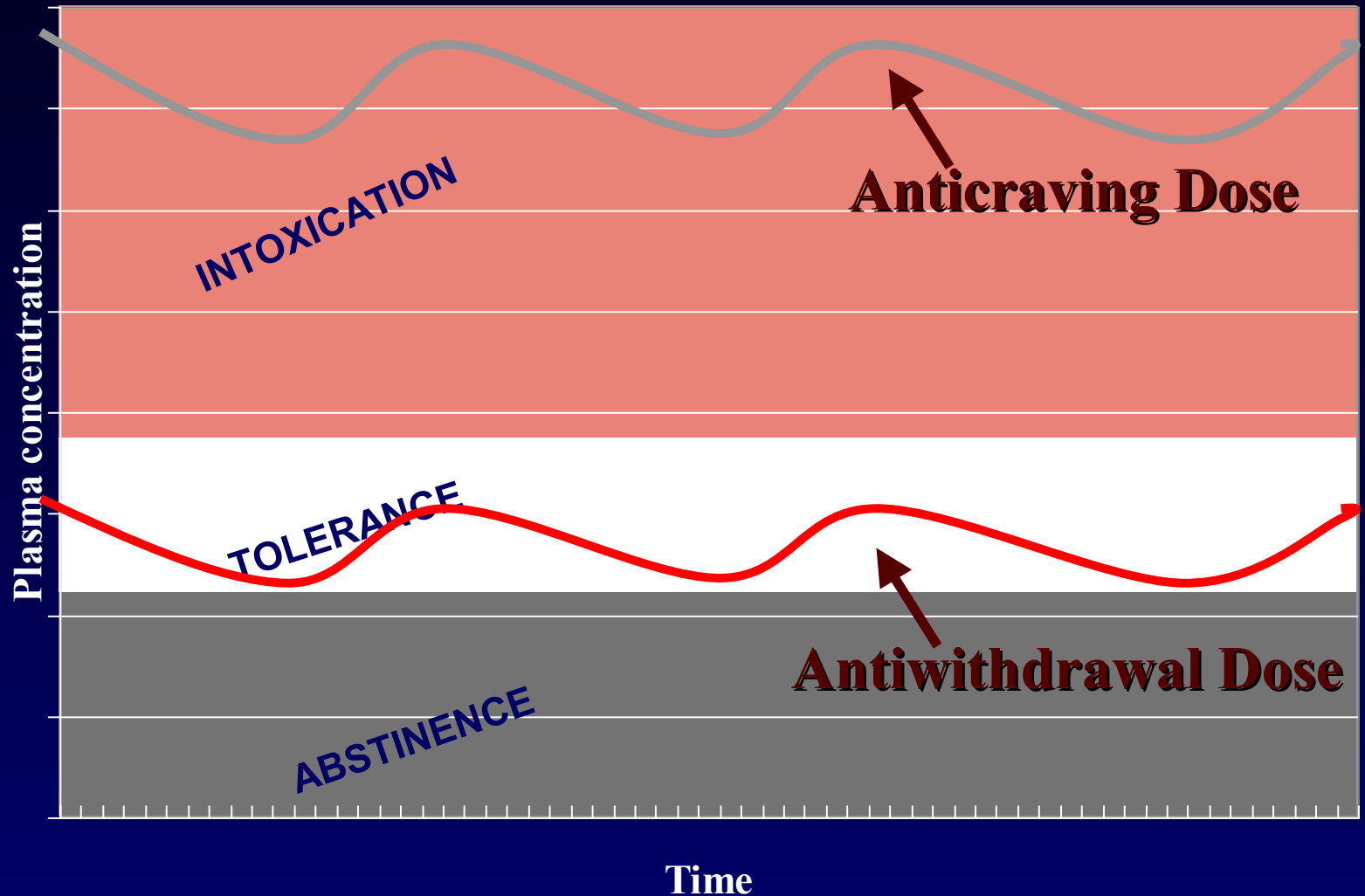
# Comparison of Year 1 Outcomes by Length of Stay in LTR



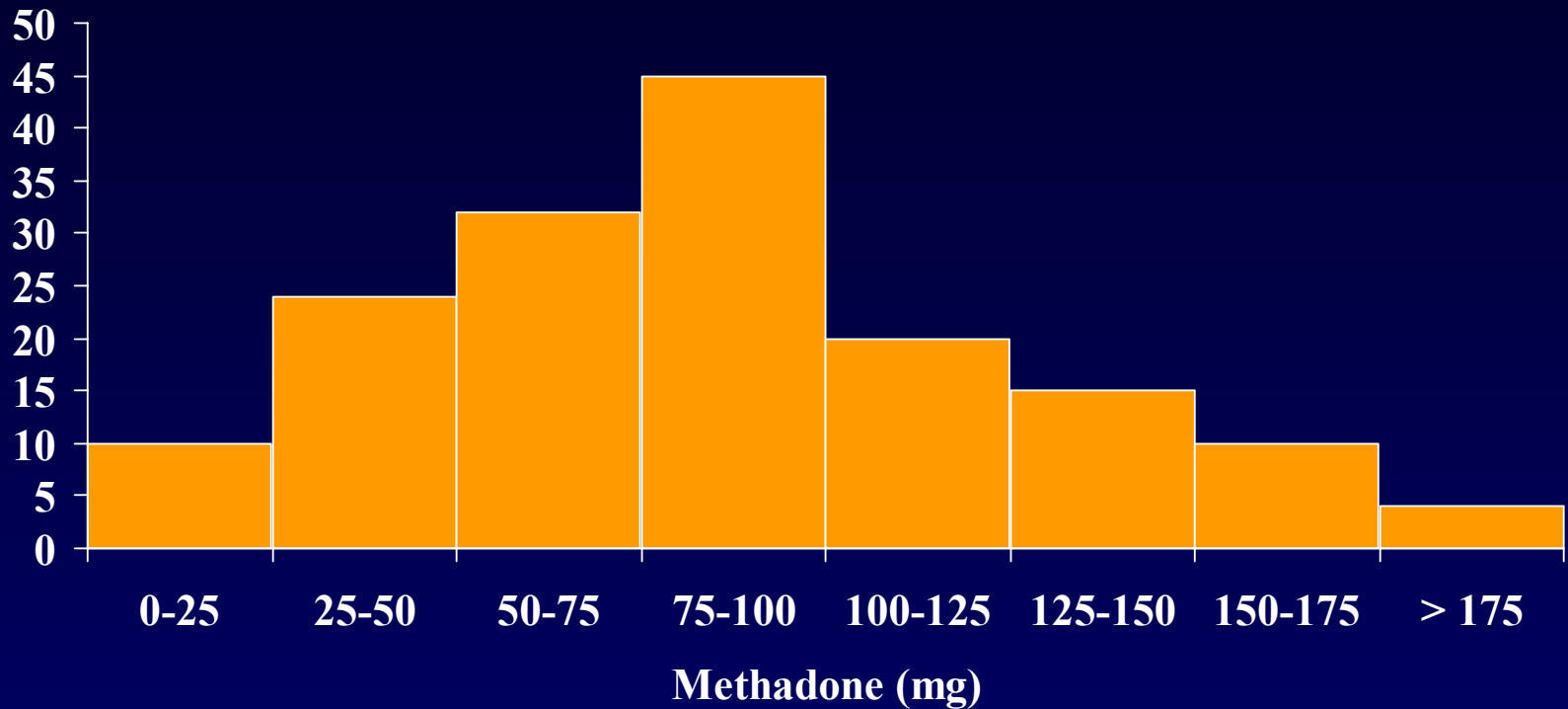
# MMTP EFFECT OF THE DOSE OF METHADONE

	Dose	Outcome	OR / RR	IC 95%
Caplehorn et al., 1993	80 vs 40	use of heroin	2.2	
Caplehorn et al., 1994	<60 vs 60-80	drop-out	0.47	0.33 - 0.67
	<60 vs >80		0.21	0.12 - 0.38

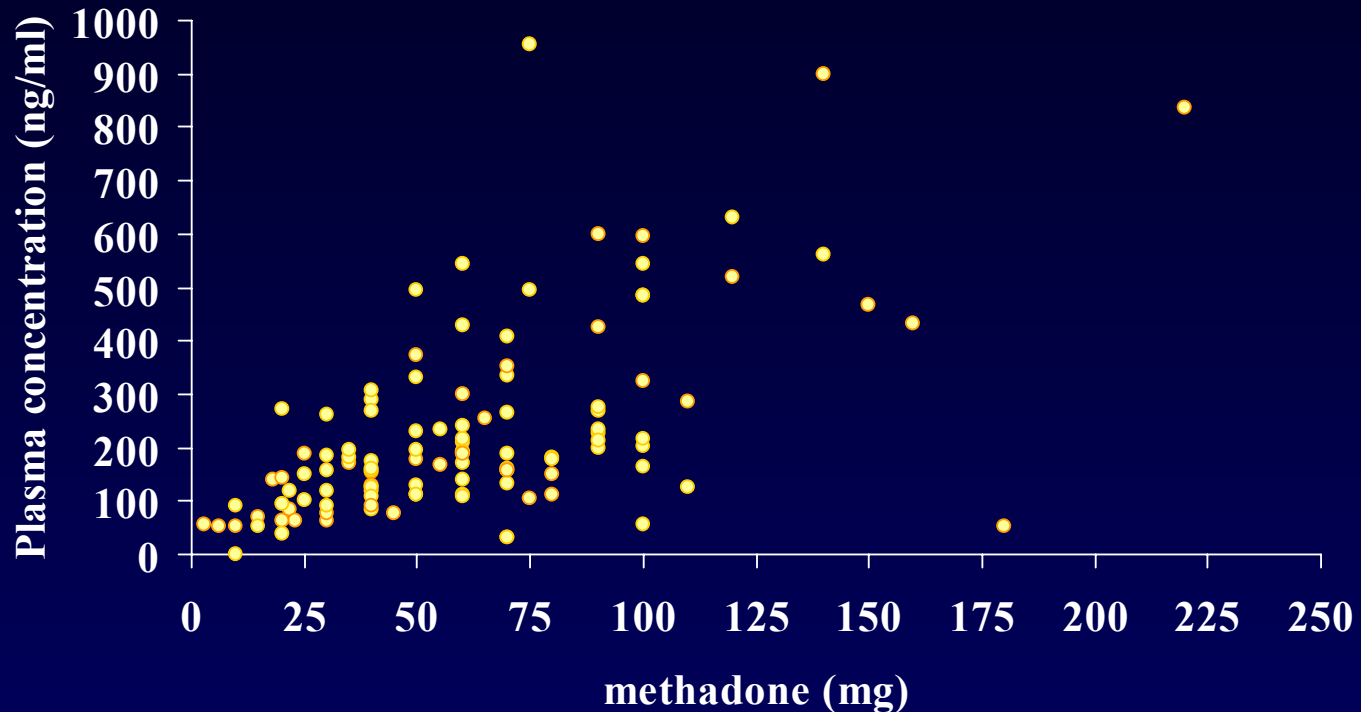
# METHADONE: ANTIWITHDRAWAL AND ANTICRAVING EFFECT



# METHADONE DOSAGES: FREQUENCY DISTRIBUTION



# METHADONE PHARMACOKINETIC: DOSE- CONCENTRATION RELATIONSHIP



# FACTORS INVOLVED IN DETERMINATION METHADONE DOSE

- Tolerance level
- Genetic factors (metabolic)
- Physiologic factors (diet, pregnancy)
- Pharmacological interferences
- Physical pathology
- Psychic pathology

## Psychiatric Severity and Treatment Response in Methadone Maintenance Treatment Programmes: New Evidence

Pier Paolo Pani, Emanuela Trogu, Gianfranco Carboni, Patrizia Palla and Anna Loi

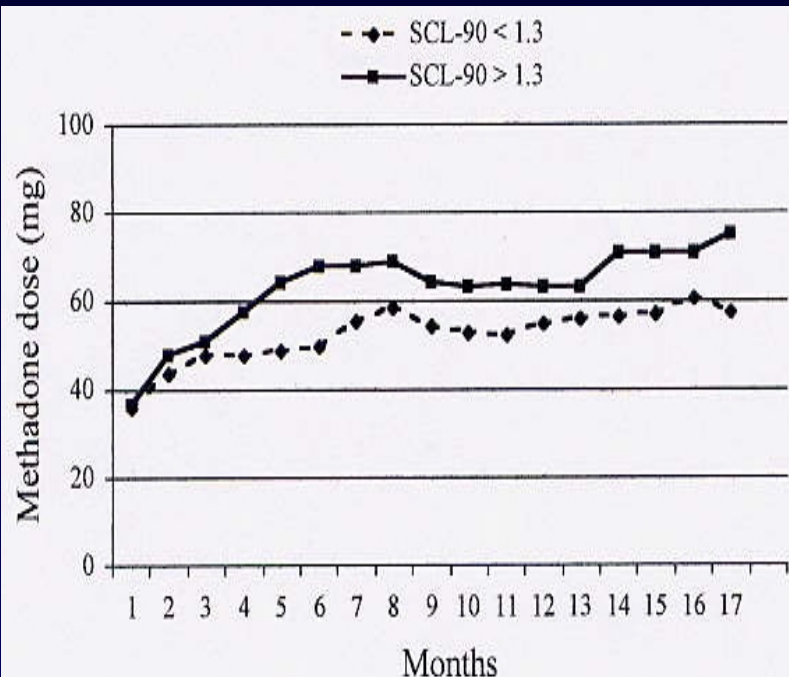


Figure 4. Methadone mean daily dose per month

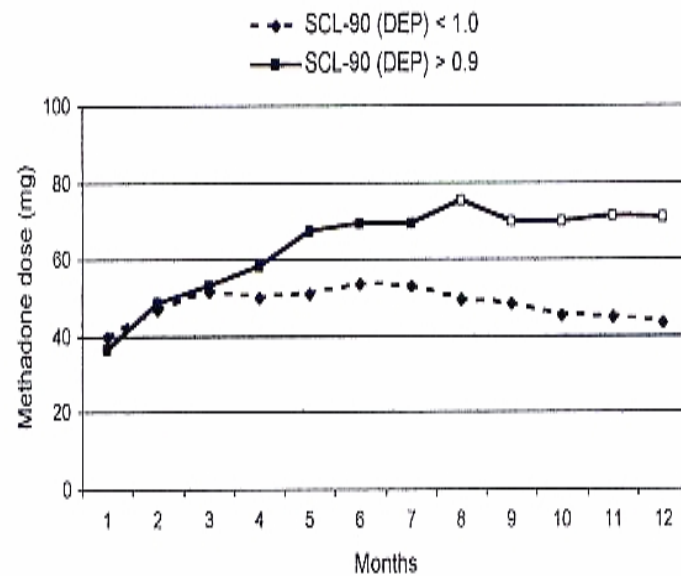
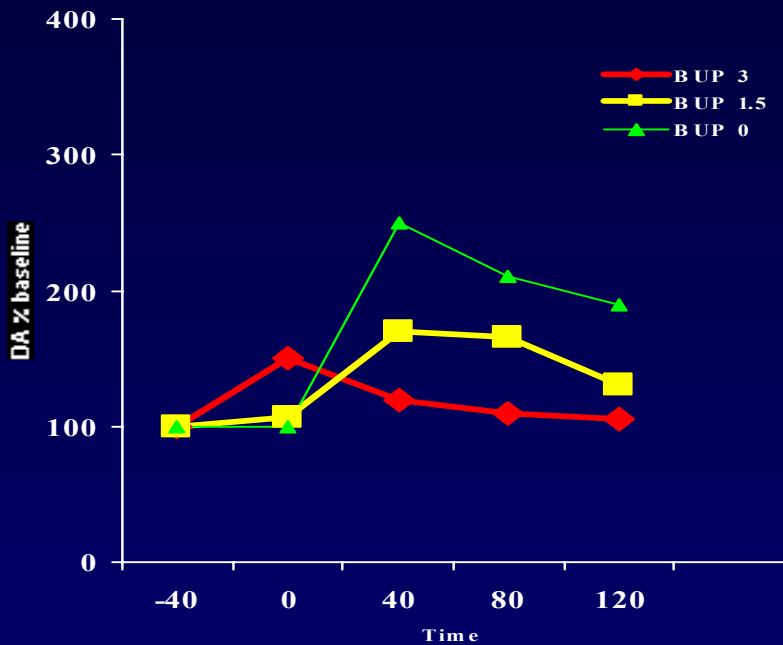


