PHARMACOTHERAPY
OF FORENSIC PSYCHIATRIC PATIENTS WITH A SUBSTANCE- RELATED DISORDER

BCNBP National Day

Forensic psychiatry, biological aspects

December 8, 2017

Frieda Matthys, MD, PhD

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DISCLOSURE

- In the last 12 months, I have received fees for the following activities:
  - Advisory boards: Lundbeck, Johnson & Johnson
  - Lecturing: Eli Lilly Benelux
  - Research funding : Johnson & Johnson

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Overview

- Some figures
- What is the problem
- Why is treatment so important
- Pharmacotherapy
  - Opiates
  - Alcohol
  - Benzodiazepines
  - Cannabis
  - Stimulants

SOME FIGURES

Drug use among offenders

- In de US in 2010[1]
  - 70% of male prisoners were drug abusers
  - in the entire male population the rate of drug abuse is 11,2 %
- If it were not for alcohol and other drugs 60% of those currently incarcerated in the US could go home
- 21,4% of violent crimes are committed under the influence of alcohol and drugs simultaneously [2]

1. The Relationship Between Substance Abuse And Crime In IDAHO. United States: Idaho state police statistical analysis center; 2010.
2. Young UK. The relationship between drugs and crime. Australia: Australian Government Attorney-General's Department Canberra.; 2004

Research consistently demonstrates a strong connection between crime and addiction

- 84% of state prison inmates were involved with alcohol or other drugs at the time of their offense
- 45% were under the influence when the crime was committed
- 21% report they committed their crime for money to buy drugs
- 64% of male arrestees tested positive for at least one of five illegal drugs at arrest
- 57% report binge drinking in the 30 days prior to arrest another 36% report heavy drinking

Bureau of Justice Statistics

Prevalence of SUD

Table 17 – Prevalence of substance abuse disorders in general and prison populations

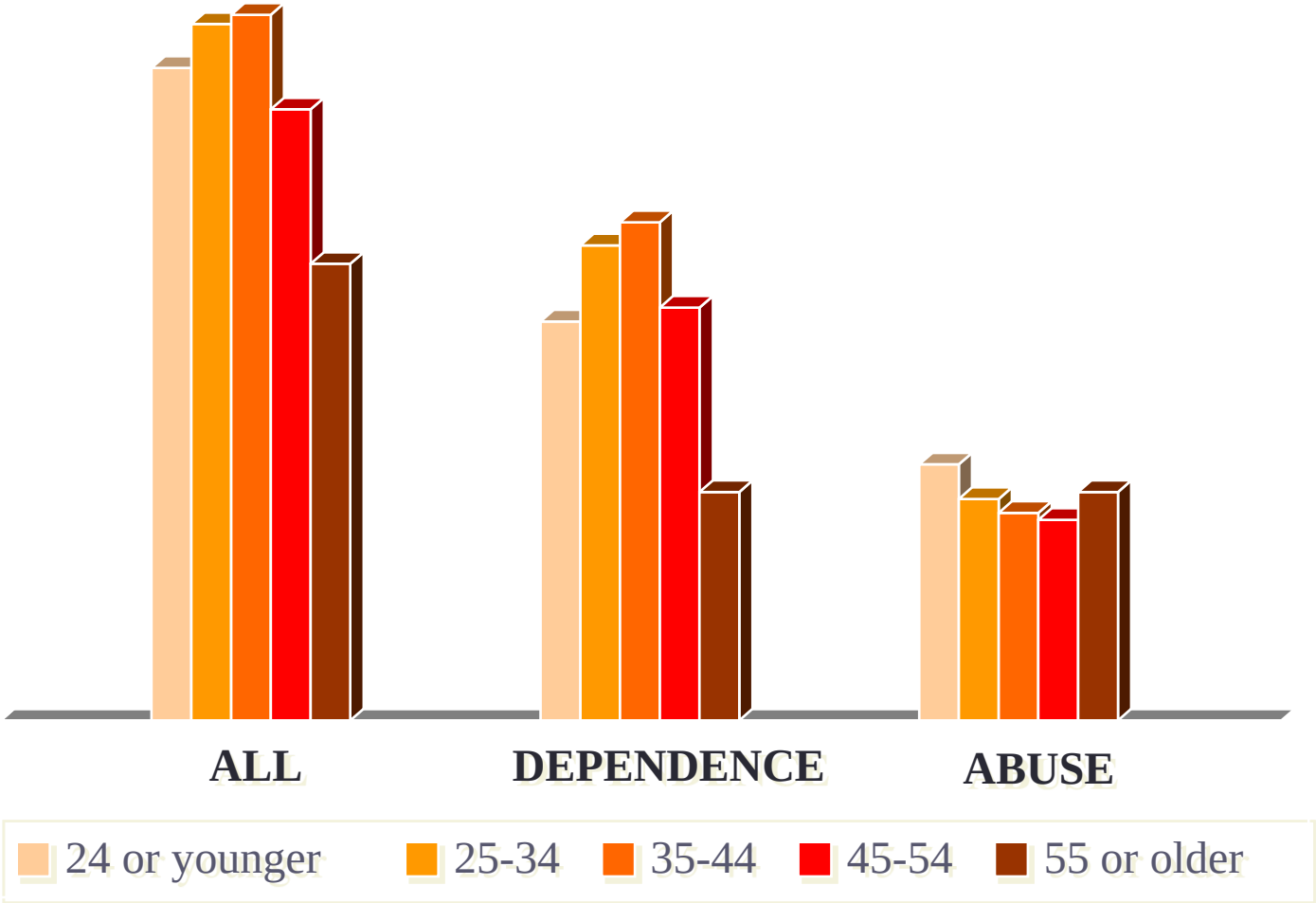
Disease	General population	Prison population
Alcohol abuse	3.1%[177]†	Prevalence of alcohol abuse and dependence[91]: • Male prisoners: 18% to 30% • Female prisoners: 10% to 24%
Alcohol dependence	1.3%[177]†	
Drug abuse	1.4%[177]†	Prevalence of drug abuse and dependence[91]: • Male prisoners: 10% to 48% • Female prisoners: 30% to 60%
Drug dependence	0.4%[177]†	
Substance use disorder	39.6%[118]	87.2%[118]

†12-month prevalence (US adult population)

[91]Fazel S, Bains P et al, Substance abuse and dependence in prisoners, systematic review. ADDICTION 2006;101(2): 181-91

[118]Kouyoumdjian F, Schuler A, Matheson FI, Hwang SW. Health status of prisoners in Canada Narrative review. Can. Fam. Phys.2016;62(3):215-22.

Substance Dependence Or Abuse Among Jail Inmates by Age



Source: Substance Dependence, Abuse and Treatment of Jail Inmates, 2002, DOJ, BJS, 2005.

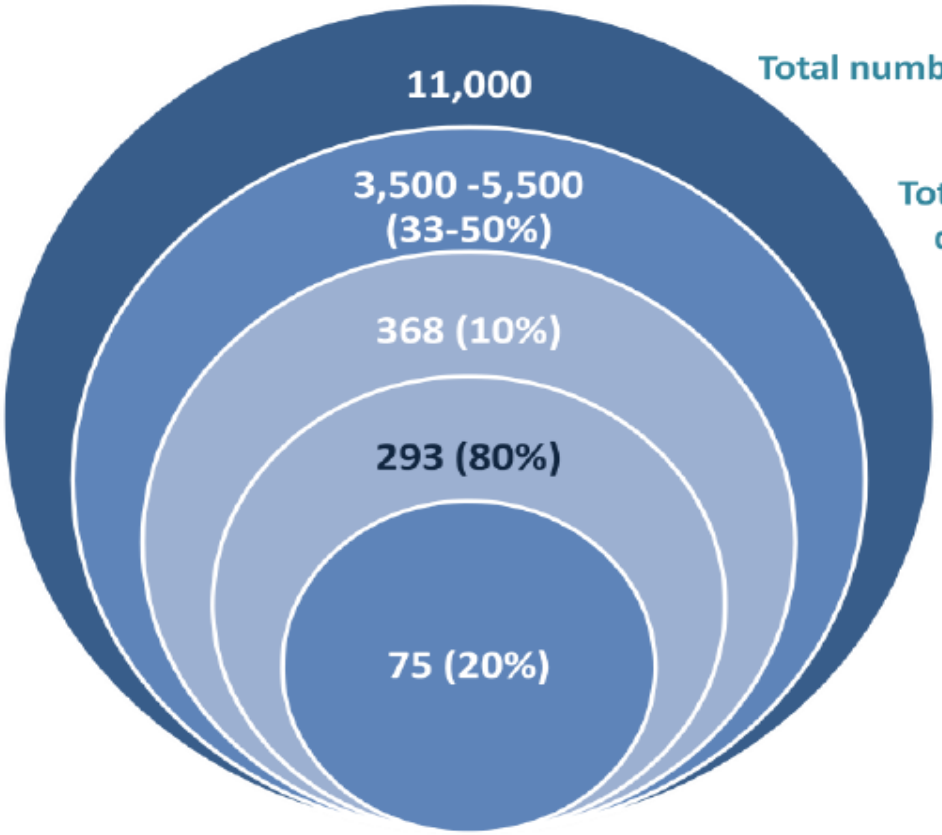
Opiate use in Belgian prisons

Table 15 – Self-reported opiate use and substitution treatment in Belgian prisons in 2008

