Il Ruolo del Trattamento Farmacologico con Agonisti nella Prevenzione delle Patologie Correlate: Le Evidenze

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The methadone treatment in harm reduction measures are opposed to abstinece-oriented treatments?

The ~~methadone treatment in~~ harm reduction measures are opposed to abstinece-oriented treatments?

“The harm reduction measures attemp to reduce the harms associated with use, without the user giving up his or her use at present time”

Singh E (1995), Defining harm reduction, Drug and Alcohol Rev., 14, 287-290

“conceiving of harm reduction in this way means that abstinence-induced programs would not be considered harm reduction measures”

Singh E (1995), Defining harm reduction, Drug and Alcohol Rev., 14, 287-290

Use

Abstinence

Continuum Treatment

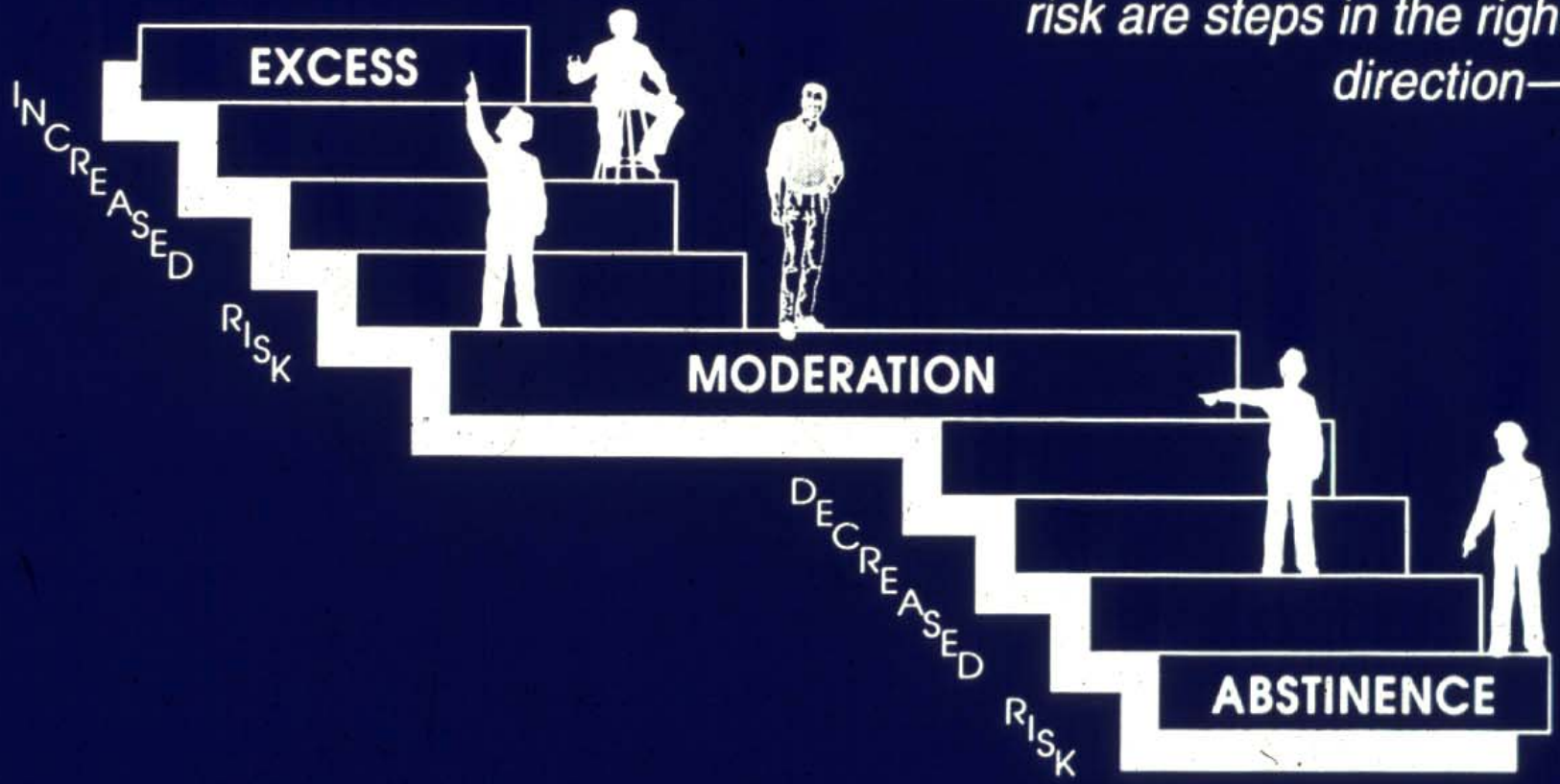
Marlatt G.A. (1998) (Ed.) Harm Reduction Pragmatic Strategies for Manging High-Risk Behaviours. New York: The Guilford Press

“Harm reduction – including the harm reduction approach of methadone treatment - may be considered as any attempt to move the clients from the negative pole towards the positive”

Marlatt G.A. (1998) (Ed.) Harm Reduction Pragmatic Strategies for Manging High-Risk Behaviours. New York: The Guilford Press