Figure 5. Methadone: mean daily dose per month in patients with high and low depression severity

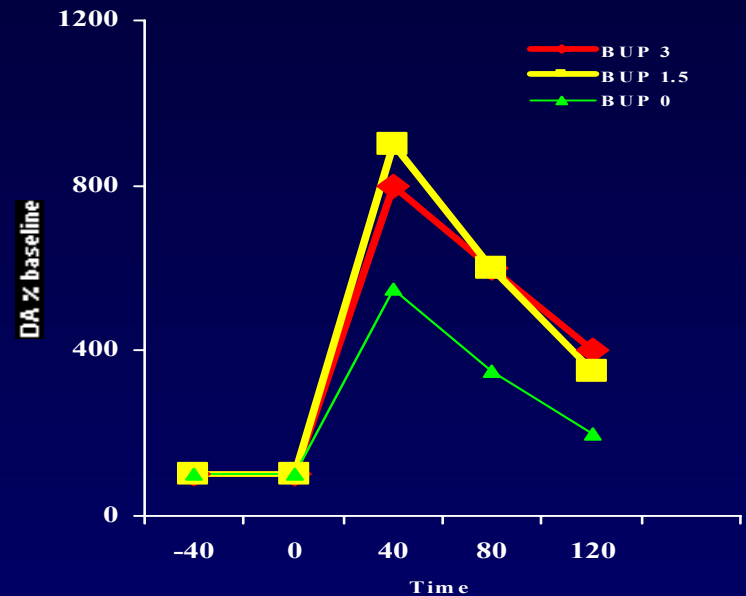
# RATS MAINTAINED CHRONICALLY ON BUPRENORPHINE SHOW REDUCED HEROIN AND COCAINE SEEKING IN TESTS OF EXTINCTION AND DRUG-INDUCED REINSTATEMENT

Sorge et al. Neuropsychopharmacol. 2005

Increase in extracellular dopamine in nucleus accumbens in response to acute injections of heroin.



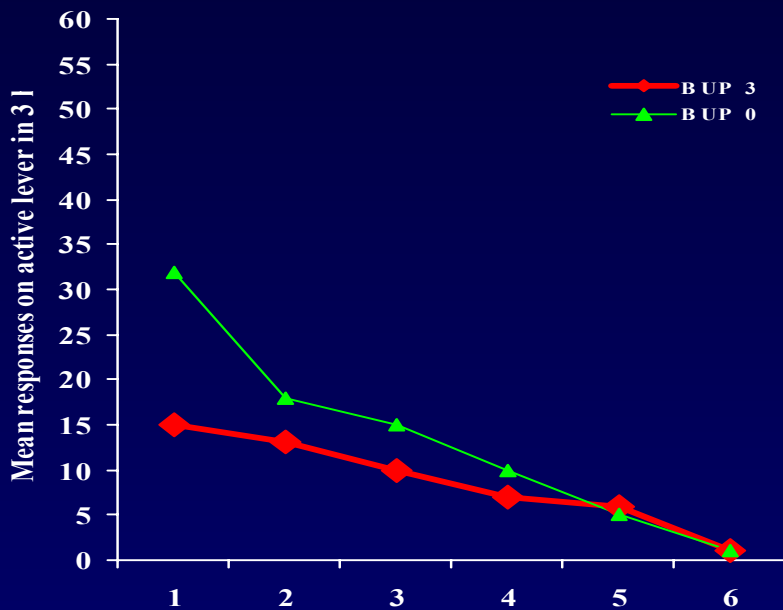
Increase in extracellular dopamine in nucleus accumbens in response to acute injections of cocaine.



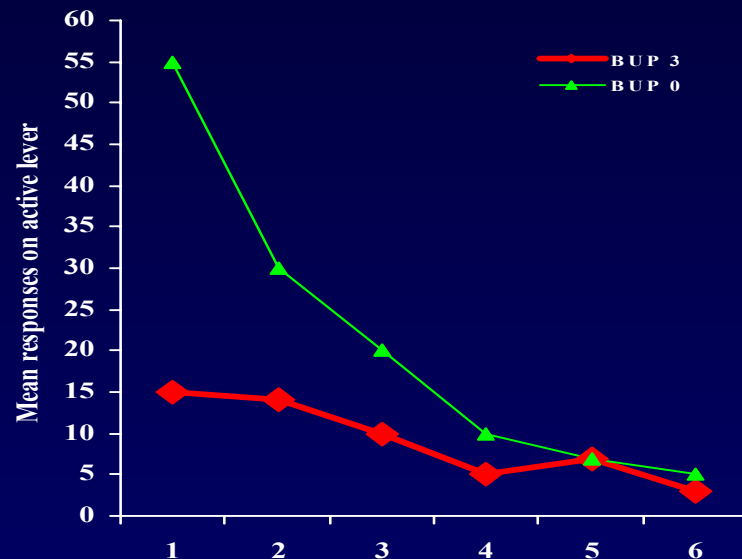
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Extinction session: heroin.



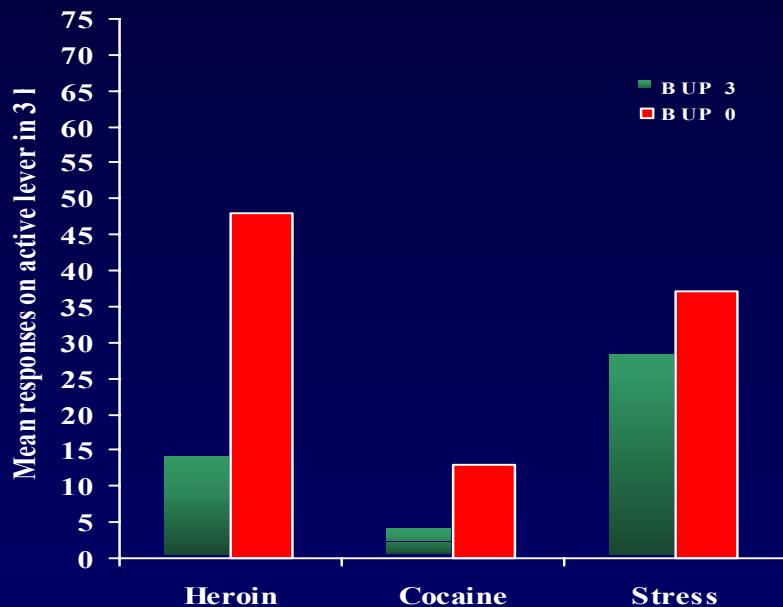
Extinction session: cocaine.



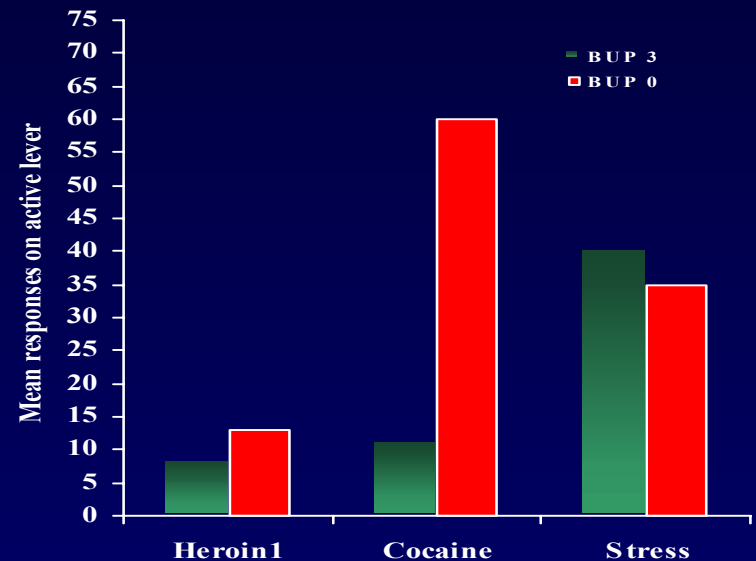
# RATS MAINTAINED CHRONICALLY ON BUPRENORPHINE SHOW REDUCED HEROIN AND COCAINE SEEKING IN TESTS OF EXTINTION AND DRUG-INDUCED REINSTATEMENT

Sorge et al. Neuropsychopharmacol. 2005

Reinstatement session: heroin.

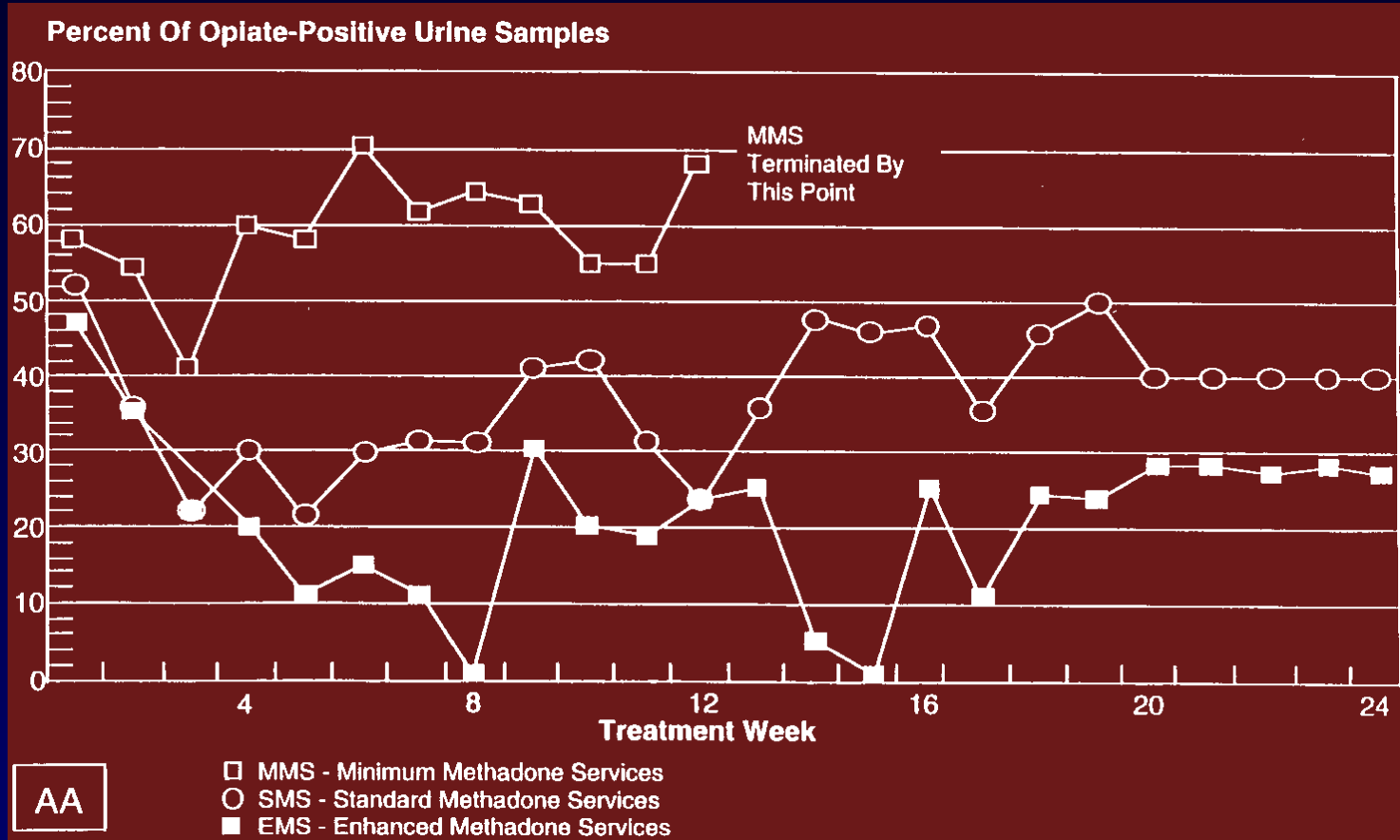


Reinstatement session: cocaine.



# ROLE OF PSYCHOSOCIAL SERVICES IN REDUCING ILLICIT OPIOID USE

(Adapted From McLellan et al., 1993)





# LA PERSONALIZZAZIONE DEL TRATTAMENTO

Il clinico vorrebbe sapere come può aiutare al meglio il suo paziente e in che modo la conoscenza della condizione dello stesso può aiutarlo a mettere assieme il migliore programma di trattamento.

# COSA AGGIUNGE VEDETTA

- Ci informa su aspetti non esplorabili dai trial clinici.
- Permette di verificare cosa accade nella realtà del trattamento.