Opiate use	N (%)
% opiate use in prison	125 (32.2)
% intravenous opiate use in prison	34 (8.7)
% of use black market methadone or buprenorphine	51 (13.1)
% substitution therapy in Belgian prisons	71 (18.25)
Heroin initiation in prison	61 (15.7)
Total sample	389 (100)

Table from Vander Laenen et al, 2013.[179]

Opioid use in prisons in Belgium



[17]) SPF Justice, Belgium, data provided by Arnaud Quede, March 2013. Prevalence rate validated with EMCDDA data, EMCDDA, Prisons and drugs in Europe: the problem and responses, Lisbon 2012

WHAT IS THE PROBLEM

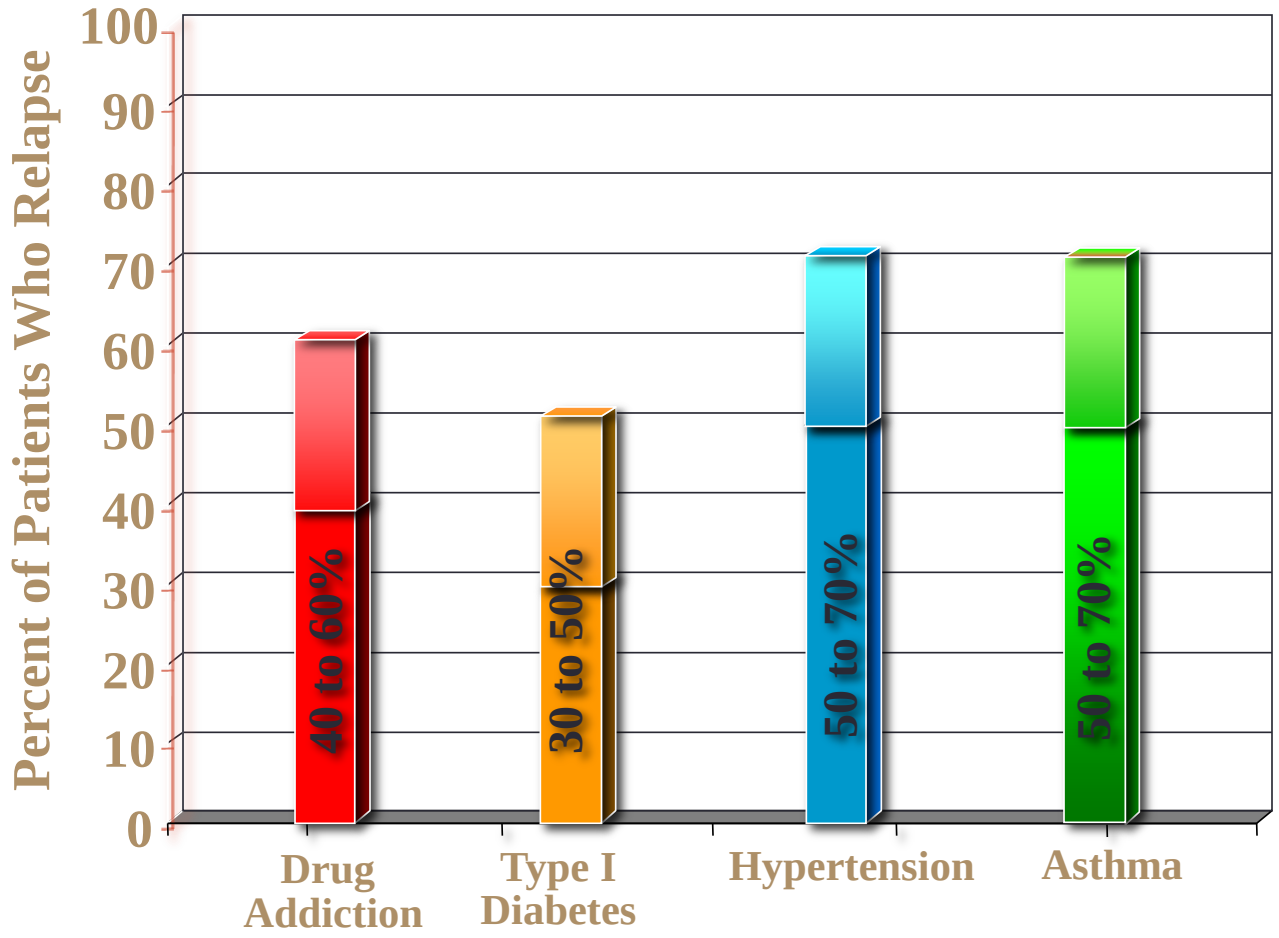
Drug dependence

- A chronic relapsing disease

- Cluster of behavioural, cognitive and physiological phenomena that develop after repeated substance use & that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state (WHO)

- Physical and/or pyschological reliance on a psychoactive substance to such an extent that cessation of use will cause physical or mental disequilibrium (withdrawal symptoms) (UK Gov definition)

Relapse Rates for Drug Addiction are Similar to Other Chronic Medical Conditions



McLellan AT, Lewis DC, O'Brien CP, Kleber HD;
Drug Dependence, A Chronic Medical Illness, JAMA, Oct 4, 2000

Drug dependence

- Because it is a chronic relapsing disorder, drug dependence and drug seeking do not stop at intake to the corrections system!

- Drug use often continues in prison, and requires treatment

- Drug use often starts in prison

There is a close relationship between drug abuse and crime.

- Drug abusers commit crimes to pay for their drugs and this inflicts damages to the society.
- Many criminals are under the influence of drugs while committing crimes.
- Drug trafficking is another outcome of drug abuse *

* World Drug Report 2012. USA: United Nations Office On Drugs And Crime; 2012.