Continuum of Excess, Moderation, and Abstinence

—Any steps toward decreased risk are steps in the right direction—



from Marlatt G.A. slides

Drug Health Polices

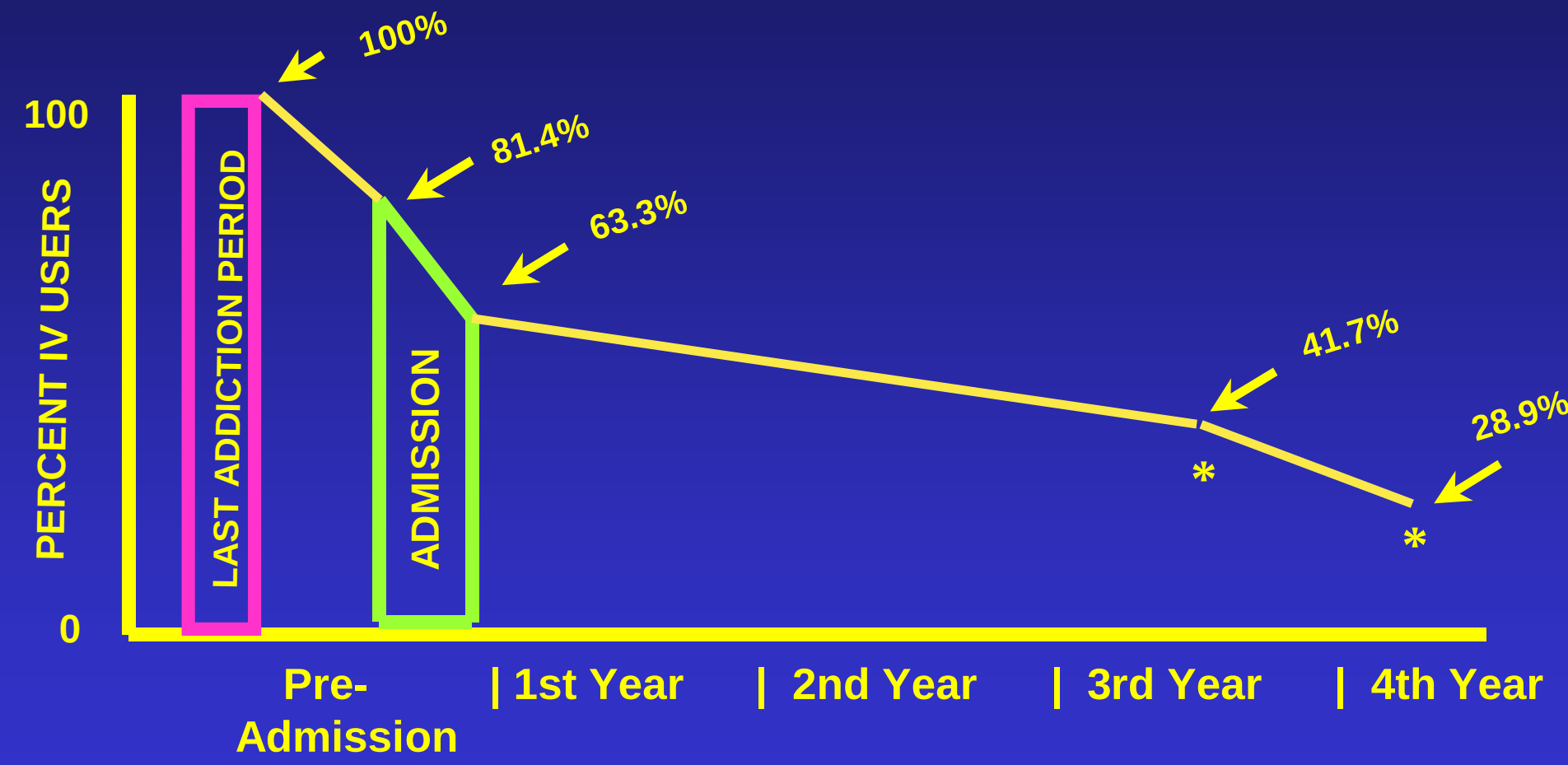
	Consequentialist Strategy	Causalist Strategy
Treatment Goals	Harm reduction opposed to abstinence	Harm reduction not opposed to abstinence
Treatment Focus	Consequentialist Non focus on addiction	Causalist Focus on addiction
Relationship Methadone-Heroin	Methadone different from heroin	Methadone similar to heroin (medically speaking)