# Opiate Addiction Treatment Outcome\*

<b>Methadone Maintenance</b>	<b>50 – 80%</b>
<b>LAAM Maintenance</b>	<b>50 – 80%</b>
<b>Buprenorphine-Naloxone Maintenance</b>	<b>40 – 50%**</b>
<b>Naltrexone Maintenance</b>	<b>10 – 20%</b>
<b>“Drug Free” (non-pharmacotherapeutic)</b>	<b>5 – 20%</b>
<b>Short-term Detoxification (any mode)</b>	<b>5 – 20% (limited data)</b>

---

\* *One year retention in treatment and/or follow-up with significant reduction or elimination of illicit use of opiates*

\*\* *Maximum effective dose (24mgsl) equal to 60 to 70 mg/d methadone. Data base on 6 month follow-up only.*

# Retention Predicts Outcomes

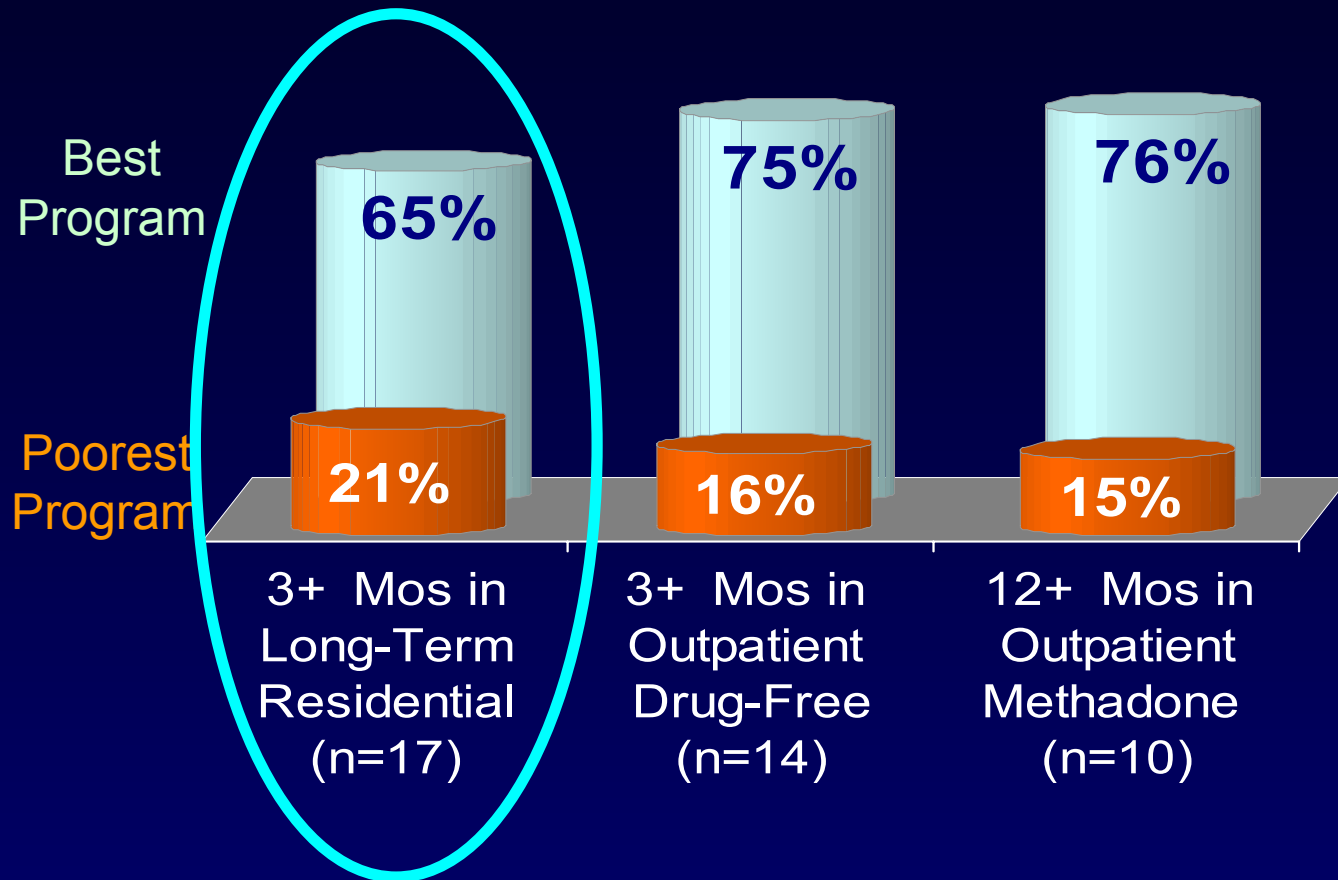
- **Findings Consistent from National Studies**

- 1970s (44,000 admissions in DARP)
- 1980s (11,000 admissions in TOPS)
- 1990s (10,000 admissions in DATOS)
- ➔ Also in England's NTORS (1990s)!

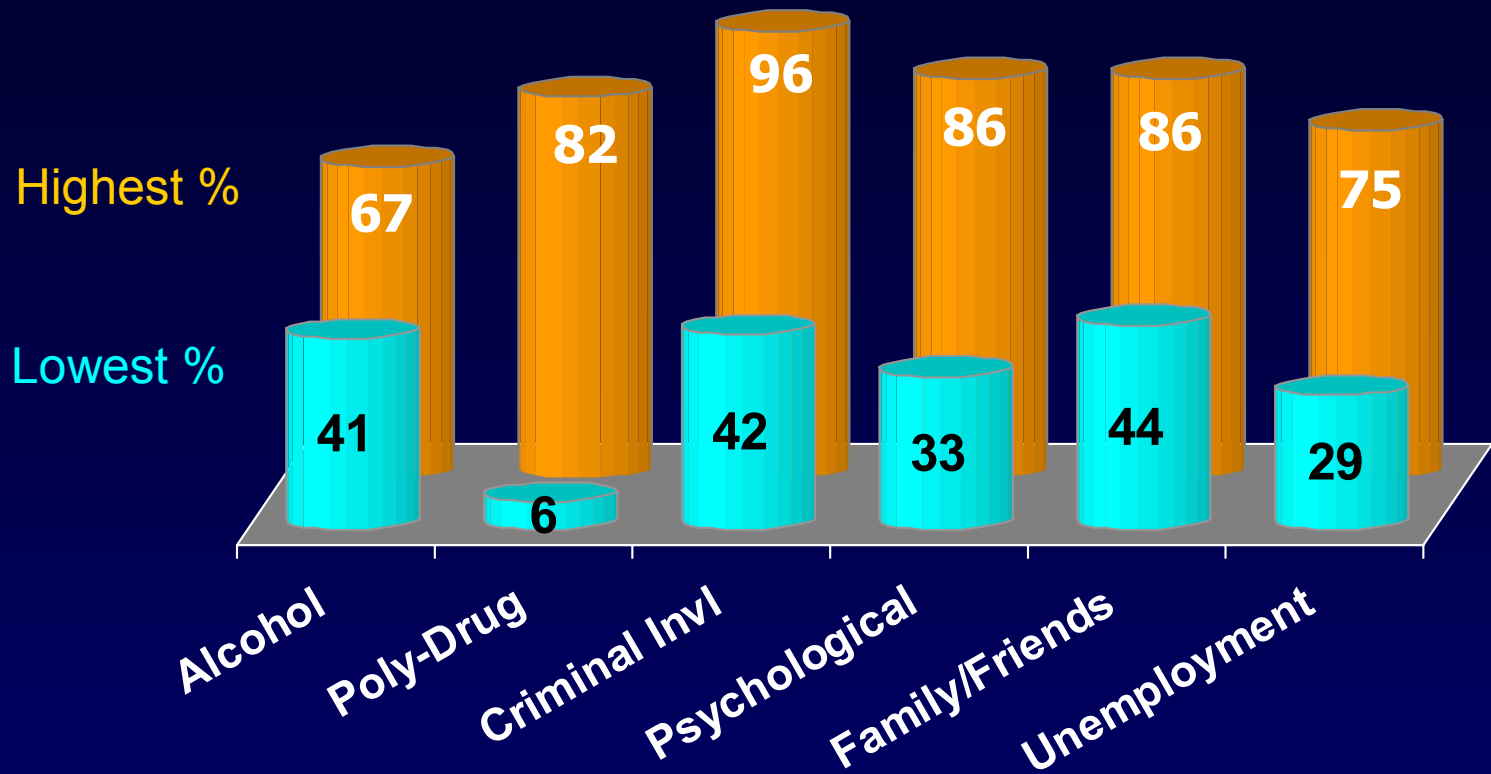
- **Conclusions from Major Reviews**

- **The "Black Box" of Treatment?**
- Institute of Medicine ('90, '96, & '98)

# Patient Retention Rates for Programs (beyond minimum “thresholds”)



# Patient Problems in LTR Programs



# Programs with Lower Retention had more “troubled” caseloads!

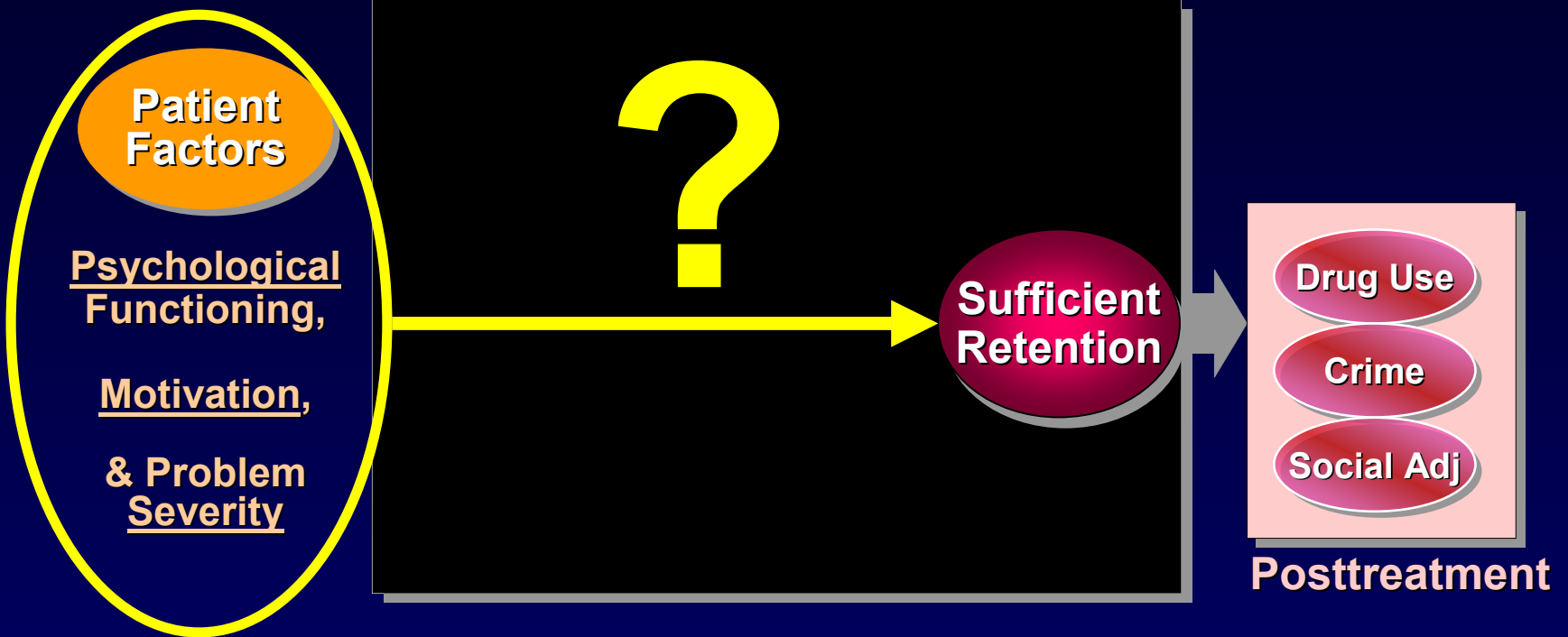
**Admissions to these programs had --**

- More cocaine & alcohol problems
- More time in previous treatments
- More psychological problems

**But these patient problems *did not* explain all program differences in retention rates!**

Fine

# Elements of a “Model” for Treatment Process?

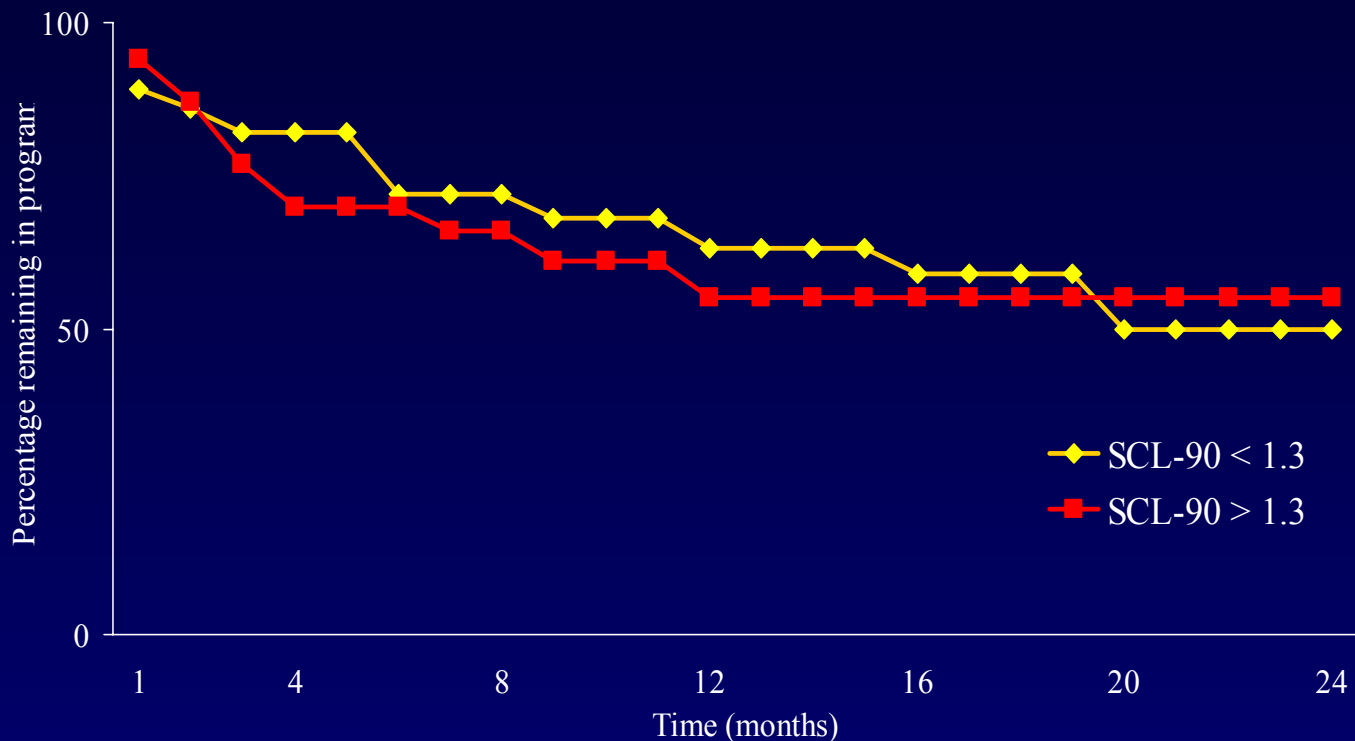


# Conclusions

- **Treatment reduces drug use & crime**
  - Problem severity & retention of patients
  - Setting, program functioning, & staff skills
- **Treatment programs are different**
  - Types of patients served
  - Engagement & retention of patients
  - Readiness for change & resources available
- **Pressing issues for treatment field**
  - “Treatment process” (quality & performance)
  - “Technology transfer” (research-to-