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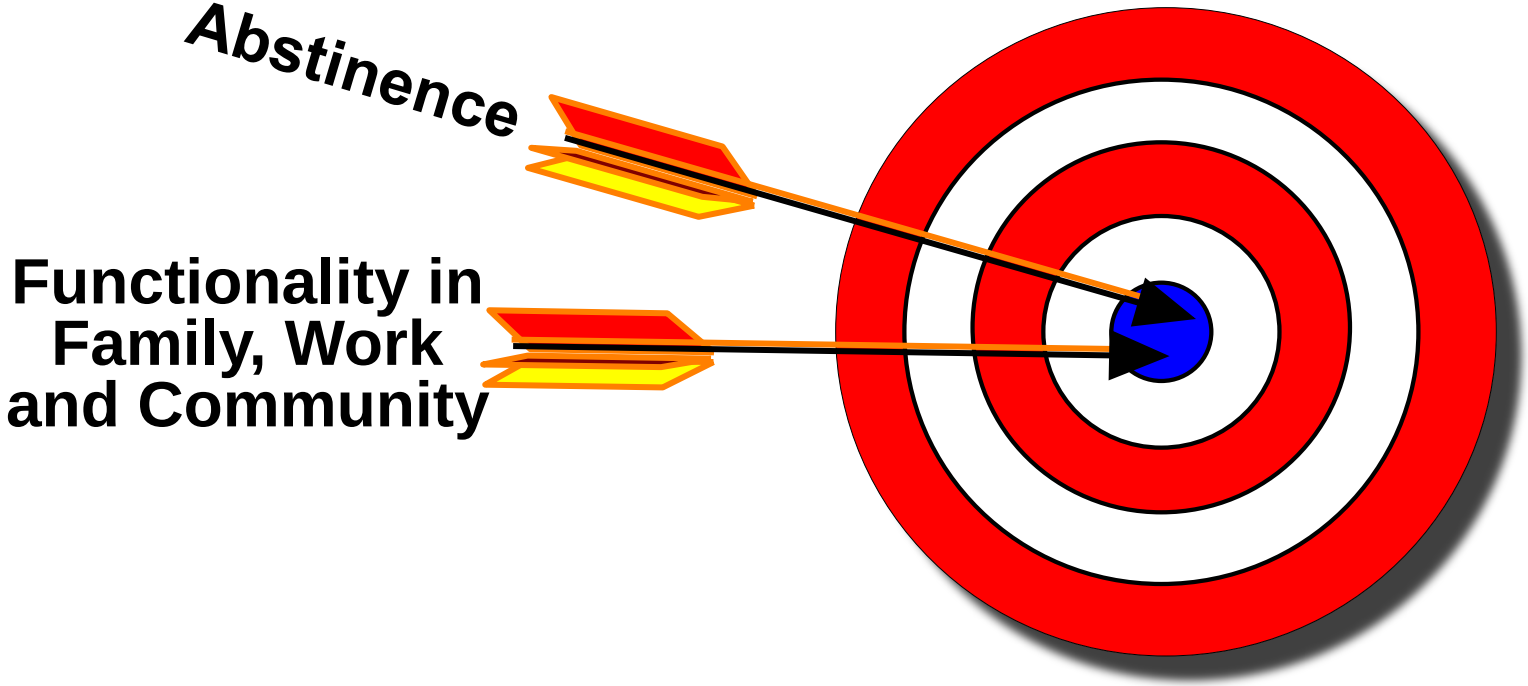
WHY IS TREATMENT SO IMPORTANT

In Treating Addiction…

We Need to Keep Our Eye on the Real Target



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We Need to Keep Our Eye on the Real Target

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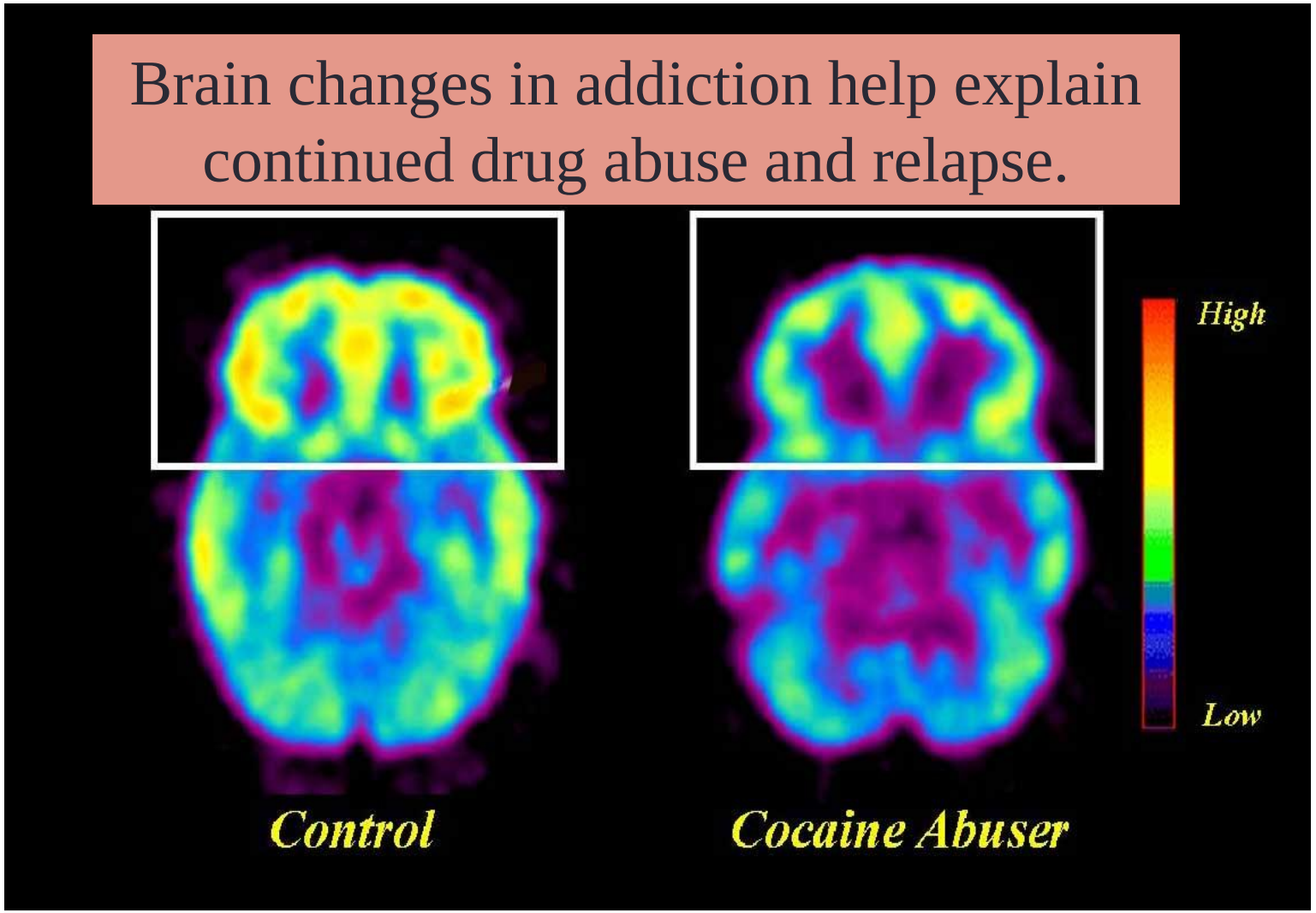
Drug addiction is a brain disease that affects behavior.



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Assessment is the first step in treatment.

- Nature/extent of drug problem
- Strengths:
  - Family support
  - Employment history
  - Motivation
- Threats to recovery:
  - Criminal behavior
  - Mental health
  - Physical health
  - Family Influences
  - Employment
  - Homelessness
  - HIV/AIDS