Modified by Jarvinen, 2008

EVIDENCE

EVIDENCE

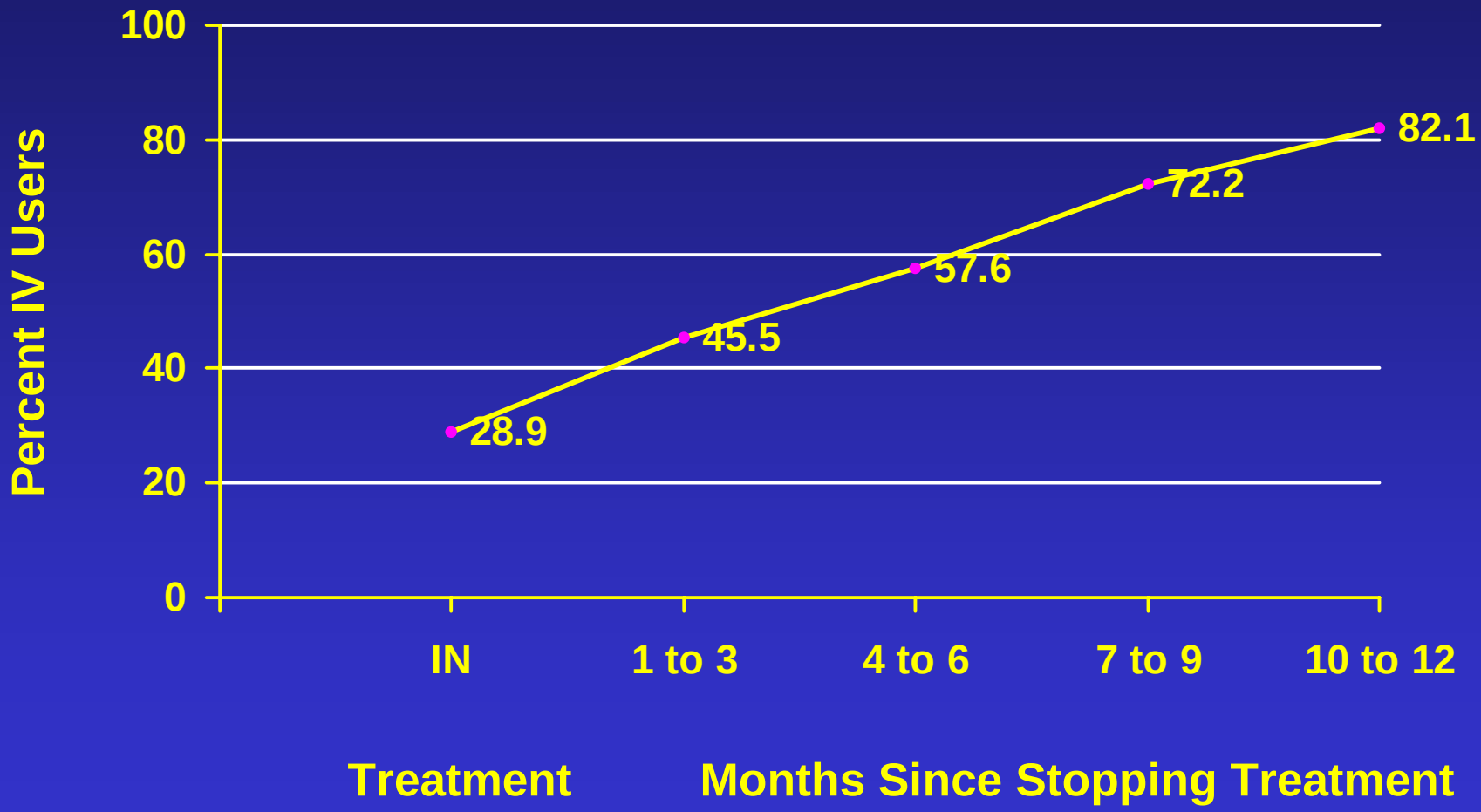
Impact of MMT on IV Drug Use for 388 Male MMT Patients in 6 Programs