## Psychiatric Severity and Treatment Response in Methadone Maintenance Treatment Programmes: New Evidence

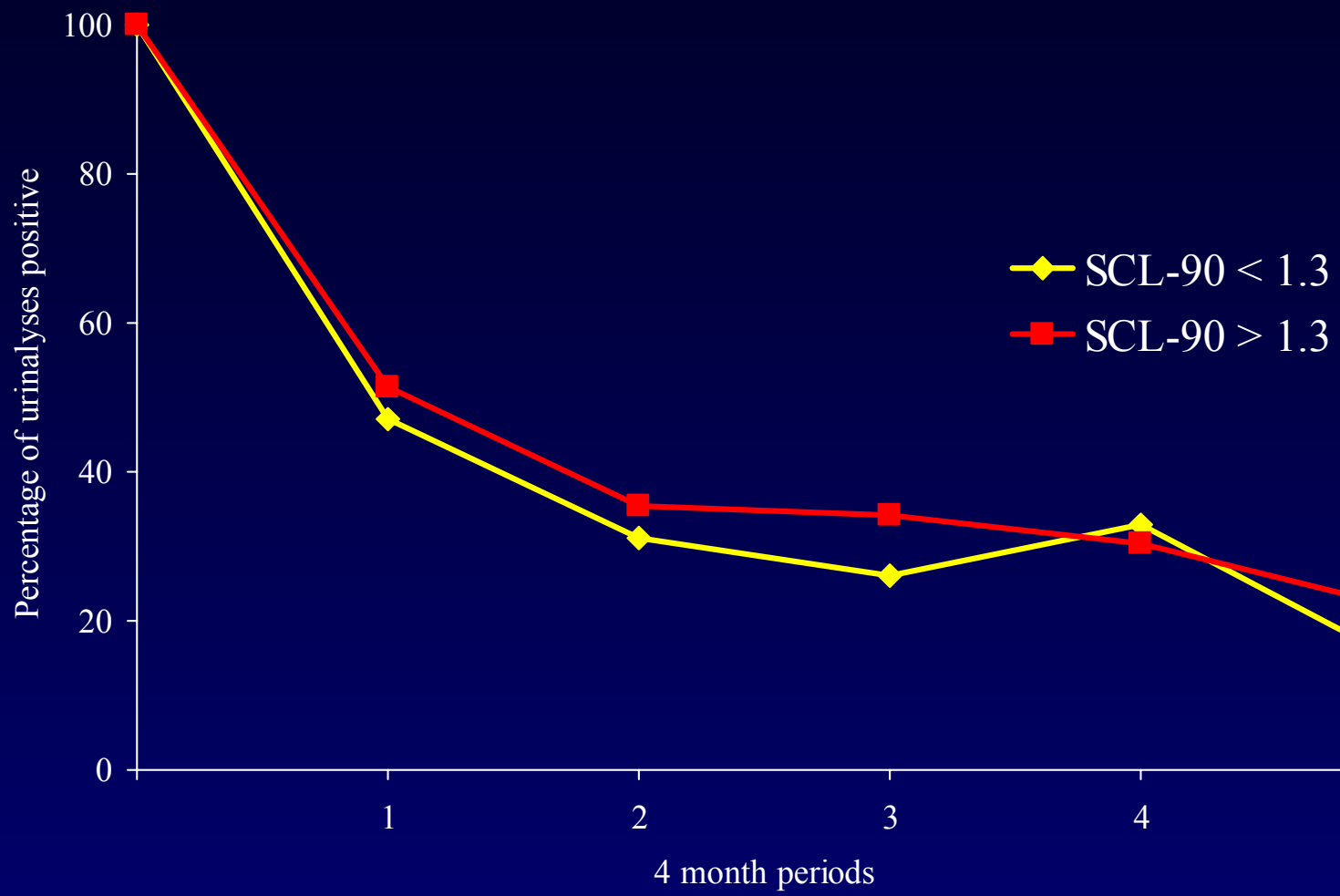
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Pani PP, Trogu E, Carboni G, Palla P, Loi A. Heroin Add & Rel Clin Probl 2003

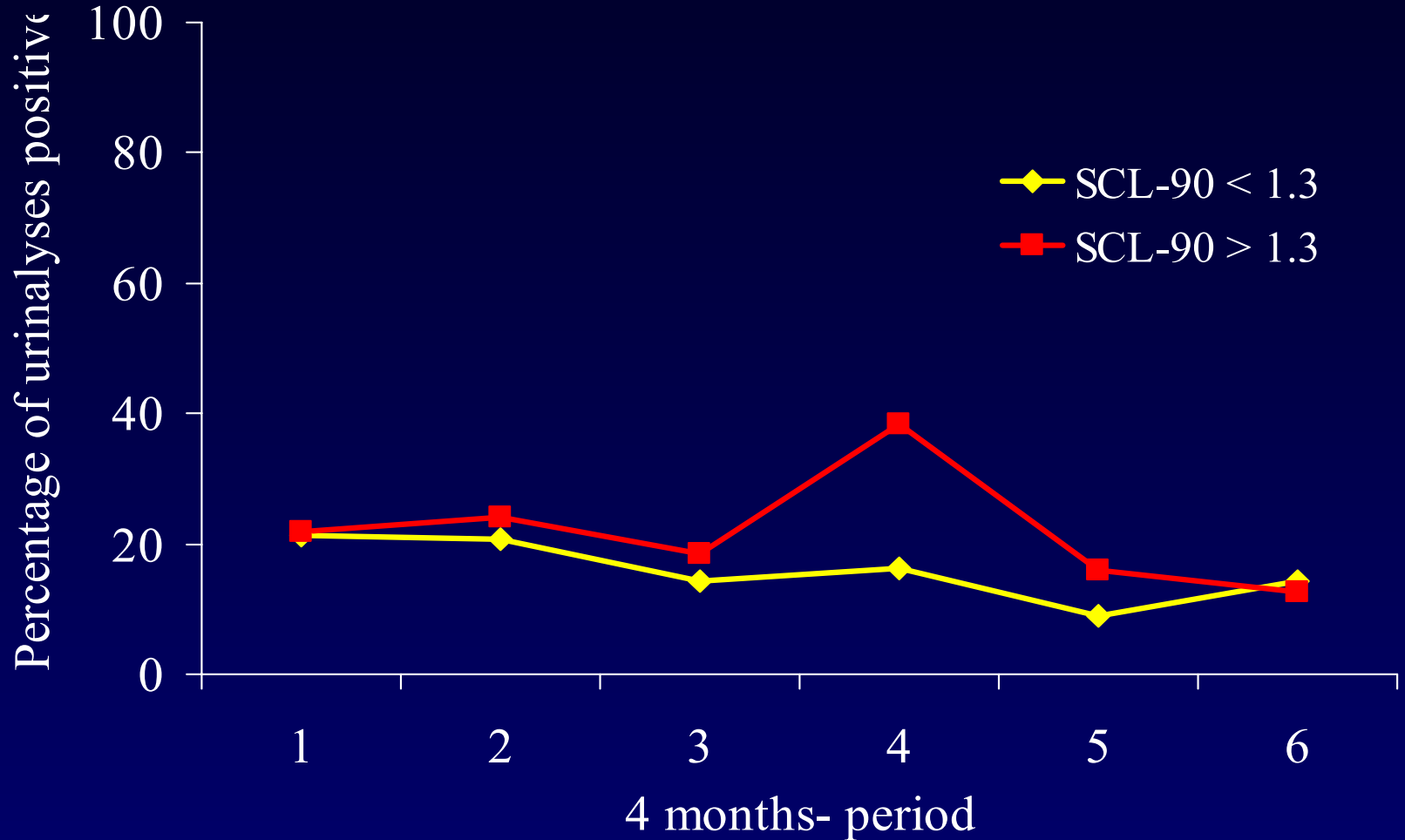
## URINE POSITIVENESS FOR MORPHINE (PCC)



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Pani PP, Trogu E, Carboni G, Palla P, Loi A. Heroin Add & Rel Clin Probl 2003

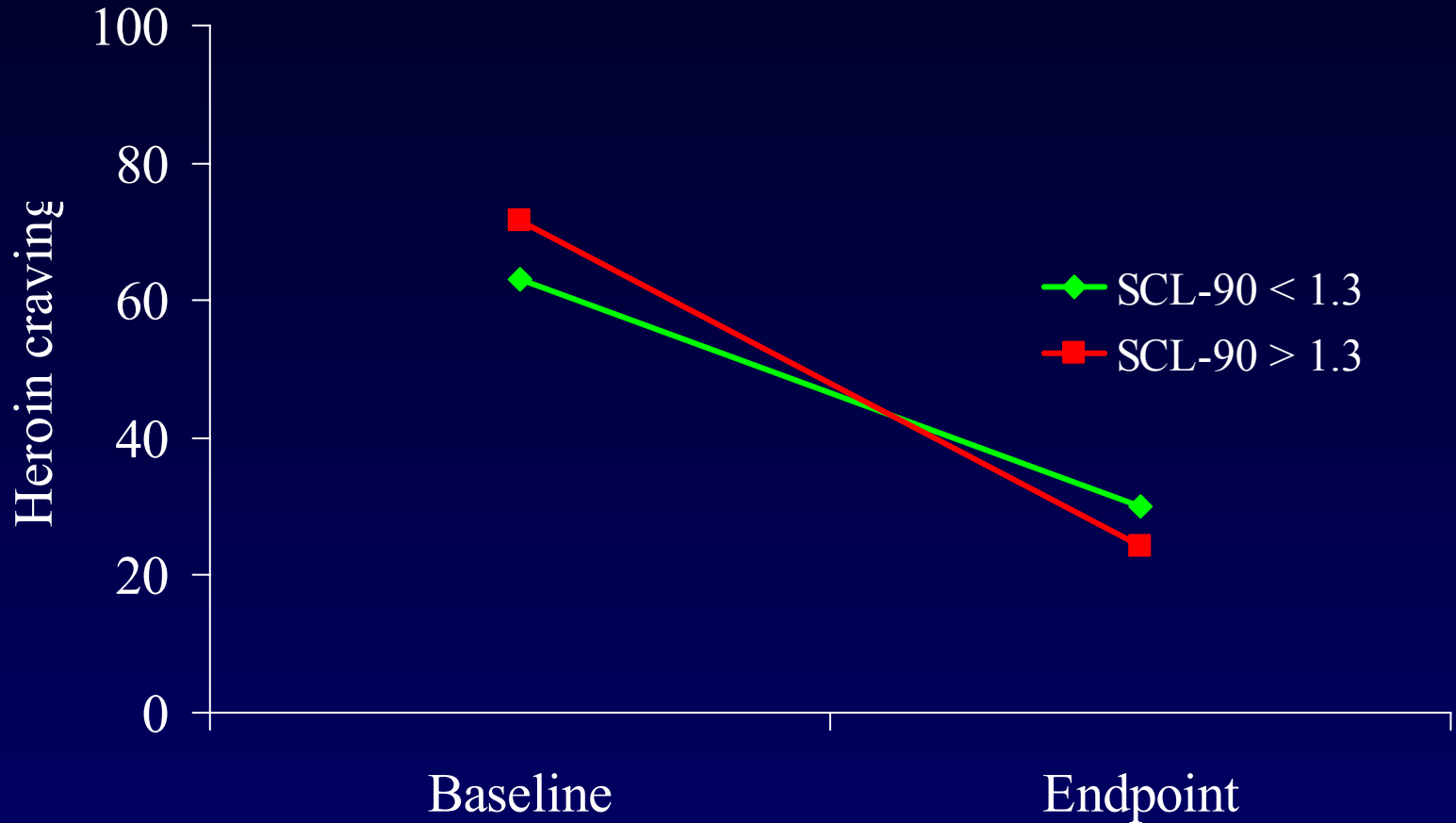
## URINE POSITIVENESS FOR COCAINE PER MONTH



# Psychiatric Severity and Treatment Response in Methadone Maintenance Treatment Programmes: New Evidence

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## BASELINE – ENDPOINT HEROIN CRAVING