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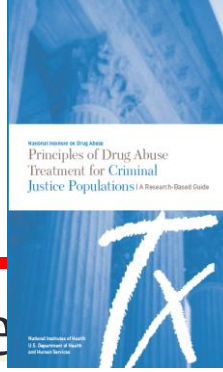
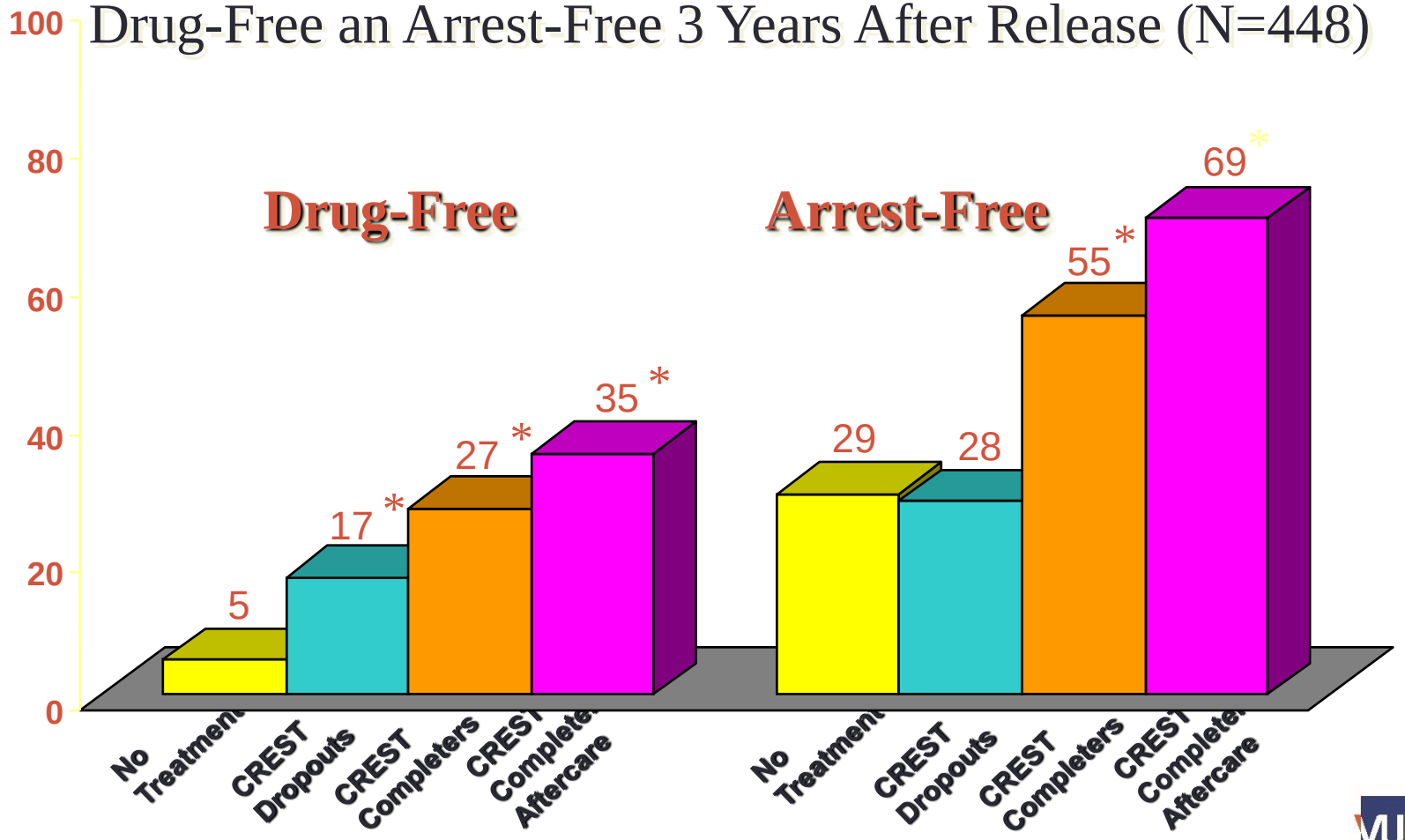
Continuity of care is essential for drug abusers re-entering the community



Delaware Work Release TC (Crest) + Aftercare

Drug-Free an Arrest-Free 3 Years After Release (N=448)



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* p < .05 from Comparison

Martin, Butzin, Saum, & Inciardi (1999), The Prison Journal

Treat co-existing mental disorders in an integrated way.

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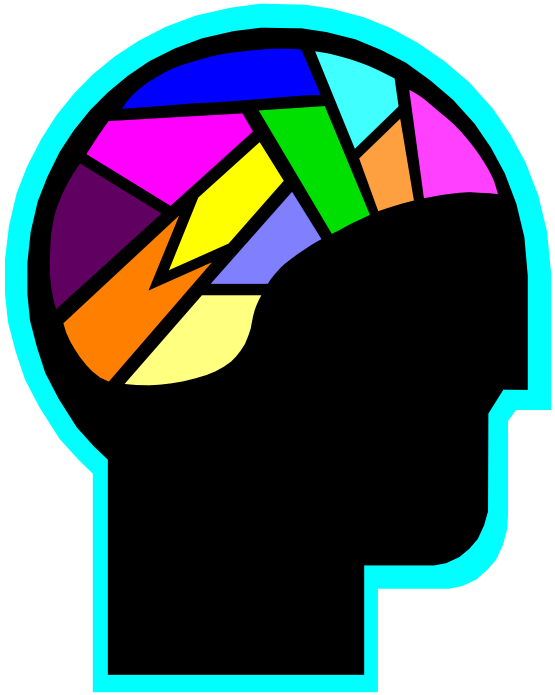
Three chronically relapsing disorders

1. addiction
2. mental illness
3. criminal behavior

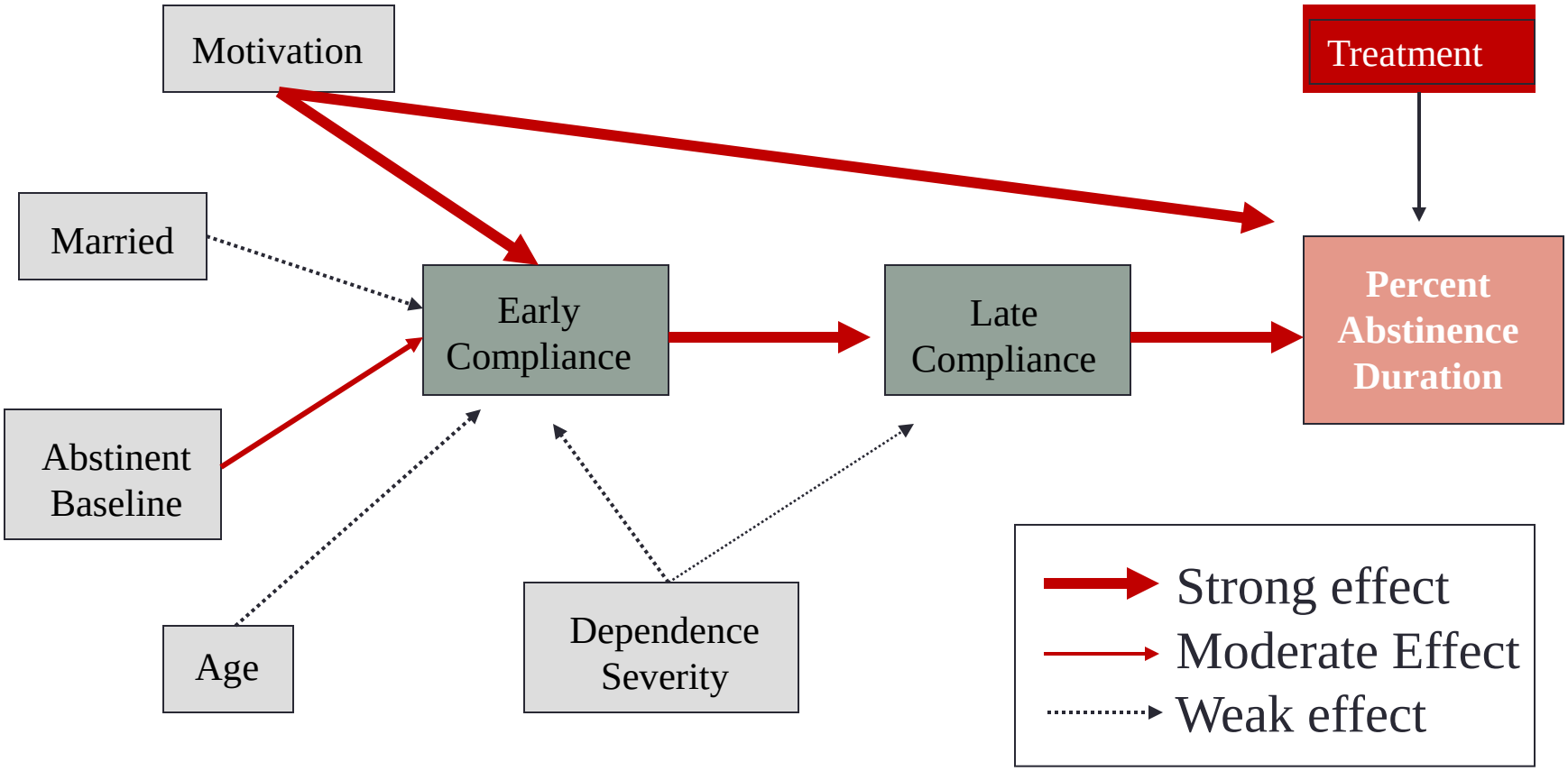


Interventions for Drug Abusing Offenders

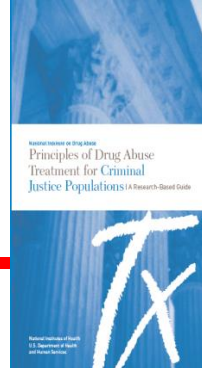
Not Effective	Effective	Promising	Research Needed
Boot Camp	Residential Substance Abuse Treatment	Drug Courts	Reentry
Intensive Supervision	Cognitive-Behavioral Treatment	Break the Cycle	Serious Violent Offender Reentry Initiative (SVORI)
Generic Case Management	Contingency Management	Diversion to Treatment	Strengths-Based Case Management
	Medications	Moral Reasoning	
		Motivational Interviewing	