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

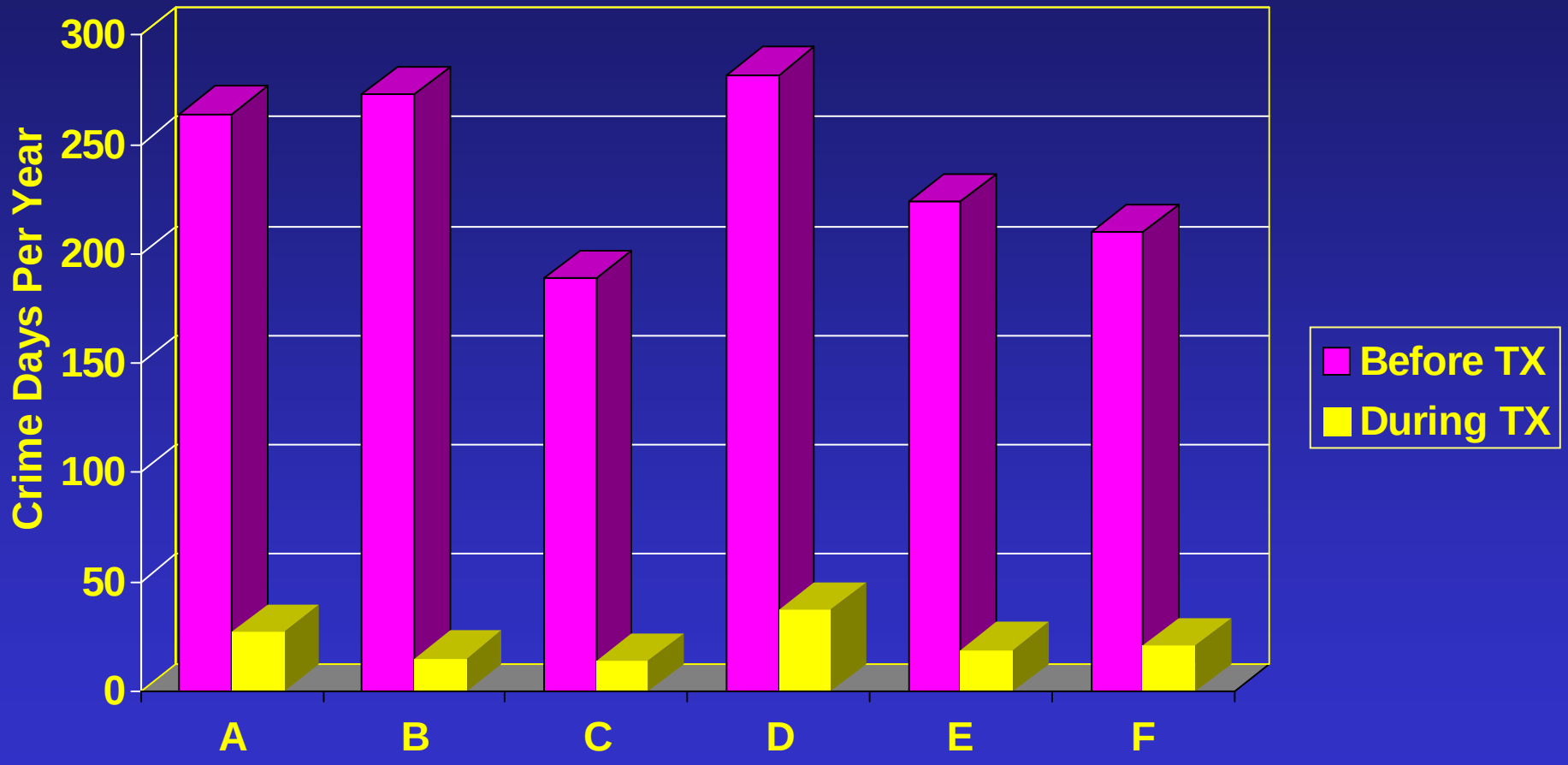
Relapse to IV drug use after MMT

105 male patients who left treatment



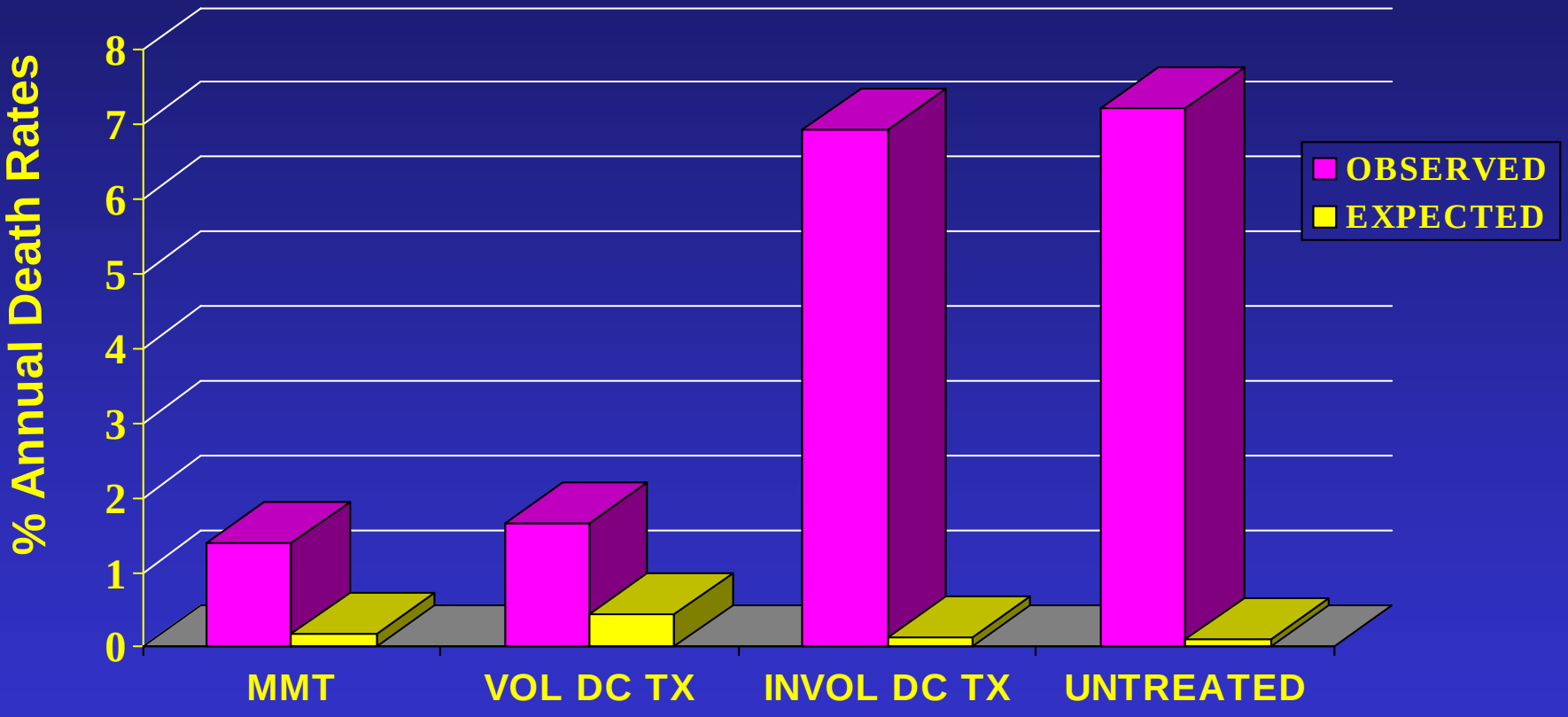
Adapted from Ball & Ross - *The Effectiveness of Methadone Maintenance Treatment*, 1991