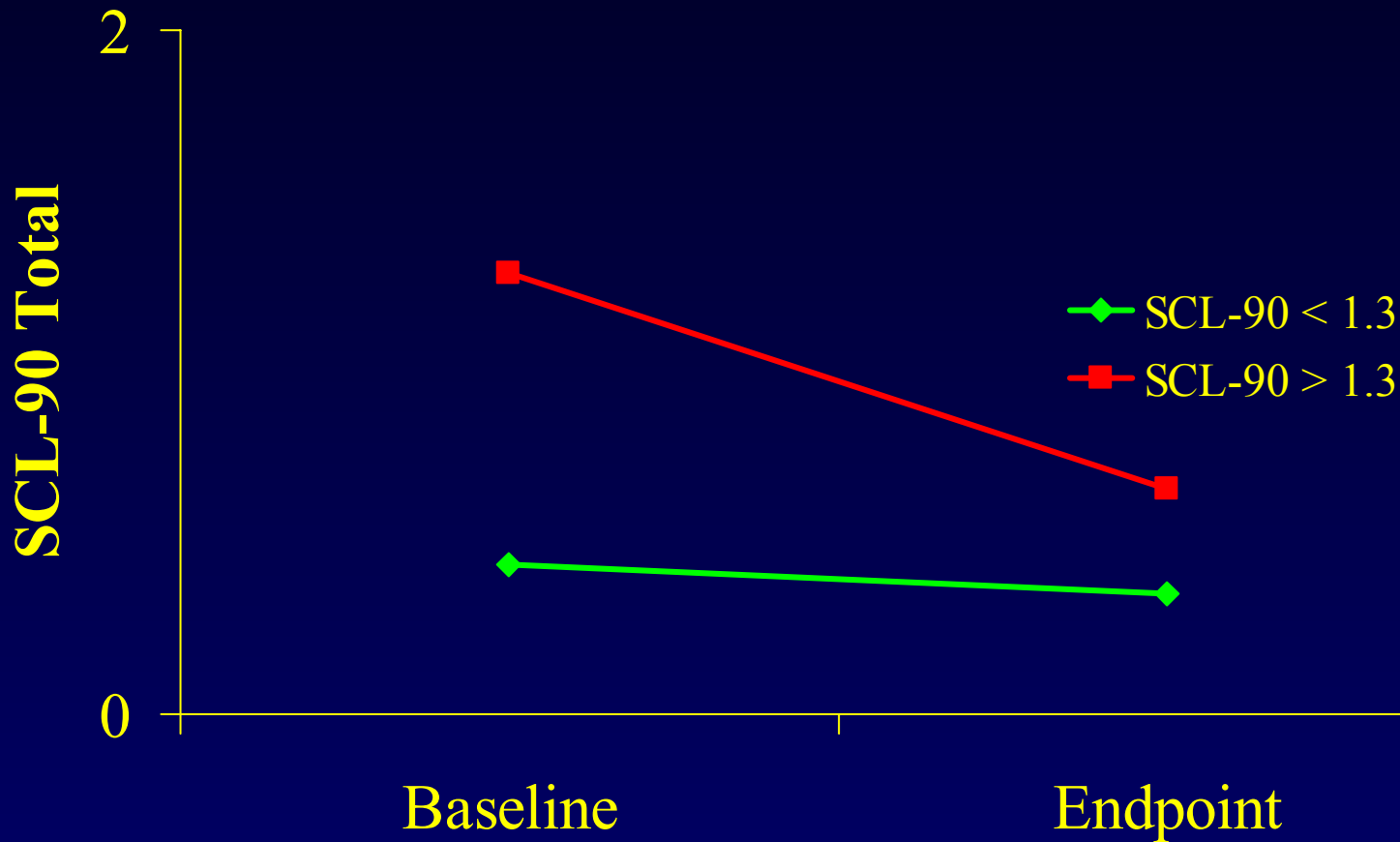
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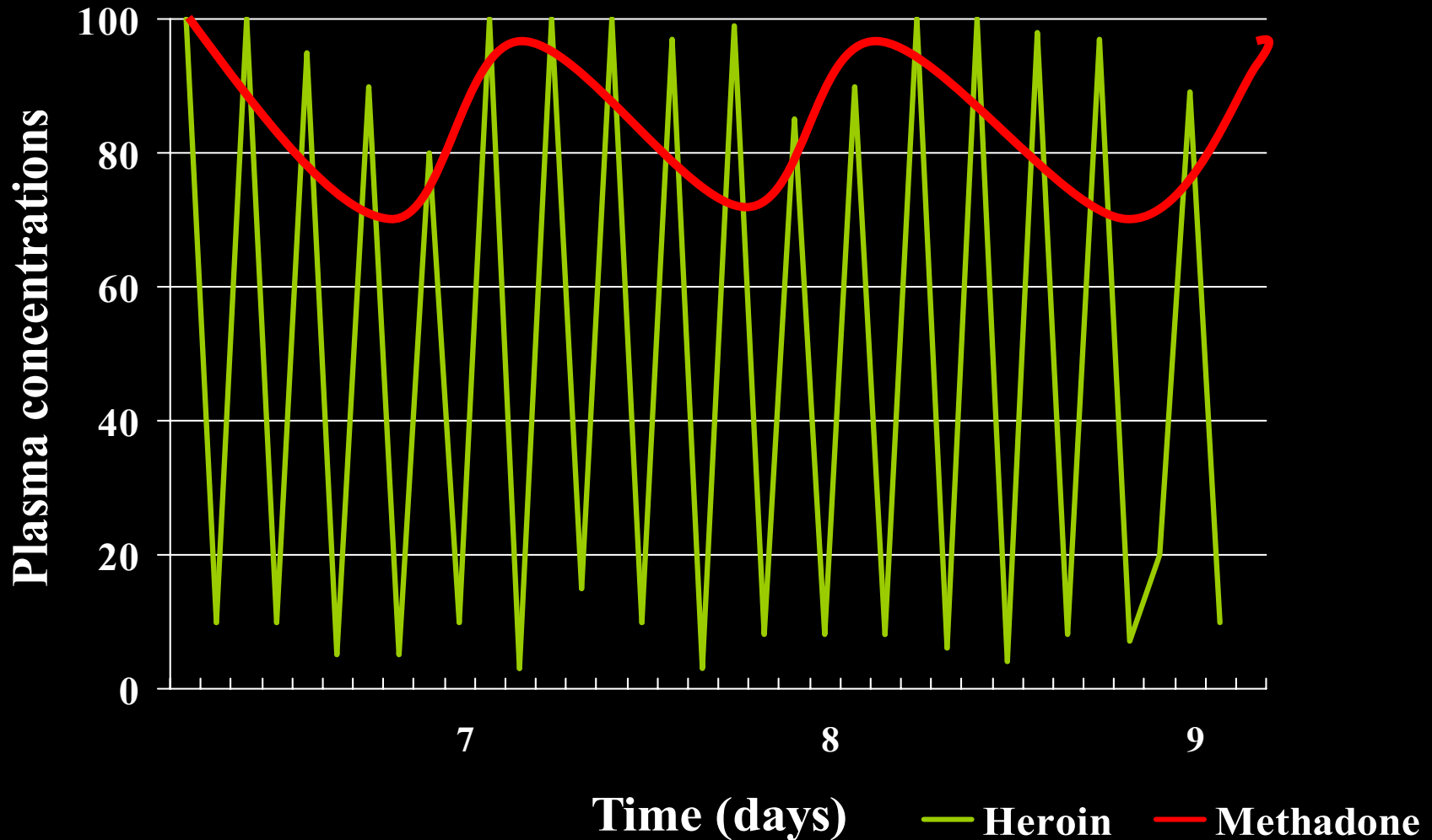
## BASELINE-ENDPOINT CHANGES IN SCL-90

	Low severity		High severity		Time	Group-time
	Baseline	Endpoint	Baseline	Endpoint		
Total	0.44	0.35	1.29	0.66	0.000	0.000
Anxiety	0.37	0.32	1.22	0.75	0.001	0.005
Anger-hostility	0.45	0.40	1.02	0.53	0.002	0.011
Phobic anxiety	0.06	0.13	0.50	0.17	0.008	0.000
Paranoidism	0.42	0.31	1.07	0.62	0.000	0.006
Psychoticism	0.24	0.29	0.92	0.52	0.007	0.001
Somatization	0.52	0.38	1.71	0.97	0.000	0.001
Obsess-compuls	0.52	0.46	1.41	0.73	0.000	0.000
Interper sensitivity	0.35	0.29	1.10	0.52	0.000	0.000
Depression	0.55	0.43	1.65	0.92	0.000	0.000