Compliance and Outcome

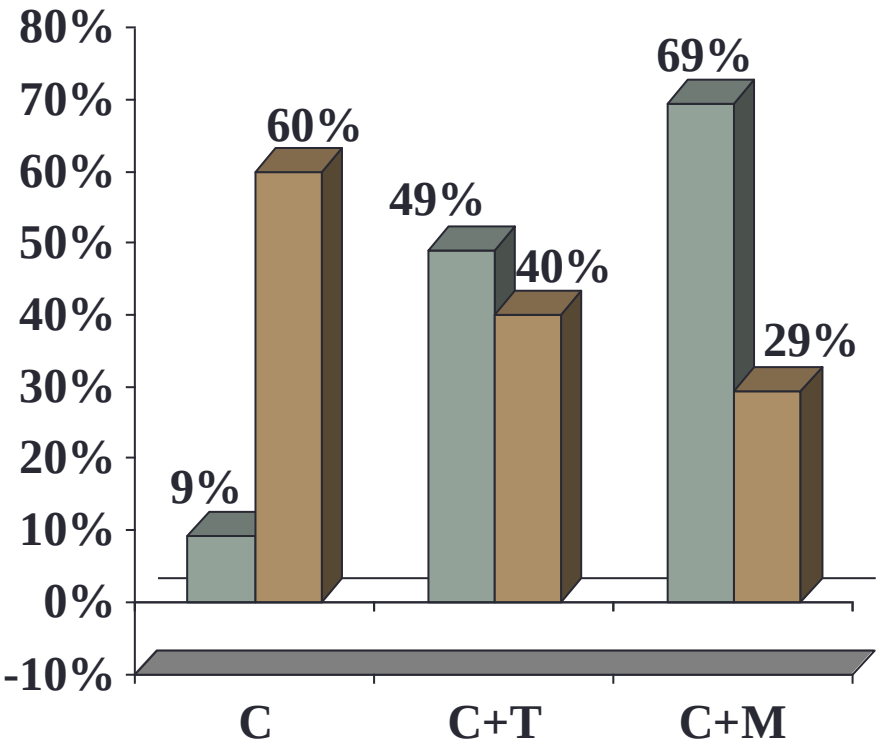
Koeter, Van den Brink, Lehert, 2010 (n=2305)



Medications are an important part of treatment for many drug abusing offenders



Maryland Prison Study: Treatment Linkage and Opiate-Free One Month Post Release



In Treatment

C vs. C+M, C vs. C+M p< .001

Urine Test Positive

C vs. C+M p< .01

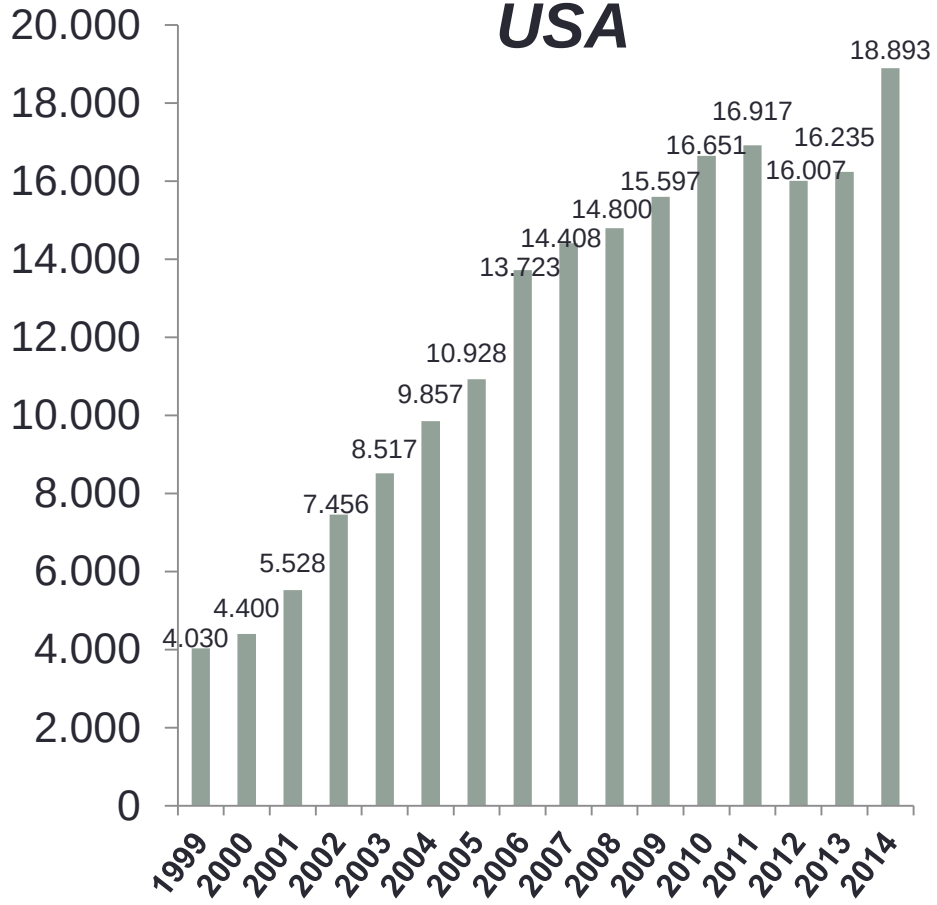
N=166

C = Counseling Only;
C+T = Counseling & Treatment Referral;
C+M = Counseling & Methadone Started in Prison

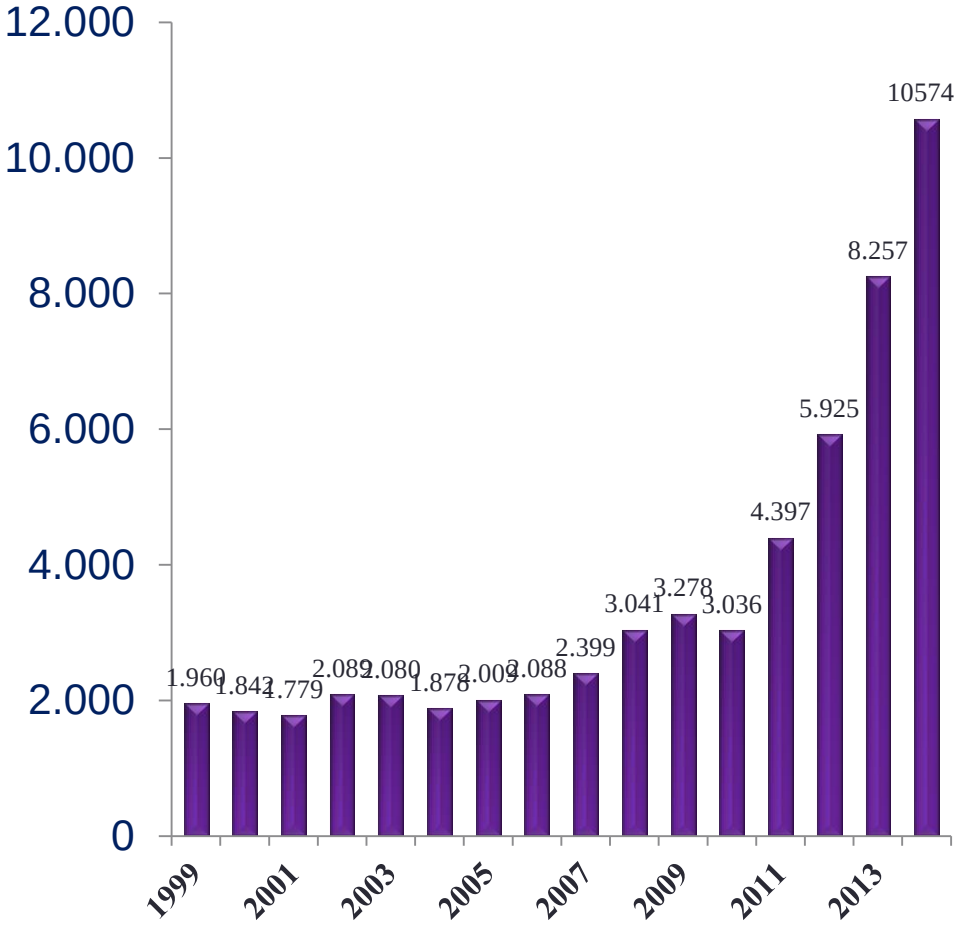
Preliminary Analysis: Tim Kinlock, et al., 2006