Crime among 491 patients before and during MMT at 6 programs



Adapted from Ball & Ross - The Effectiveness of Methadone Maintenance Treatment, 1991

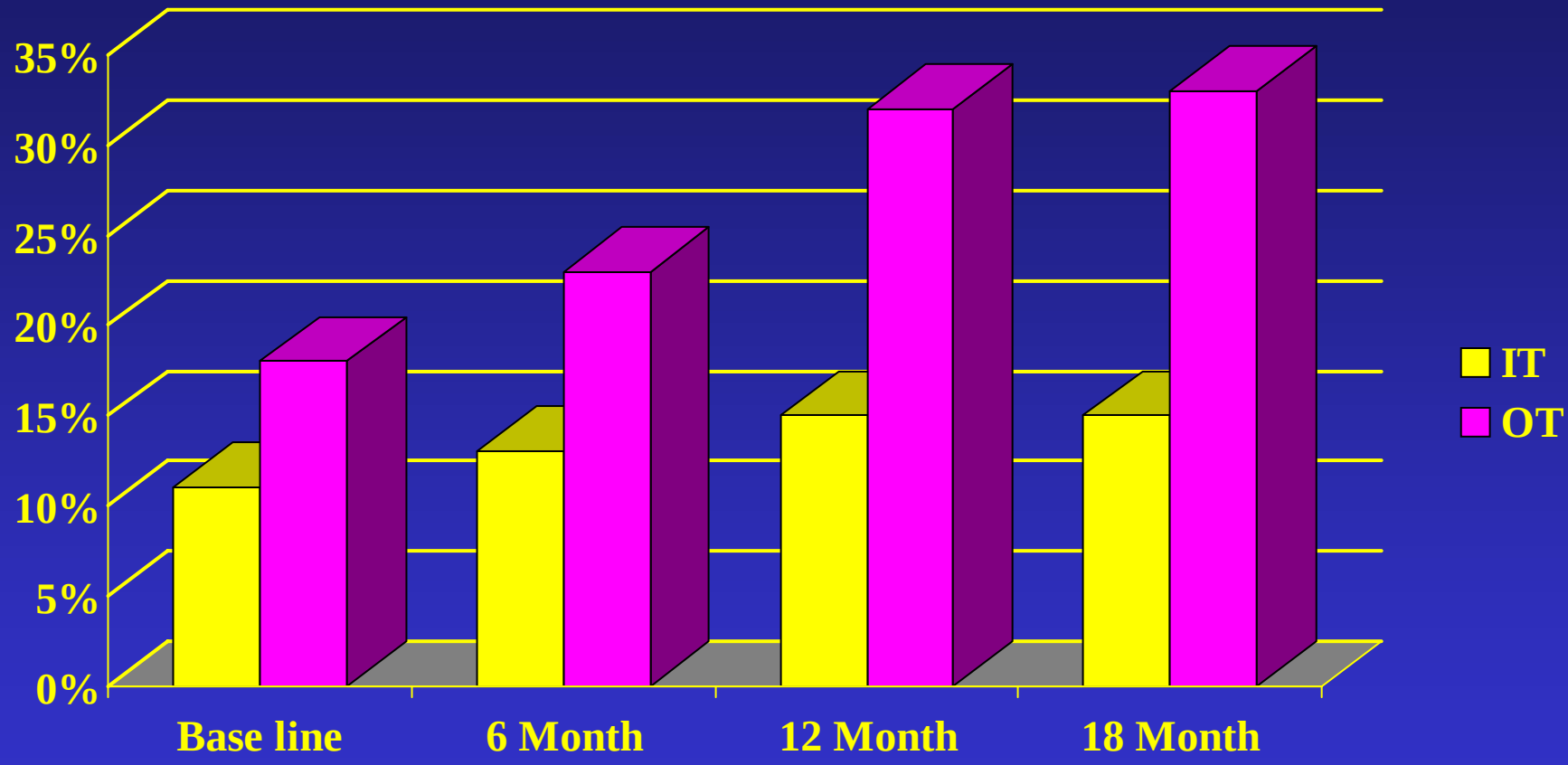
Death Rates in Treated and Untreated Heroin Addicts



Slide data courtesy of Frank Vocci, MD, NIDA

Grondblah et al., 1990, ACTA Psychiatr. Scand., 223-227

HIV Conversion in Treatment



HIV infection rates by baseline treatment status. In treatment (IT) n=138, not in treatment (OT) n=88
Source: Metzger et. al., 1993, J. AIDS, 6: p.1052

Perinatal Complication

- Intrauterine Growth Restriction
- Respiratory Distress
- Preterm labor and delivery
- Abruption
- Fetal death
- Decreased head circumference
- Depressed Apgar scores
- Meconium staining of amniotic fluid
- Chorioamnionitis
- Neonatal abstinence syndrome
- Opioids are NOT teratogenic!