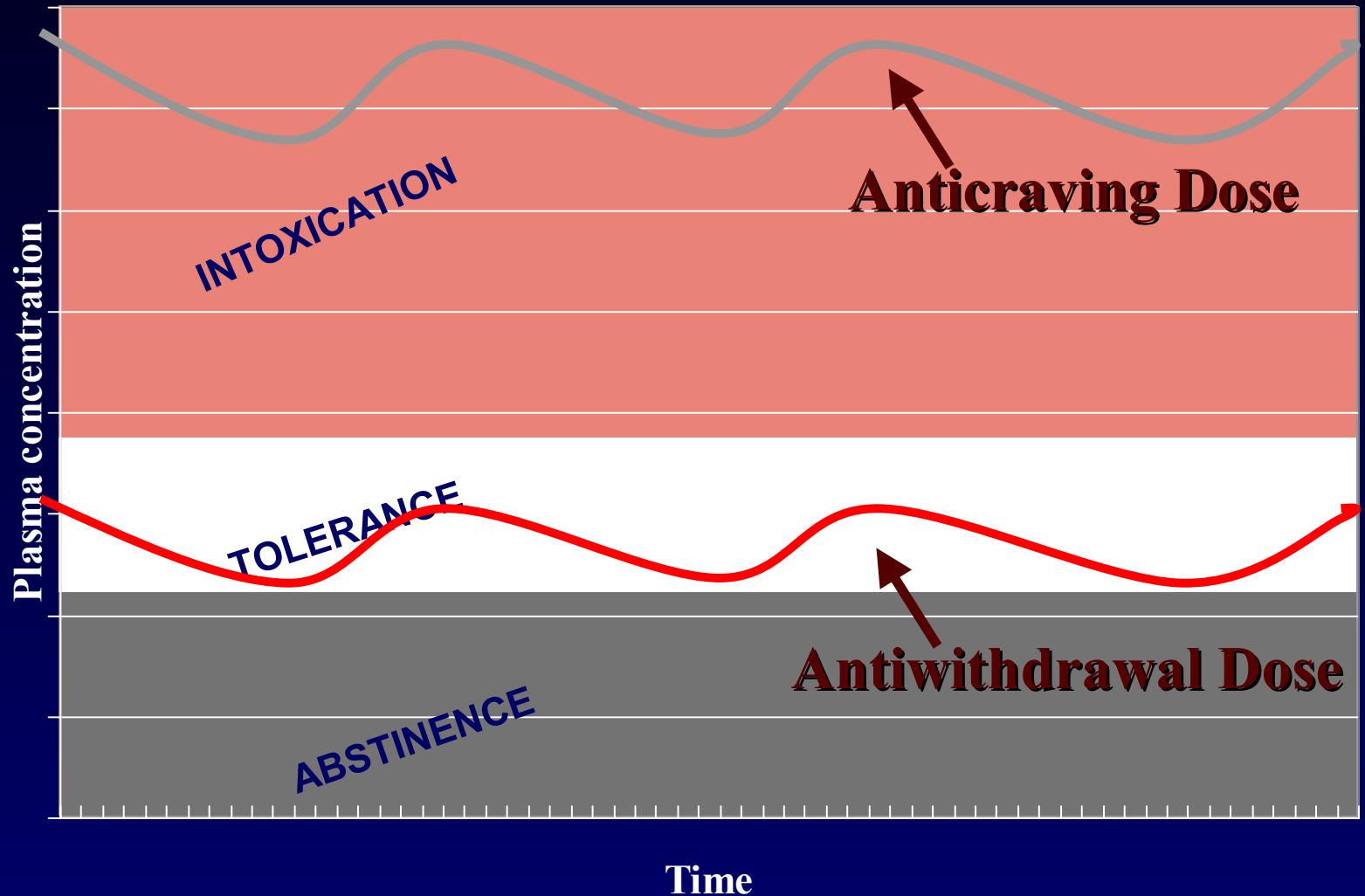
PROSPECTIVE PSYCHIATRIC SEVERITY STUDY  
**BASELINE – ENDPOINT SCL-90: TOTAL**



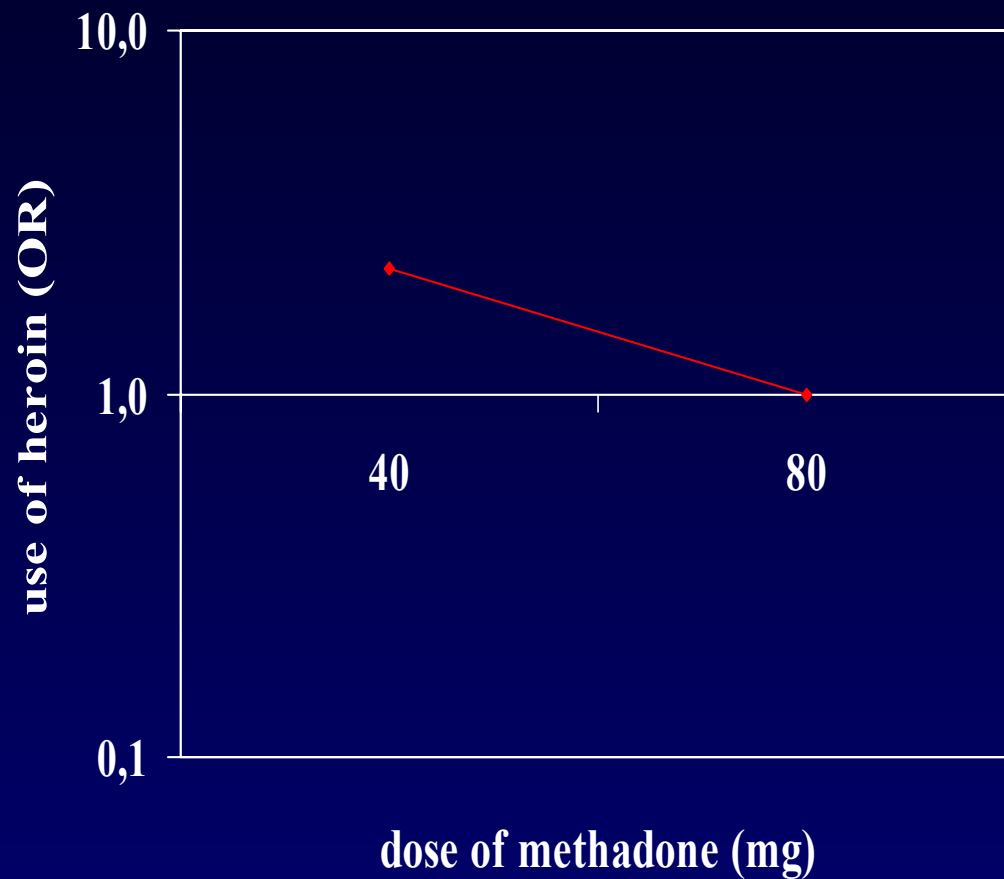
# HEROIN ADDICTION: PLASMA VARIATIONS FOR HEROIN AND METHADONE



# METHADONE: ANTIWITHDRAWAL AND ANTICRAVING EFFECT



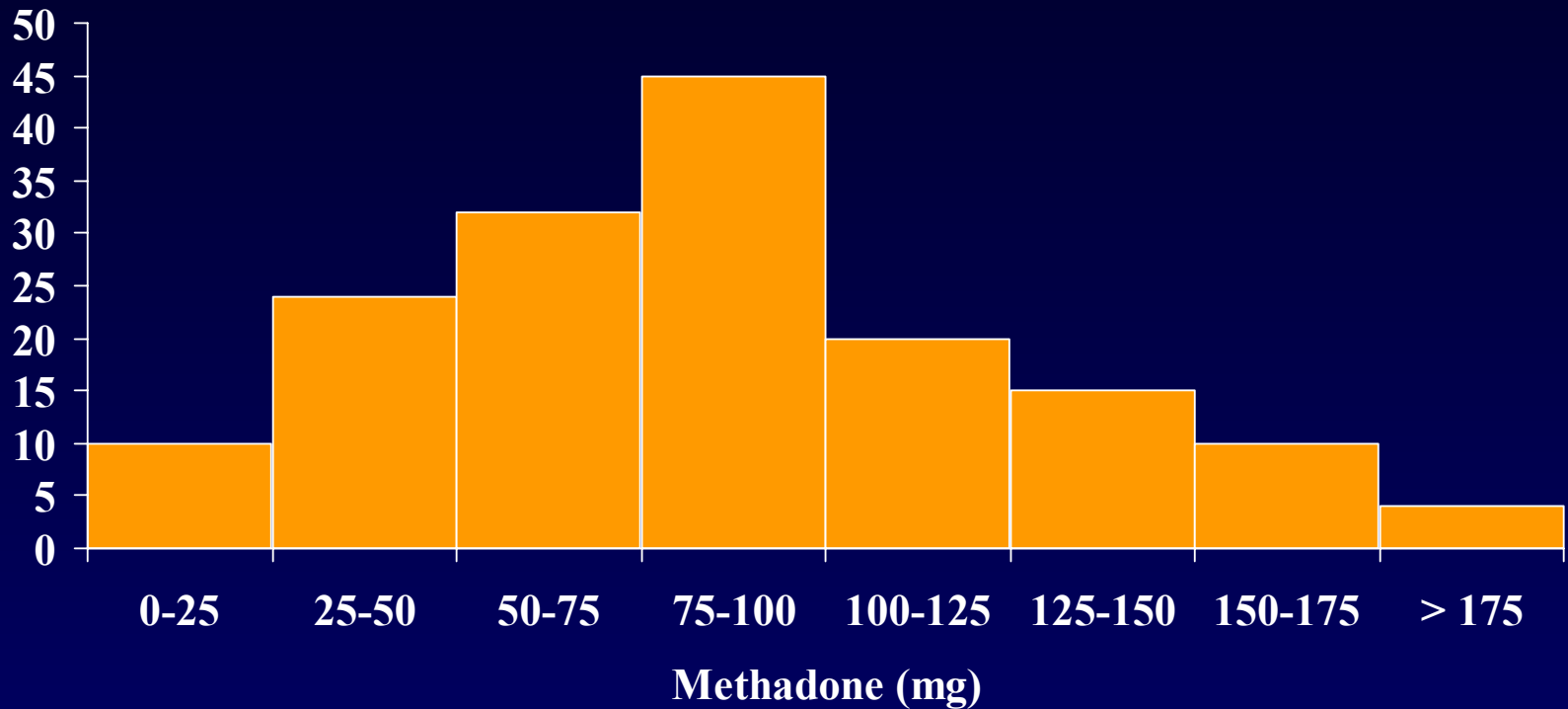
# RELATIONSHIP BETWEEN THE DOSE OF METHADONE AND THE USE OF HEROIN



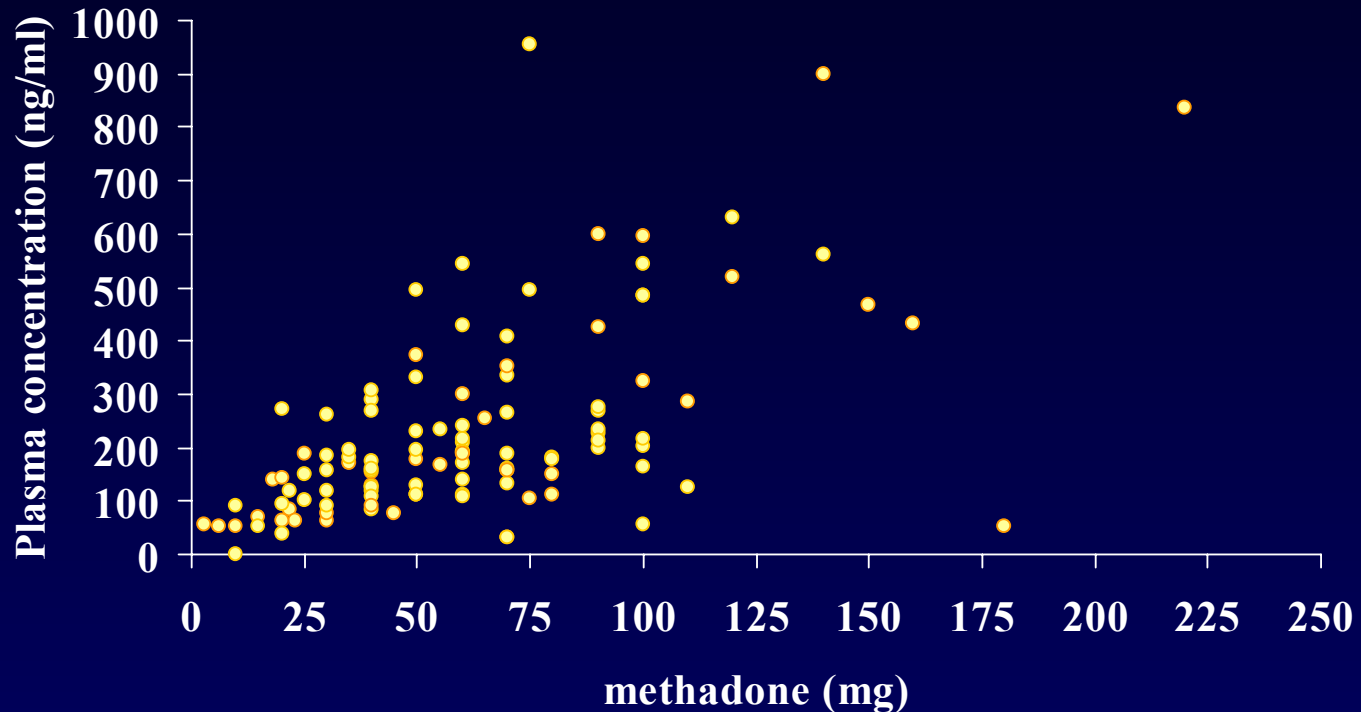
**Clinical guidelines for the use of methadone**  
Consensus panel on methadone treatment,  
Pietrasanta 2001

“In a range between 80 - 120 mg/day usually we get the therapeutic response in terms of control of heroin use”.

# METHADONE DOSAGES: FREQUENCY DISTRIBUTION



# METHADONE PHARMACOKINETIC: DOSE- CONCENTRATION RELATIONSHIP



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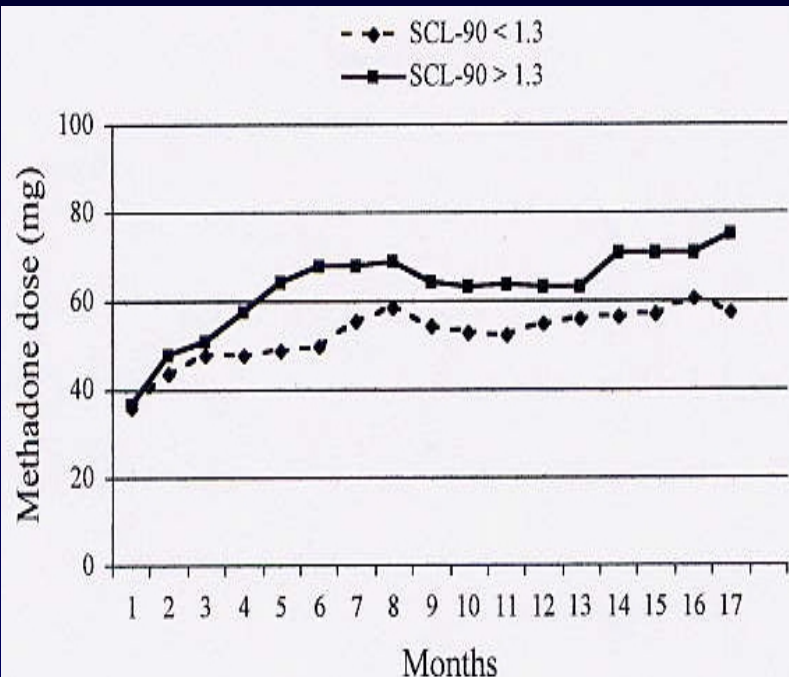


Figure 4. Methadone mean daily dose per month

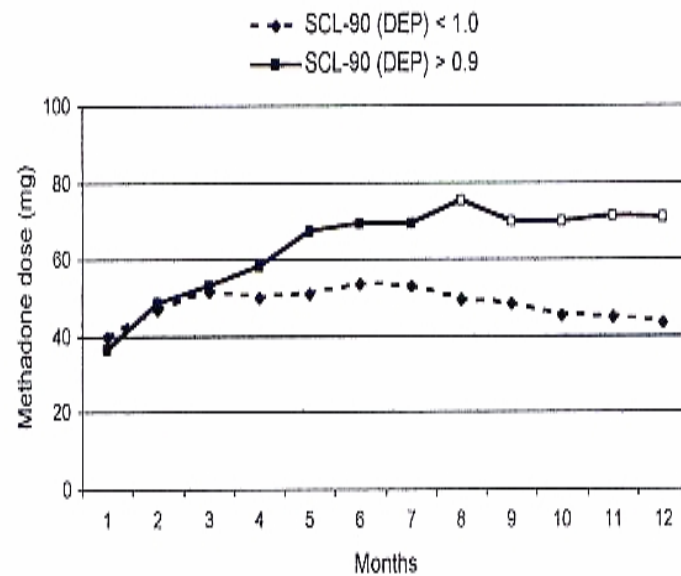
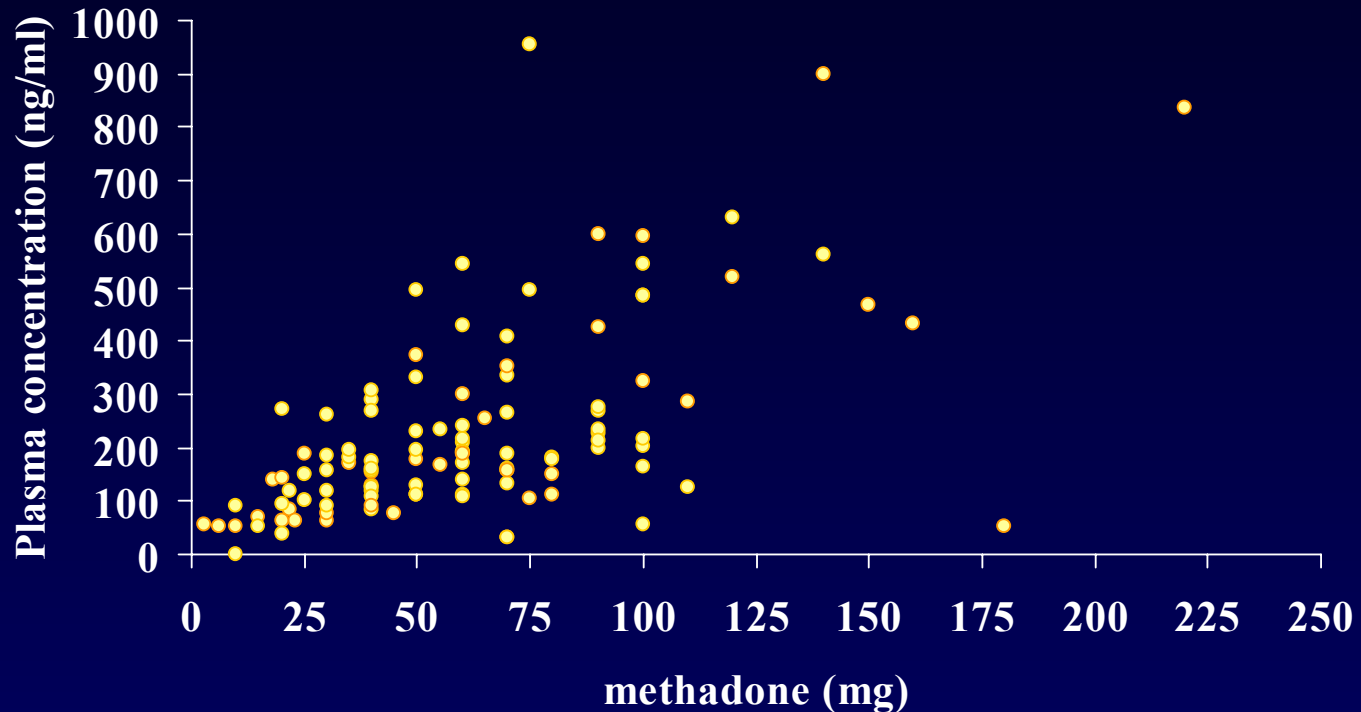


Figure 5. Methadone: mean daily dose per month in patients with high and low depression severity

# Methadone dose of heroin addicts with Axis I psychiatric comorbidity (Maremmani, et al., J Addict Dis, 2000).

	Dually diagnosed patients		Only heroin addicted patients		T
	Mean	SD	Mean	SD	
Methadone dose	154	84	99	49	P <.001

# METHADONE PHARMACOKINETIC: DOSE- CONCENTRATION RELATIONSHIP



# METHADONE INTERFERENCES: CLINICAL CASE

**A.Y.**

**Methadone = 100 mg**

**Plasma concentration = 57 ng/ml  
(14 hours after intake)**

**Craving = 80**

**(range: 0 – 100).**

**Medications:**

**carbamazepine**

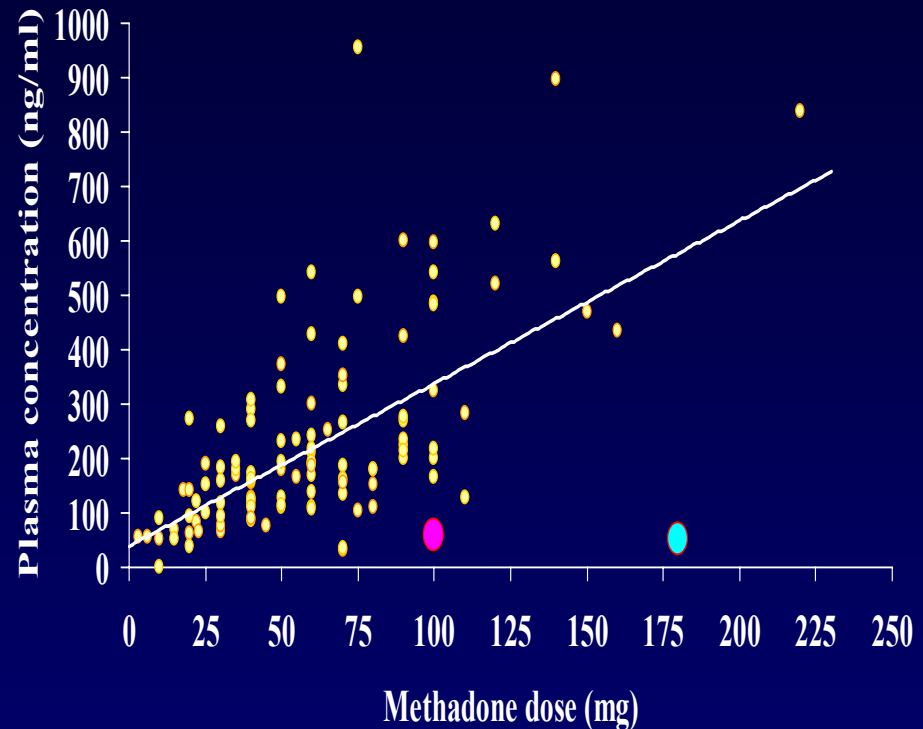
**X.J.**

**Methadone = 180 mg**

**Plasma concentration = 52 ng/ml**

**Craving = 70 for cocaine, 0 for  
heroin.**

**Medications: carbamazepine**



# MEDICATIONS INTERFERING WITH METHADONE

## REDUCE PLASMA CONCENTRATION:

### Sure

Barbiturates  
carbamazepine  
fenitoin  
rifampicine  
amprenavir  
abacavir  
efavirenz  
nevirapina

### Possible

alcohol  
didanosine  
ritonavir  
stavudine  
ascorbic acid and other urine  
acidifiants.