PHARMACOTHERAPY MORE SPECIFIC

Opioid Analgesic Overdose Deaths in the USA



Heroin Overdose Deaths in the USA



Centers for Disease Control and Prevention. Wide-ranging Online Data for Epidemiologic Research (WONDER). Multiple-Cause-of-Death file, 2000–2014. 2015 (http://www .cdc .gov/ nchs/ data/health_policy/ AADR_drug_poisoning_involving_OA_Heroin_US_2000-2014 .pdf)

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Medications for opioiddependence

- Methadone

- Naltrexone

- Buprenorphine

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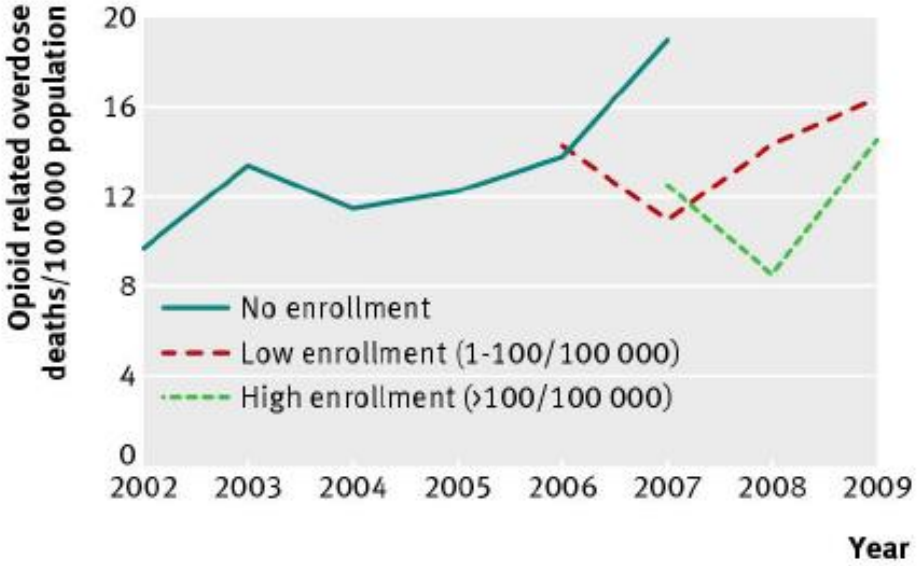
Opioid OD Death were Reduced In Communities that Implemented Nasal Naloxone Distribution Program

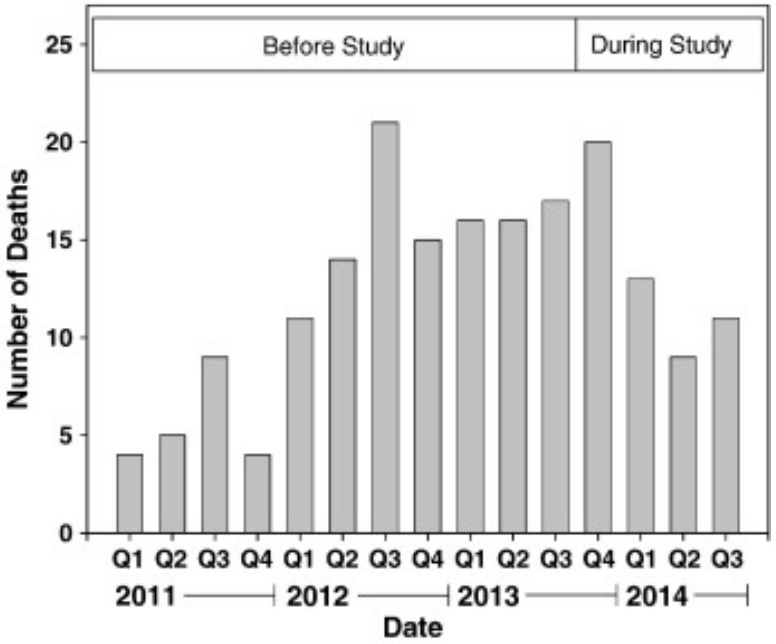
Unadjusted Unintentional Opioid-Related Overdose Death Rates



Unadjusted Opioid-Related Acute Care Hospital Utilization Rates

Walley AY et al., BMJ 2013; Published 31 January 2013.

Intranasal Naloxone Administration By Police First Responders In Ohio



Intranasal naloxone administration by police first responders is associated with decreased OD deaths

Rando et al., Am J Emerg Medicine 2015.

Recommendations SUBANOP study

Based on the legal principle of equality (in health care) and on the basis of scientific evidence that highlight the positive results of substitution treatment in the prisons, we strongly recommend that substitution as a maintenance dose be extended to all Belgian prisons (Council of the European Union, 2012).

Opioid maintenance treatment in prison

Situation Augustus 2012

	Methadon	Suboxone
België	305	105
Vlaanderen	169	33
Wallonië	136	72

4 prisons without substitution

Situation April 2015

	Methadon	Suboxone
België	345	194
Vlaanderen	133	64
Wallonië	212	130

Thanks to pharmacist Van Meir

What dose ?

Average recommended daily dose

Methadon: 60 – 100 mg

Suboxone: 12 – 24 mg

Average daily dose used in Belgian prisons

Methadon: 49,50 mg

Suboxone: 7,93 mg

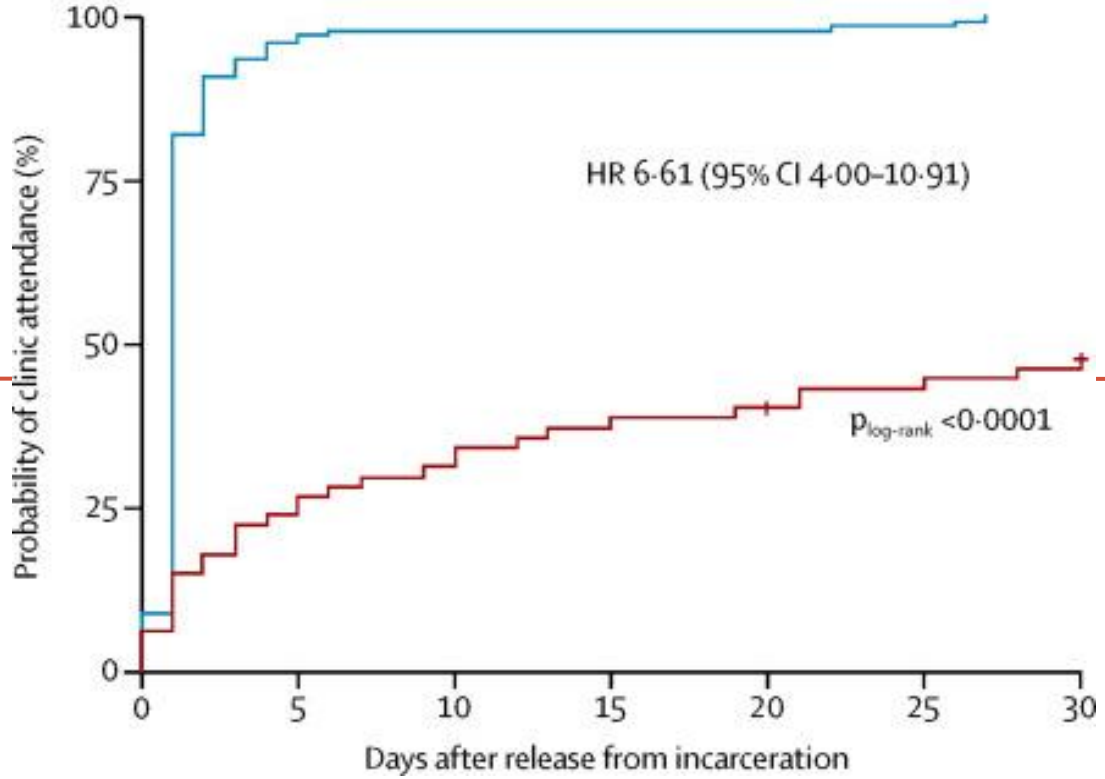
Treatment opioid dependence

First choose the treatment goal

- Withdrawal if
  - Short addiction history
  - Network care after detention
  - Little comorbidity
  - The patient is motivated for abstinence

- Maintenance treatment if
  - Long addiction history
  - A lot of comorbidity
  - The patient lives isolated
  - Little motivation

Methadone Continuation Versus Forced Withdrawal On Incarceration In A Combined US Prison and Jail: A Randomized, Open-label Trial



Continuation of methadone maintenance during incarceration as compared to forced withdrawal increased the likelihood of re-engaging in methadone treatment

Rich et al., The Lancet Published online May 29, 2015.