Methadone Maintenance for Opiate Dependent Pregnant Patients

- Improve perinatal outcome, decreases IUGR
- Avoidance of IV drug use
  - Decreased risk of HIV, hepatitis, subacute bacterial endocarditis
- Minimization of “drug-seeking” behaviors
  - Prostitution, STDs
- Scheduled administration
  - Circumvents recurrent withdrawal
  - Decreased fluctuations in opioid level

Archie C, 1998, Methadone in the management of narcotic addicts in pregnancy. Current Opin Obstetrics and Gynecology, 10, 435-440

Take Home Message

- Il metadone riduce l'uso i.v. dell'eroina
- La ricaduta nell'uso di eroina aumenta in maniera crescente con il passare del tempo dall'interruzione dell'uso del farmaco
- I soggetti in trattamento con metadone riducono l'attività criminale
- Il metadone riduce la mortalità nella popolazione eroinomane
- I soggetti in trattamento con metadone hanno una minore probabilità di sieroconversione per l'HIV e (l'HCV)
- Il metadone riduce le complicanze fetali e ostetriche nel nascituro

Methadone maintenance treatment modalities in relation to incidence of HIV: results of the Amsterdam cohort study

Miranda W. Langendam[a], Giel H.A. van Brussel[b], Roel A. Coutinho[a,c] and Erik J.C. van Ameijden[a]

Study objective: To evaluate methadone maintenance treatment modalities, prescribed within the concept of harm reduction, in relation to incidence of HIV infection among drug users with a history of methadone treatment in Amsterdam, The Netherlands.

Design: Prospective observational cohort study among 582 HIV-negative drug users. To ensure valid and detailed assessment of methadone treatment, data from the Central Methadone Register in Amsterdam were linked to the Amsterdam cohort study among drug users.

Methods: Poisson regression analysis was used to identify independent and significant predictors of incidence of HIV.

Main results: During 1906 person years, 58 drug users seroconverted, the overall incidence of HIV being 3.0 per 100 person years with a declining trend for current injectors. An increase in frequency of methadone programme attendance [relative risk (RR), 2.4; 95% confidence interval (CI), 1.2–4.6, compared with no change] and increase in methadone dosage (RR, 0.8; 95% CI, 0.6–1.0, per category of change of 10 mg/day) were significantly associated with incidence of HIV in multivariate analysis. Methadone dosage and frequency of programme attendance in itself were not significant predictors. Other multivariate significant risk factors were homelessness, current injecting and in-patient hospital care.

Conclusions: Among drug users who receive methadone maintenance treatment in a harm-reduction setting, which includes ancillary services such as needle-exchange programmes and HIV testing and counselling, prescription of high methadone dosages is not sufficient to stop the spread of HIV. However, an individual increase of the methadone dosage and measures to achieve high treatment retention could contribute to the prevention of HIV among drug users.

AIDS 1999, **13**:1711–1716

Keywords: Substance abuse, methadone treatment programmes, HIV infection, evaluation

Lo Studio

- Studio prospettico osservazionale di coorte:

  582 TD HIV neg (con storia di assunzione di Metadone)

- 58 sieroconversioni

  incidenza 3 per 100 per anno

Take Home Message

- Il dosaggio di metadone e la sua frequenza di assunzione non sono legati all'incidenza della sieroconversione
- Il luogo di assunzione modica l'incidenza di sieroconversione
- La frequenza ai programmi non modica l'incidenza di sieroconversione

Table 1. Univariate associations between methadone treatment modalities and incidence of HIV among drug users in the Amsterdam cohort study.

Treatment modality	No. of seroconverters	PY	Incidence rate per 100 PY	RR	95% CI
Mean methadone dosage (mg/day)					
0	3	283	1.1	0.3	0.1–0.9
< 20	4	149	2.7	0.7	0.2–2.0
21–40	11	460	2.4	0.6	0.3–1.3
41–60	22	578	3.8	1.0	
61–80	15	274	5.5	1.4	0.8–2.8
> 80	3	162	1.9	0.5	0.2–1.6
Change in methadone dosage (mg/day) [a]					
decrease > 10	10	132	7.6	2.4	1.0–5.5
decrease ≤ 10	12	316	3.8	1.2	0.5–2.6
no change	12	375	3.2	1.0	
increase ≤ 10	10	371	2.7	0.8	0.4–2.0
increase > 10	5	171	2.9	0.9	0.3–2.6
Main site of prescription					
no methadone	3	283	1.1	0.4	0.1–1.2
local outposts	19	645	2.9	1.0	
outpatient clinic addicted prostitutes and foreigners	12	194	6.2	2.1	1.0–4.3
methadone bus	14	394	3.6	1.2	0.6–2.4
GP	4	276	1.5	0.5	0.2–1.5
outdoor addiction clinic	1	58	1.7	0.6	0.1–4.4
other	5	58	8.6	2.9	1.1–7.9
Change in site of prescription [a]					
No	43	1317	3.3	1.0	
Yes	7	159	4.4	1.4	0.6–3.0
Frequency of program attendance (%)					
100	32	1063	3.0	1.0	
76–99	10	259	3.9	1.3	0.6–2.6
25–75	7	205	3.4	1.1	0.5–2.6
1–24	6	96	6.2	2.1	0.9–5.0
0 (no methadone)	3	283	1.1	0.4	0.1–1.2
Change in frequency of dispensing [a]					
no change	26	1008	2.6	1.0	
higher frequency	14	232	6.1	2.3	1.2–4.5
lower frequency	10	236	4.2	1.6	0.8–3.4

[a]Less seroconverters and person-years due to selection on methadone on two subsequent visits. PY, person-years; RR, relative risk; CI, confidence interval.