## INCREASE PLASMA CONCENTRATION:

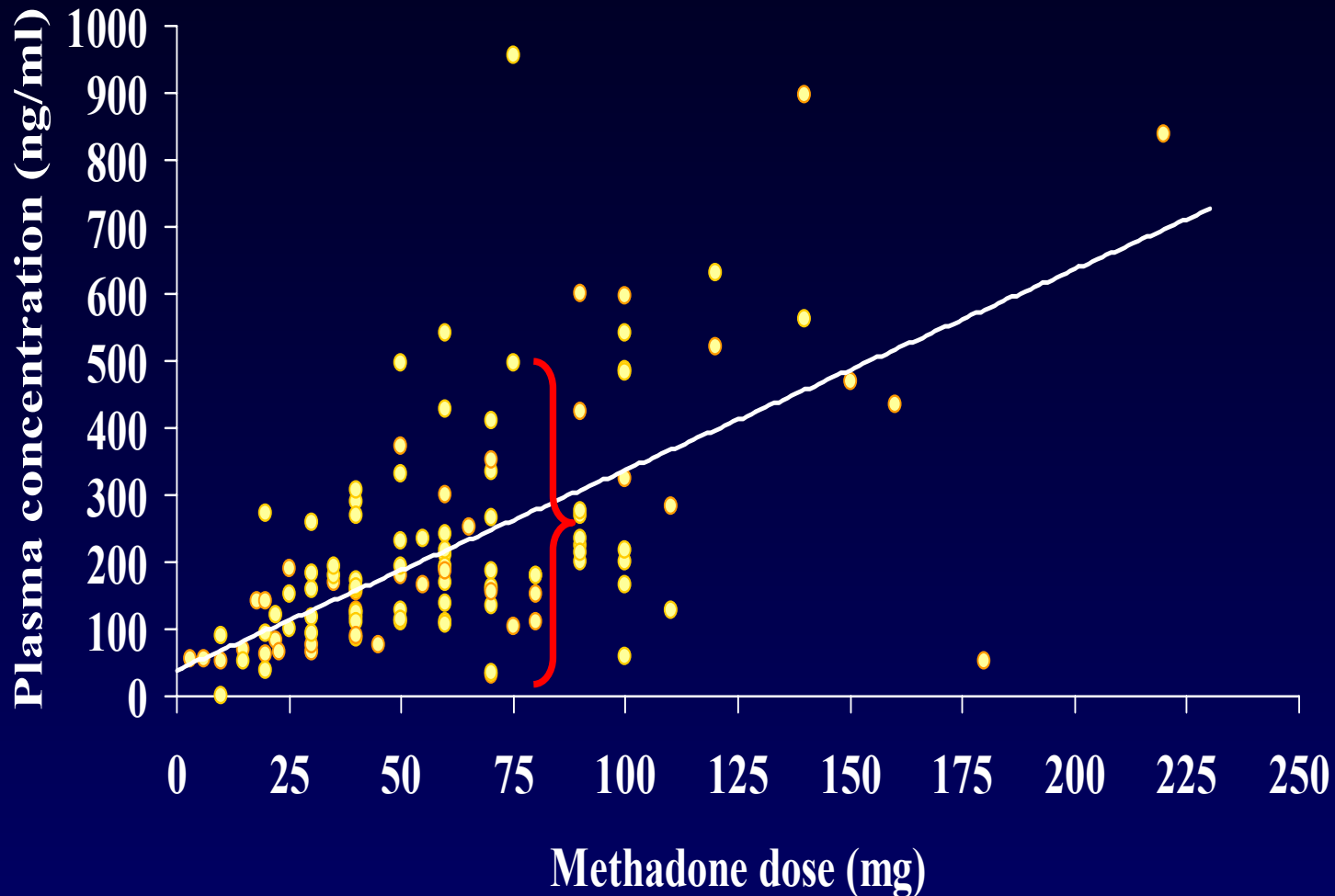
### Sure

fluvoxamine  
fluconazol  
chetoconazol

### Possible

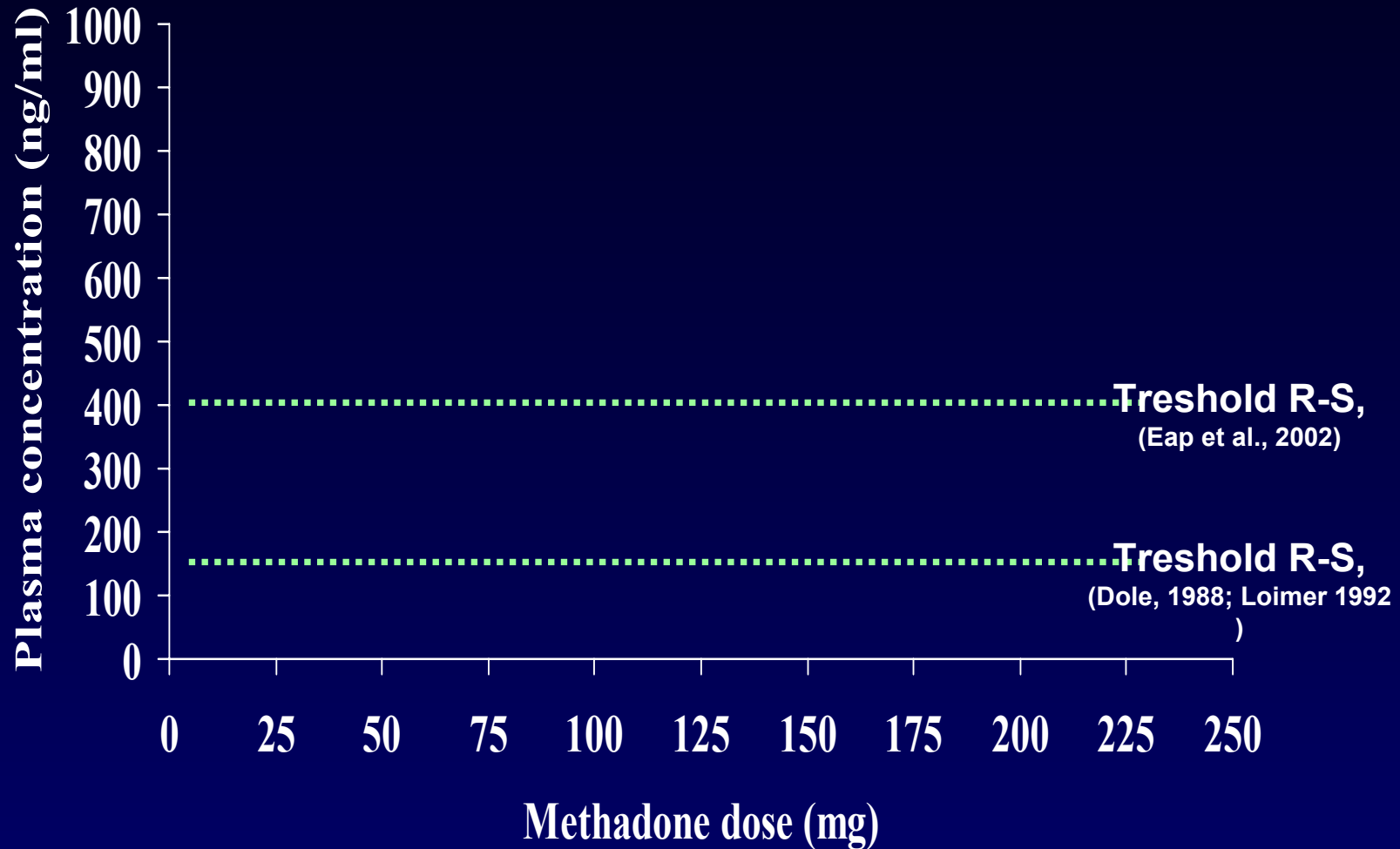
Cimetidin  
ciprofloxacin  
fluoxetine  
Nefazodone  
paroxetine

**FIG. 2 REGRESSION PLASMA METHADONE CONCENTRATION (FPIA) BY DOSE TAKEN**



A 17 fold variation has been found in the dose of methadone needed to obtain a 250 ng/ml plasma concentration of R-methadone (Eap et al., 2000).

# METHADONE CONCENTRATION TRESHOLD



# PHARMACOLOGY OF BUPRENORPHINE

Buprenorphine acts as

Partial agonist for  $\mu$  receptors

Antagonist for  $\kappa$  receptors

Buprenorphine has a high affinity for  $\mu$   
and (less) for  $\kappa$  receptors