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Opioid: abstinence syndrome

- 6 - 12 hours after the last dose of heroin; with peak after 36 to 72 hours and disappears after 7 to 10 days.
- 12 - 48 hours after stopping methadone, peak around three days and ending in a few weeks.

➢ Complaints:
  - Back pain, muscle pain, abdominal pain,
  - Agitation, anxiety and dysphoria
  - Difficulty sleeping, irritability

➢ Symptoms:
  - Yawning, tearing eyes, running nose, goose bumps, hyperperistalsis, vomiting, diarrhea, tachycardia
  - Anxiety and optionally psychosis; insult

OD is deadly ... withdrawal is horrible and sometimes dangerous

Detoxification with methadone inpatient

- start 20 mg per 0,1 g of heroin (max 40 mg) or used dose of methadone
- depending on the withdrawal symptoms increase by 5-20 mg
- As a rule of thumb, this reduction schedule is used:
  - above 60 mg with 20 mg per day;
  - between 60 and 40 mg with 10 mg per day;
  - between 40 and 20 mg with 5 mg per day;
  - under 20 mg with 4 mg per day.
- A reduction period of more than 3 weeks is not useful
- Optionally add at
  - Severe sleep disorders: Lorazepam 5 mg, short-term
  - Anxiety and agitation: Diazepam 10 mg, max 2 dd short-term !!!!
  - Muscle pains: NSAIDs

Detoxification with buprenorfine inpatient

- Available as Subutex ® of Suboxone ® (buprenorfine/naltrexon) (2mg/0,5mg; 8mg/2mg)
- Benefits:
  - safer: less OD and less intoxication
  - limited abstinence and long duration of action
  - lower potential for abuse: IV the naltrexone occupies opiate receptors
- Cons:
  - Partial agonist with high receptor affinity
  - Less suitable as > 30 mg methadone
- Reduction schedule for heroin users or when Methadon < 50mg dd
  - Day 1: 4mg **when withdrawal symptoms** + 4 mg 4 hours later
  - Day 2: 12 mg
  - Day 3 untill dag 7: reduce by 2 mg per day

Substitution
Recommendation dose methadon

- Induction: (first 14 days!)
  - 10 mg per 0.1g of heroin (max 40 mg); usually 20 mg is enough; 30 mg can be used as a high tolerance
  - adjust per 5-10 mg every few days
  - max 20 mg increase per week
  - first physical withdrawal, then craving as a guide
- Maintenance:
  - between 70 and 120 mg
- Higher dosages needed with:
  - Anti epileptics; carbamazepine, phenobarbital, phenytoin
  - Antiretroviral agents: ritonavir
  - Anti-tuberculosis means
- Lower dose with:
  - Amprenavir (antiretroviral)
  - Benzodiazepines and alcohol

Clinically most relevant interactions

- QT extension:
  - Certain antiarrhythmics, cisapride, domperidone, certain antipsychotics, erythromycin, oxifloxacin, levofloxacin, pentamidine, saquinavir
  - cocaine
- CYP450 inducers: M blood level drops
  - Carbamazepine, phenobarbital, phenytoin, rifampicin, St. John's wort, alcohol
- CYP450 inhibitors: M blood level rises
  - Fluvoxamine, fluoxetine, paroxetine, antimycotics, bupropion, erythromycin, clarithromycin, indinavir, ritonavir, saquinavir
  - grapefruit

Recommendation dose buprenorfine

- Induction
  - overdose risk is small
  - starting dose 4 - 8 mg
  - adjusting can be done quickly
- Maintenance
  - Between 8 mg and 24 mg (recognition Belgium)
  - up to 32 mg (international guidelines)
- Characteristics
  - Sublingual use
  - Partial agonist of the μ receptor
  - High affinity and low intrinsic activity
  - Long operating time
  - Few side effects and safe product

Psychopharmaca in prison

Tabel 1 – Geneesmiddelen voorschriften per ATC1-klasse

ATC1 klasse	% van voorschriften	% van behandelingsdagen	% van behandelingsdagen in algemene bevolking in 2014 (RIZIV)[44]	% gevangenen met minstens 1 voorschrift	% gevangenen die 12 maanden tijdens observatieperiode verbleven met minstens 1 voorschrift
N - Zenuwstelsel	43.3	53.2	11.5	58.8	76.4
waarvan middelen gericht op:					
• angst of slaapstoornissen				30.6	38.1
• depressie				25.4	31.5
• psychose				21.2	30.5
• afhankelijkheid van opioiden				7.3	6.9
R - Ademhalingsstelsel	13.8	9.1	8.7	35.4	60.6
waarvan middelen gericht op:					
• Astma/Chronisch obstructief longlijden (COPD)				8.4	14.9
M - Bewegingsapparaat (bv. ontstekingremmers)	12.3	2.6	5.0	39.0	
A - Spijsverteringsstelsel	11.3	14.0	13.5	33.9	
waarvan middelen gericht op:					
• diabetes				2.6	
J - Antimicrobiële middelen voor systemisch gebruik (bv. antibiotica)	6.3	2.2	2.5	25.0	47.3
waarvan middelen gericht op:					

Treatment of Benzodiazepine addiction

- The cessation of benzodiazepines after prolonged use can cause serious withdrawal symptoms
  - generalized anxiety disorder
  - epileptic seizures.

- Therapy:
  - Set to equivalent dosing of long-acting agent eg. Diazepam (at least 30 mg dd)
  - Stabilize 1st week
  - Then reduce by 25% of the dosage per week.
  - Sometimes it is needed slower

Cannabis

- There is no medication against cannabis dependence
- Research on Sativex (THC + CBD)
- There are indications that N-acetylcysteine (Lysomucil ®) reduces craving and use

Gray K, 2010; MS Duailibi,2017

N-acetylcysteine

A Double-Blind Randomized Controlled Trial of *N*-Acetylcysteine in Cannabis-Dependent Adolescents

Kevin M. Gray, M.D.

Matthew J. Carpenter, Ph.D.

Nathaniel L. Baker, M.S.

Stacia M. DeSantis, Ph.D.

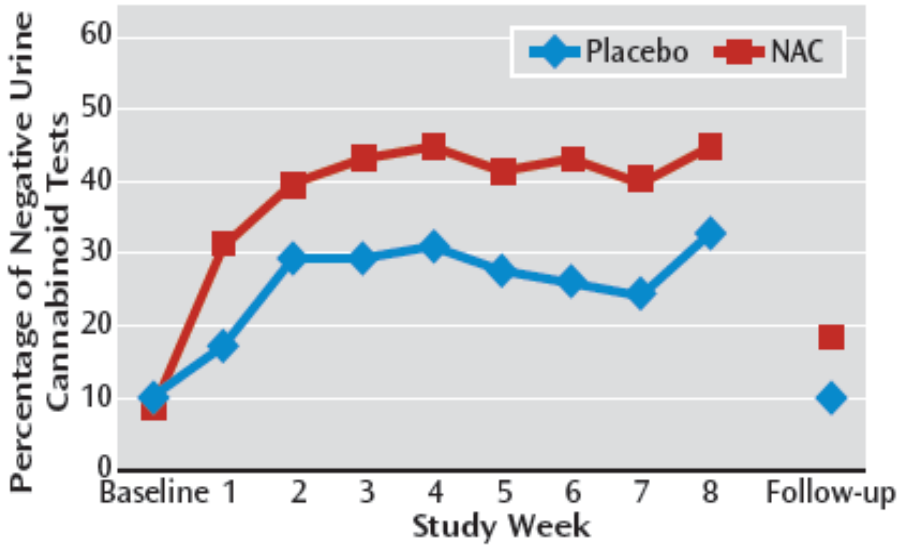
Elisabeth Kryway, P.A.-C.