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Addiction (2000) 95(4), 591–600

RESEARCH REPORT

Methadone maintenance and cessation of injecting drug use: results from the Amsterdam Cohort Study

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Abstract

Aims. *To assess relationships between characteristics of methadone maintenance treatment and long-term cessation of injecting (≥ 1 year).* **Design and participants.** *The incidence of cessation of injecting and relapse from non-injecting to injecting was estimated among 488 participants of the Amsterdam cohort study among drug users. We used a nested matched case–control design to identify methadone treatment characteristics significantly and independently related to cessation of injecting. To ensure detailed and valid assessment of methadone treatment, data of the Central Methadone Register were linked with cohort data. For 339 of 488 subjects of the initial study group methadone data were available.* **Findings.** *The incidence of cessation of injecting increased from 2.2 /100 person years in 1985–89 to 5.5 /100 per year in 1995–97 ($p_{trend} = 0.005$). Relapse to injecting was high: 17.2 /100 person years (no trend). Methadone dosage and frequency of methadone programme attendance in themselves were not significantly related to cessation of injecting. However, an individual increase of 5 mg or more per year (OR 4.20, 95% CI 1.54–11.46) and receiving methadone mainly via the outpatient clinic for drug-abusing prostitutes and foreigners (OR 0.18, 95% CI 0.05–0.59) were independent predictors of cessation of injecting. After cessation of injecting, there were no HIV-seroconversions during the period of non-injecting (129 person years). After relapse to injecting there was one seroconverter; however, follow-up was small (23 person years). The HIV-incidence of those who continued injecting was 3.2 /100 per year.* **Conclusions.** *Steadily increasing the methadone dosage in a harm reduction setting may be useful in supporting injecting drug users in the process of cessation of injecting and reducing the spread of HIV-infection.*

Lo Studio

- Studio prospettico osservazionale di coorte:

  488 TD in MMT

- Incidenza cessazione uso e.v.

  da 2.2 per 100 per anni 1985-89

  a 5.5 per 100 per anni 1995-99

Take Home Message

- Il progressivo aumento del metadone di una quantità > di 5 mg ed il luogo di somministrazione possono essere dei fattori utili per diminuire la probabilità d'uso della sostanza e della sieroconversione

Table 3. *Multivariate predictors of cessation of injecting*

	Model 1		Model 2	
	OR	95% CI	OR	95% CI
Long-term change in methadone dosage[1]				
decrease	1.00		1.00	
0–4 mg/year increase	1.18	0.40–3.46	1.57	0.39–6.27
>5 mg/year increase	4.20	1.54–11.46	9.19	2.37–35.70
Main site of prescription[2]				
no methadone	1.79	0.39–8.21	1.89	0.20–17.99
local outpost	1.00		1.00	
outpatient clinic for addicted prostitutes and foreigners	0.18	0.05–0.59	0.40	0.08–1.96
methadone bus	0.68	0.28–1.65	0.64	0.20–2.03
GP	2.27	0.74–6.97	3.04	0.70–13.14
other	1.17	0.27–5.11	0.77	0.14–4.27

Model 1: significant and independent methadone variables. Model 2: significant and independent methadone variables adjusted for frequency of injecting, percentage new needles obtained via needle-exchange programme and current prostitution. OR: odds ratio, CI: confidence interval, GP: general practitioner. [1]Slope in mean methadone dosage calculated over the total injecting period preceding index visit, [2] since previous visit.

The Impact of Harm-Reduction-Based Methadone Treatment on Mortality Among Heroin Users

Miranda W. Langendam, PhD, Giel H. A. van Brussel, MD, Roel A. Coutinho, MD, PhD, and Erik J. C. van Ameijden, PhD

TABLE 1—Cause-Specific Death Rates per 1000 Person-Years, by HIV Serostatus, in a Cohort of Drug Users: Amsterdam, the Netherlands, 1985–1996

	HIV Positive		HIV Negative		Total	
Cause of Death	No.	Rate	No.	Rate	No.	Rate
AIDS	55	33.7	. . .	. . .	55	11.1
Overdose	14	8.6	17	5.1	31	6.3
Suicide	4	2.4	7	2.1	11	2.2
Accident/violence	4	2.4	7	2.1	11	2.2
Pneumonia/sepsis	4	2.4	4	1.2	8	1.6
Liver failure	6	3.7	0	0.0	6	1.2
Cerebral/neural	4	2.4	2	0.6	6	1.2
Endocarditis	3	1.8	0	0.0	3	0.6
Other[a]	8	4.9	3	0.9	11	3.4
Unknown	4	2.4	4	1.2	8	1.6
All causes	106	64.9	44	13.2	150	30.2

[a]Carcinoma (n=3), lung embolism, thrombosis, hypothermia, exhaustion, drowning (n=2), chronic obstructive pulmonary disease, unknown natural cause.

ABSTRACT

Objectives. The purpose of this study was to investigate the impact of harm-reduction-based methadone programs on mortality among heroin users.