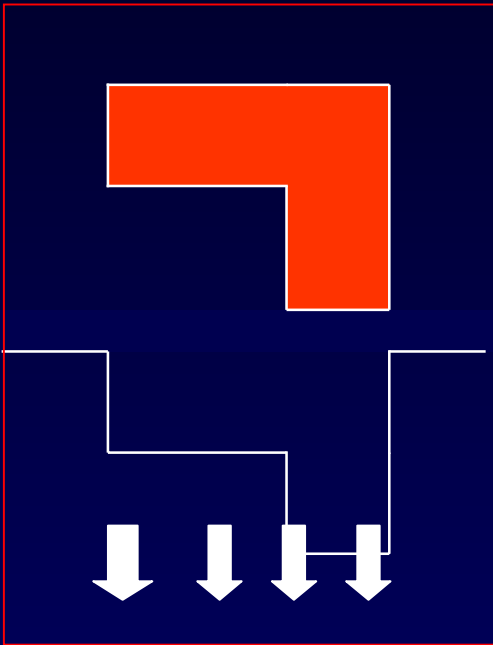
# OPIOID RECEPTORS

$\mu$

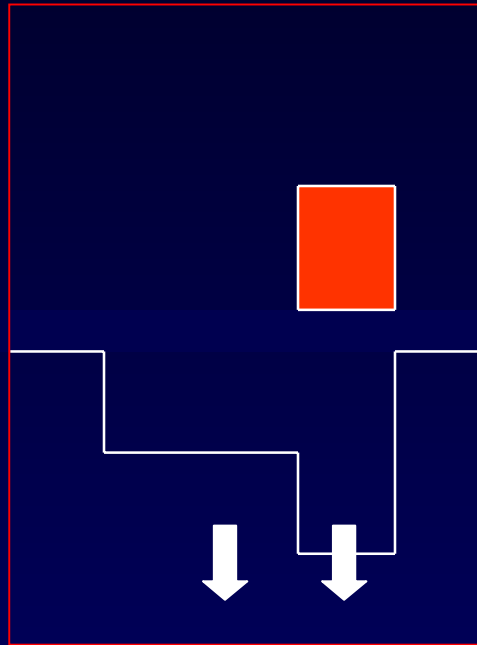
$\delta$

$\kappa$

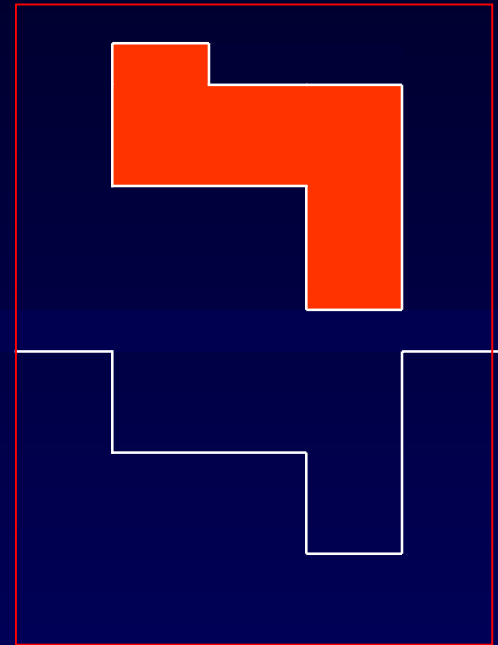
# OPIOID ACTIVITY



agonist

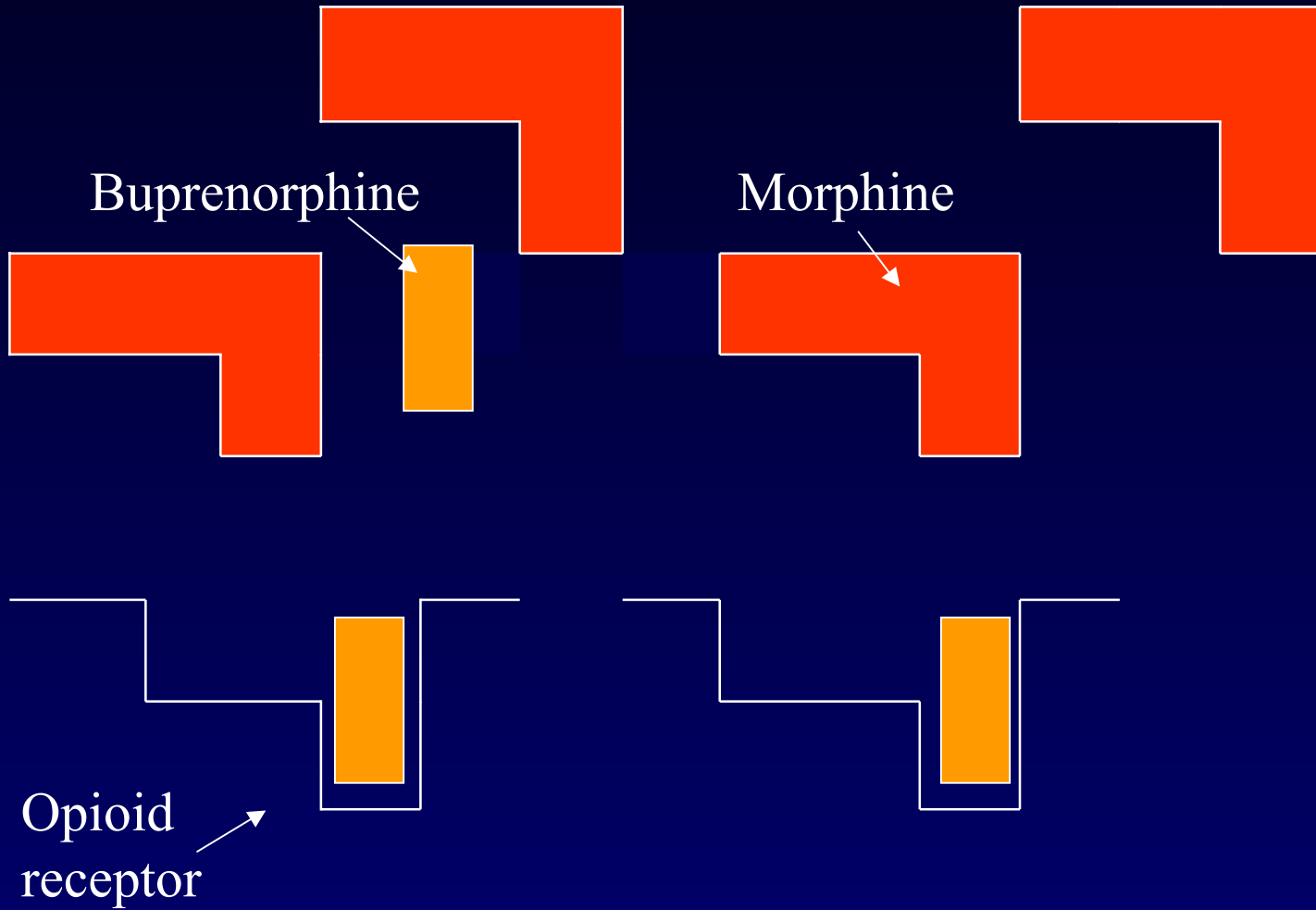


partial  
agonist



antagonist

# AFFINITY



# PHARMACOLOGY OF BUPRENORPHINE

**Buprenorphine is reinforcing but does not produce “rush”-like effects**

**Buprenorphine does not induce significant physical dependence**

**The possibility of buprenorphine lethal overdose is remote**

**Buprenorphine may be administered sublingually**

**Buprenorphine effectively suppresses heroin self-administration**

# EFFICACY OF BUPRENORPHINE FOR THE TREATMENT OF OPIOID DEPENDENCE: EFFECT OF THE DOSE

*W. Ling, D.R. Wesson / Drug and Alcohol Dependence 70 (2003) S49–S57*

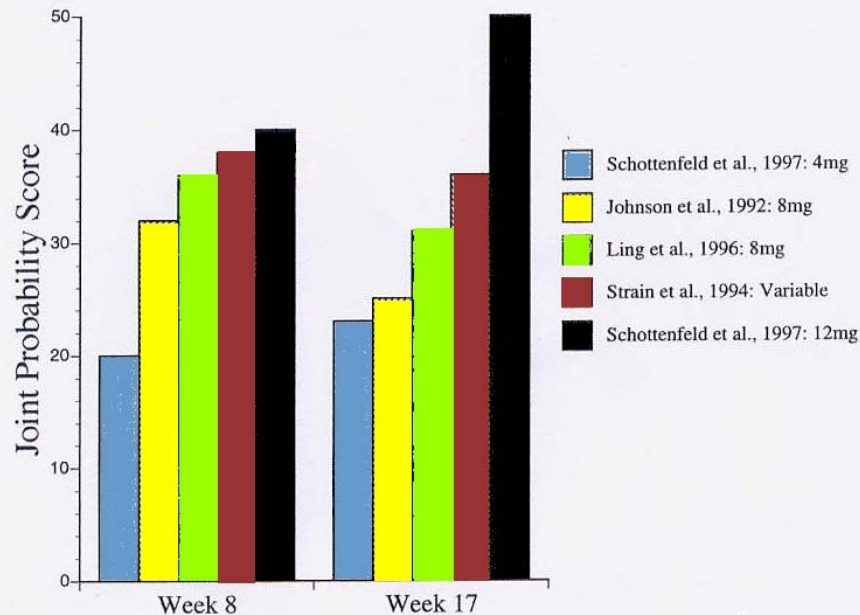
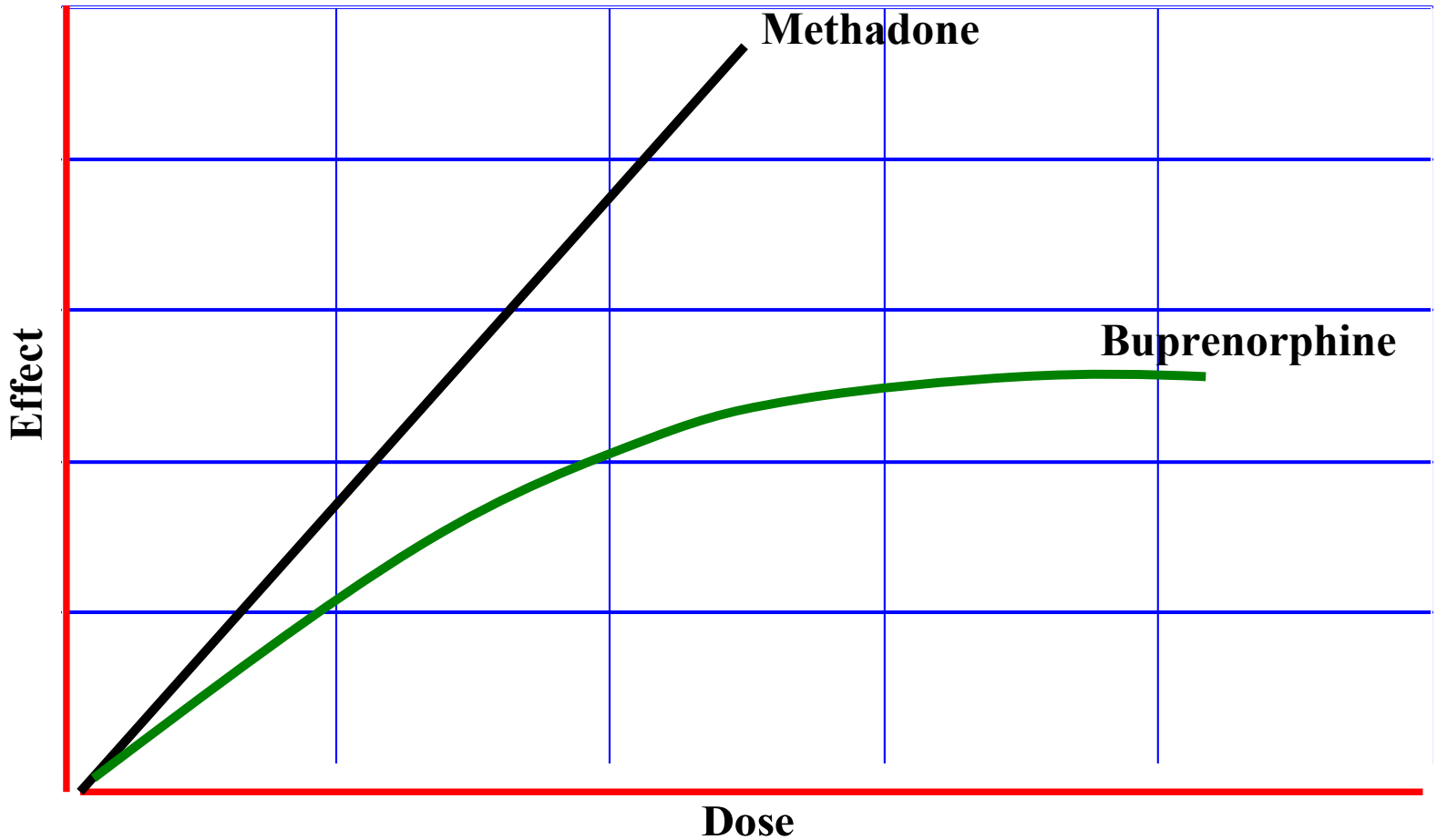
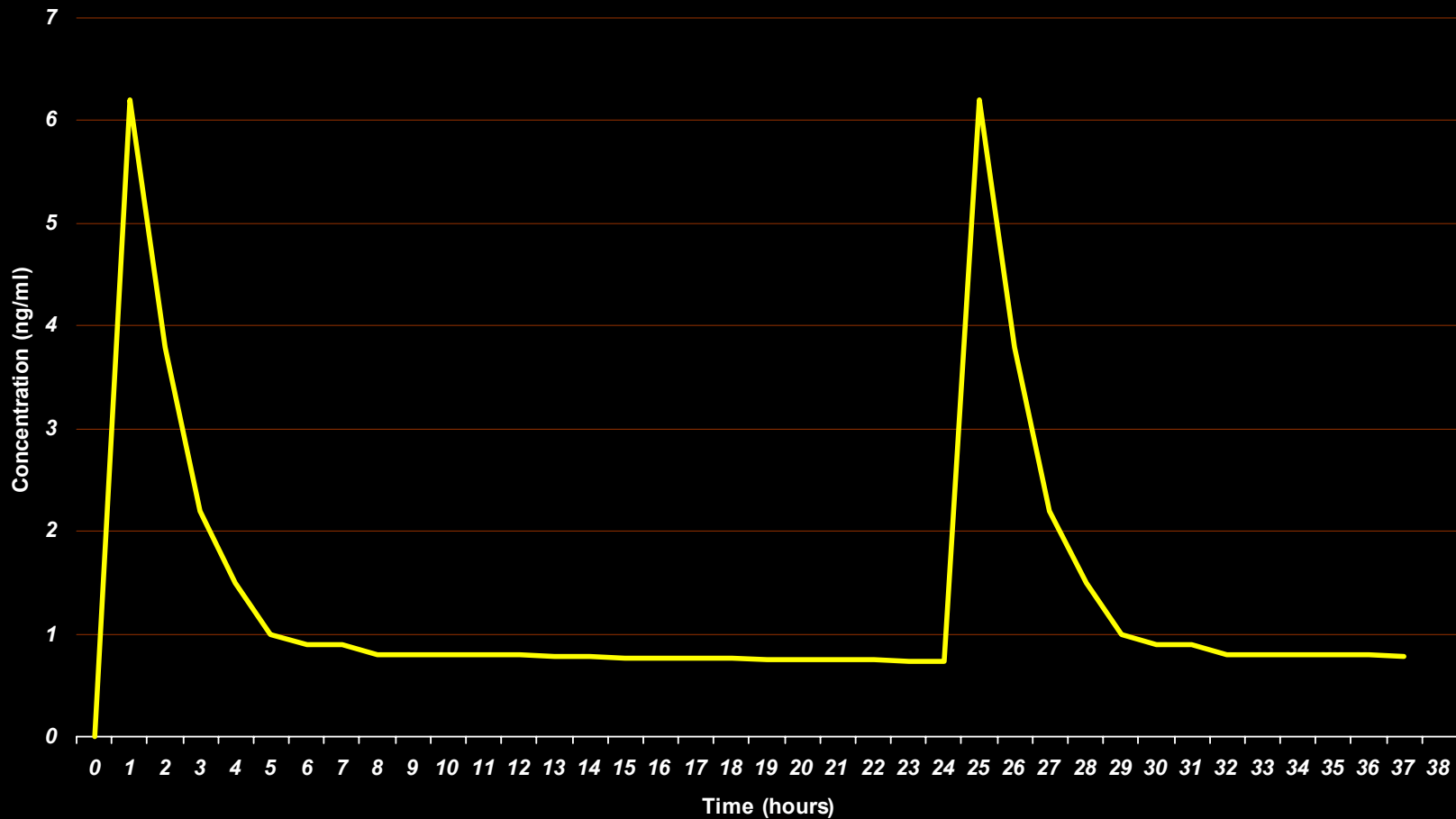


Fig. 1. The efficacy of buprenorphine for treatment of opiate dependence compared across studies and as a function of buprenorphine dose. Efficacy was measured by the JP Score, which combines treatment retention and urinalysis outcomes. Outcomes are shown for both 8 and 17 weeks of treatment.

# BUPRENORPHINE: DOSE EFFECT RELATIONSHIP

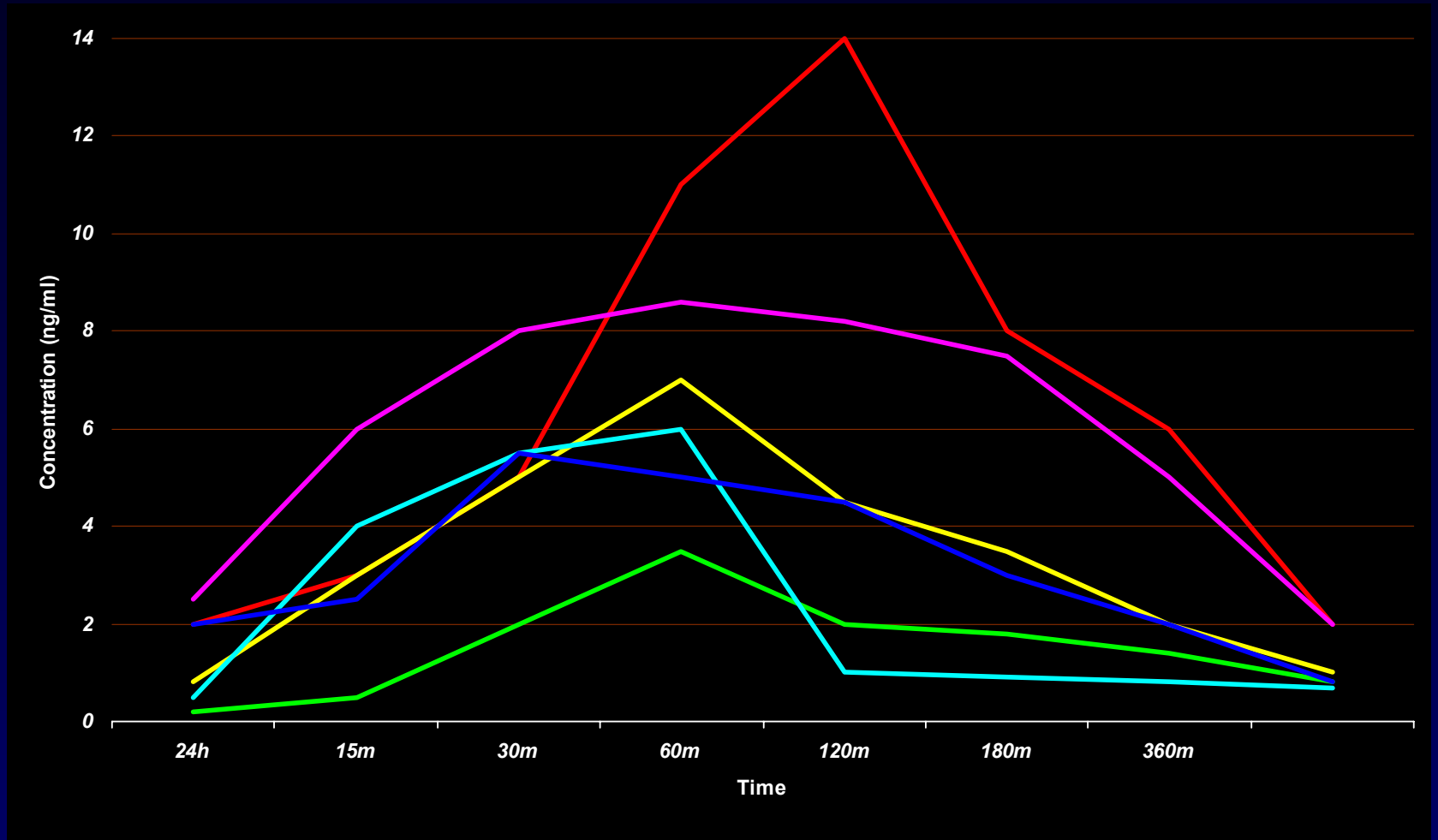


# BUPRENORPHINE PLASMA CONCENTRATION: CRONIC ADMINISTRATION



# SUBLINGUAL BUPRENORPHINE (8 mg liquid): VARIABILITY IN PLASMA CONCENTRATION

Schuh et al., 1999 (modified).



# OPIOID AGONISTS IN HEROIN ADDICTION: APPROPRIATE DOSE

- No withdrawal complains
- No use of heroin
- No craving
- No sedation, euphoria

- In Italy, a wide public treatment network (500 services) gives currently assistance to about 150.000 heroin addicts.



# METHADONE MAINTENANCE COST