Karen J. Hartwell, M.D.

Aimee L. McRae-Clark, Pharm.D.

Kathleen T. Brady, M.D., Ph.D.

FIGURE 1. Proportion of Negative Urine Cannabinoid Tests Over Time Among Cannabis-Dependent Adolescents in a Randomized Controlled Trial of *N*-Acetylcysteine (NAC)[a]



AJP, 2012

ALCOHOL: Mechanism of relapse

Repeated reward

Detection treshold

Disinhibition

Attentional Bias → Cue-Reactivity → Craving → **Relapse**

Drug related stimulus

Stress

Conflict Registration

One way does not suit everyone

Repeated reward

Antagonist

- **Disulfiram**
- **Naltrexone**
- **Nalmefene**

Attentional bias → Cue-reactivity

AB- training
CM

Stress

Druggerelateerde stimulus

Detection treshhol

rTMS
DBS

CET

Anti-craving drug

- **Acamprosate**
- *Topiramate?*
- *NAC?*

Craving

Bio feedback

- *Baclofen?*
- *Memantine?*

Desinhibitic

Agonist

Relapse

Cognitive enhancer

- *Modafinil*

CM ?
CRA

Conflict registration

MET
CBT
WM-training

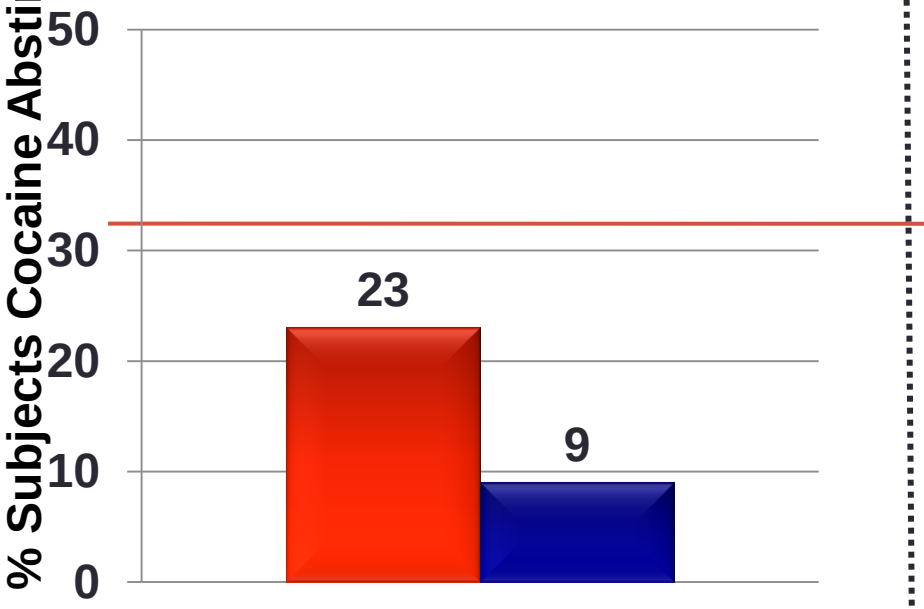
Stimulants

- There is no medication against the addiction to amphetamines or cocaine
- Vaccination is in the pipeline
- Indications for effectiveness of
  - modafinil and disulfiram in cocaine
  - naltrexone, modafinil and bupropion in amphetamine
- There are experiments to prevent illegal use and spraying with prescribing amphetamines (Australia)

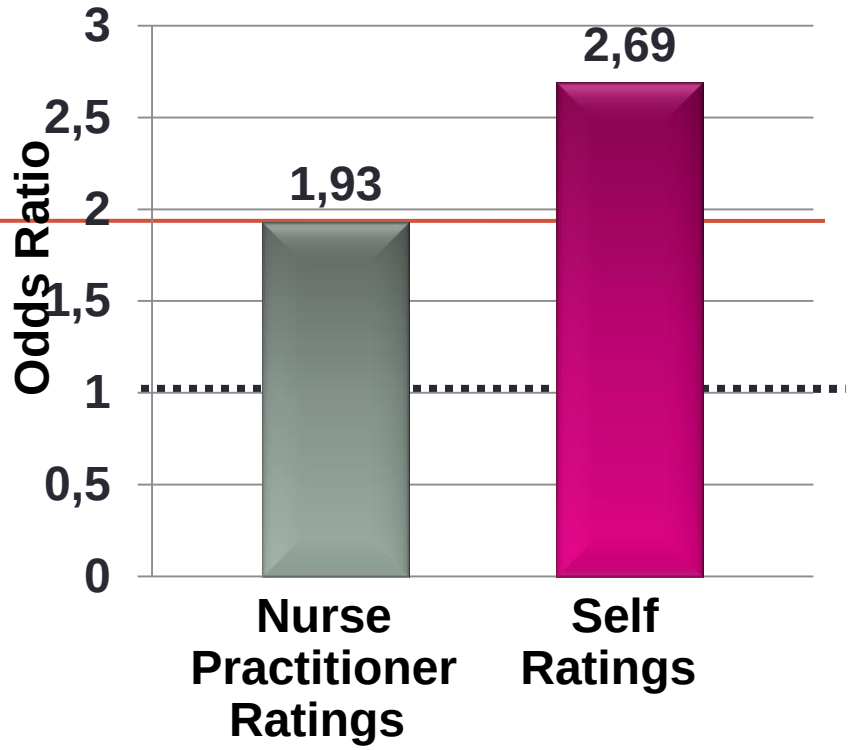
- !!! Often associated with benzo dependency

Modafinil for the Treatment of Cocaine Dependence

Percent Of Subjects Abstinent From Cocaine During Weeks 6–8



Modafinil-Treated Subjects' Ratings of "very much improved"



Kampman KM et al., Drug and Alcohol Dependence Volume 155, 1 October 2015, Pages 105–110.

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ADHD and SUD

- In some forensic populations, ADHD affects 45% of the prisoners (1)
- ADHD doubles the chances of crime among boys, even in the absence of other behavioral disorders
- ADHD in prison population (2)
  - currently meet the criteria 21.7%
  - met the criteria as a child 36.4%
- Low dopamine transporter occupancy by methylphenidate as a possible reason for reduced treatment effectiveness in ADHD patients with cocaine dependence.

(1) Mannuzza et al. 2008
(2) Young et al. Psychol Med 2015.45 (2), 247) 258
(3) Crunelle C, et al, December 2013

ADHD and SUD

- Methylphenidate treatment (up to 180 mg)reduces ADHD-symptoms and the risk for relapse to substance use in criminal offenders with attention deficit hyperactivity disorder and substance dependence [1] (Maja Konstenius)

- Patients with SUD need 40% higher methylphenidate doses than those with ADHD only
- Patients with SUD show high long-term adherence to methylphenidate treatment
- Patients with SUD are treated with methylphenidate without signs of tolerance [2]

(1) Konstenius M et al, Addiction. 2014 Mar; 109(3): 440–449
(2) CharlotteSkoglund, European Neuropsychopharmacology, November 2017

Lack of continuing care

- There is little guarantee that the provided care is continued outside the prison walls;
- there is a lack of information about the moment of release
- care givers do not systematically provide a referral letter to the inmates,
- foreign inmates do not necessarily have a general practitioner in Belgium,
- and isolated and marginalized persons experience important difficulties to find access to health care in the "parallel circuit" of regular health care, often due to lack of resources (documents, network of friends, money...).
- Even if former-inmates have access to care outside the prison walls, the exchange of medical information (medical files) between caregivers within and outside prison walls is described to be very difficult.

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BCNBP National Day

Forensic psychiatry, biological aspects

December 8, 2017

Frieda Matthys, MD, PhD

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