Methods. A prospective cohort investigation was conducted among 827 participants in the Amsterdam Cohort Study. Poisson regression was used to identify methadone maintenance treatment characteristics (dosage, frequency of program attendance, and type of program) that are significantly and independently associated with mortality due to natural causes and overdose.

Results. From 1985 to 1996, 89 participants died of natural causes, and 31 died as a result of an overdose. After adjustment for HIV and underweight status, there was an increase in natural-cause mortality among subjects who left methadone treatment (relative risk [RR] = 2.38, 95% confidence interval [CI] = 1.28, 4.55). Leaving treatment was also related to higher overdose mortality, but only among injection drug users (RR = 4.55, 95% CI = 1.89, 10.00).

Conclusions. Harm-reduction-based methadone treatment, in which the use of illicit drugs is tolerated, is strongly related to decreased mortality from natural causes and from overdoses. Provision of methadone in itself, together with social–medical care, appears more important than the actual methadone dosage. (*Am J Public Health.* 2001;91:774–780)

Lo Studio

- **Studio prospettico osservazionale di coorte (anni 1985-1996):**

  827 TD in trattamento con metadone in un contesto di riduzione del danno

- **Outcome:**

  Mortalità per cause naturali e overdose

Take Home Message

- Il trattamento con metadone in un contesto di riduzione del danno è fortemente legato ad una diminuzione della mortalità per cause naturali ed overdose (indipendentemente dal dosaggio)

TABLE 3—Determinants of Mortality Due to Natural Causes: Multivariate Results, Amsterdam, the Netherlands, 1985–1996

	Univariate		Multivariate Model 1		Multivariate Model 2	
	RR	95% CI	RR	95% CI	RR	95% CI
Mean methadone dosage, mg/d						
0	1.62	0.79, 3.30	. . .		2.40	1.13, 5.10
1–20	0.89	0.33, 2.39	. . .		0.42	0.10, 1.81
21–40	0.72	0.35, 1.50	. . .		0.80	0.36, 1.77
41–60	1.00	1.00				
61–80	1.76	0.90, 3.44	. . .		1.05	0.50, 2.18
>80	3.66	2.00, 6.71	. . .		1.40	0.73, 2.71
HIV serostatus						
Negative	1.00	1.00	1.00			
Positive, CD4≥500	6.19	2.39, 16.05	5.13	1.78, 14.79	5.36	1.84, 15.36
Positive, CD4<500	26.40	13.18, 52.87	22.22	10.62, 46.49	22.04	10.37, 46.83
Underweight (body mass index>18)						
No	1.00	1.00	1.00			
Yes	4.54	2.79, 7.38	3.77	2.32, 6.14	3.65	2.24, 3.84

Note. RR=relative risk; CI=confidence interval.

TABLE 4—Determinants of Mortality Due to Overdose: Amsterdam, the Netherlands, 1985–1996

	Injectors		Noninjectors	
	RR	95% CI	RR	95% CI
In methadone treatment and currently receiving methadone	1.00		1.00	
In methadone treatment but not currently receiving methadone	2.93	1.14, 7.56	0.48	0.06, 4.24
Not in methadone treatment	5.66	1.97, 16.28	0.51	0.06, 4.02

Note. RR=relative risk; CI=confidence interval.

Annals of Internal Medicine

EDITORIAL

First Do No Harm . . . Reduction?

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Potential Financial Conflicts of Interest: None disclosed.

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Conclusioni:
I Trattamenti Sostitutivi nei Contesti di Riduzione del Danno

Gli assunti di base:

- Sono cure mediche e come tali devono seguire le regole di “scienza e coscienza”
- Sono maggiormente efficaci se integrati (es. counseling motivazionale)
- Favoriscono la presa in carico precoce
- Possono permettere l’inserimento della persona in programmi più strutturati a medio-lungo termine

Le evidenze:

- Hanno dimostrato di ridurre l’incidenza delle sieroconversioni, l’incremento della criminalità e della mortalità, le complicanze nel nascituro, ecc.
- Hanno un effetto dose indipendente (la dose assunta deve comunque avere un effetto anti-astinenziale ed il suo aumento progressivo nel tempo ha effetti benefici), la frequenza ai programmi non modifica i risultati e quest’ultimi sono positivamente legati all’ “appropriatezza” dei luoghi di somministrazione (che devono essere diversificati in base ai bisogni)

Le Implicazioni dell'Utilizzo della Terapia Sostitutiva nella Pratica della Riduzione del Danno….

- Il medico (all'interno dell'équipe che struttura il programma d'intervento) è nel contempo sia il titolare che il responsabile dell'utilizzo della terapia sostitutiva secondo "scienza e coscienza"
- Il dosaggio da utilizzare è almeno antiastinenziale (il dosaggio deve tenere presente dell'eventuale uso persistente della sostanza e della tolleranza)
- La continuità terapeutica è auspicabile ma non rappresenta un prerequisito imprescindibile per la somministrazione del farmaco
- La somministrazione della terapia sostitutiva deve essere disponibile in più contesti (ambulatori specialistici, medici di medicina generale, unità da strada, ecc.)
- La terapia sostitutiva ha lo scopo di prevenire le patologie correlate ma nel contempo di promuovere l'astinenza e permettere il passaggio a programmi terapeutici più strutturati

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