Science and medical standards in prevention and treatment of drug use disorder

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Science is growing faster and faster in addiction medicine

Unimaginable results

The pathogenesis of substance use disorders

Recent developments in prevention and treatment
The pathogenesis of a complex health problem

Genetic predisposition
temperament

Stress during pregnancy

Disrupted attachment

Neglect and abuse

Lack of bonding to family

Lack of engagement in school

Social exclusion
frustration

Coping with stress

Coping with hunger

Early onset psychopathology

Coping with work overload

Substance Use Disorders
Epigenetic effects of cocaine
Altered histone acetylation affects behavioural sensitivity to cocaine. In the conditioned place preference test, the inhibition of histone de-acetylase potentiates the rewarding effects of cocaine.

Histone acetylation controls the saliency of a variety of environmental stimuli. Elevated histone acetylation appears to potentiate the behavioural responses to pain, stress, and cocaine.
Epigenetic changes in humans: opioid receptor gene expression affected in heroin dependent patients

Elevated levels of DNA methylation at the OPRM1 promoter in blood and sperm from male opioid addicts.
*Chorbov VM*¹, *Todorov AA*, *Lynskey MT*, *Cicero TJ*.

*Hum Genet.* 2010 Jun;127(6):639-49..
Ethnic diversity of DNA methylation in the OPRM1 promoter region in lymphocytes of heroin addicts.
*Nielsen DA*¹, *Hamon S*, *Yuferov V*, *Jackson C*, *Ho A*, *Ott J*, *Kreek MJ*.
Cocaine boosts brain-derived neurotrophic factor (BDNF) (green) expression in sperm

Gene expression changes are explaining the stability of brain-behavior changes in substance use disorders.

Recent studies challenge the idea that DNA methylation is irreversible.


Epigenetic control.

Delcuve GP, Rastegar M, Davie JR
Manitoba Institute of Cell Biology, University of Manitoba, Winnipeg, Manitoba, Canada.
Perceived Parenting Behaviour in the Childhood of Cocaine Users: Relationship With Genotype and Personality Traits
Gerra et al., 2007

Parenting moderates a genetic vulnerability factor in longitudinal increases in youths' substance use.
Brody et al., 2009

5-HTTLPR status SS linked with increases in substance use over time

the association was greatly reduced by involved-supportive parenting
short version (S) of the 5-HTTLPR

secure attachment $\rightarrow$ agreeable autonomy

insecure attachment $\rightarrow$ hostile autonomy

Zimmermann et al., 2009
brain-derived neurotrophic factor (BDNF) gene

first postnatal week infant rats exposed to stressed caretakers with abusive behaviors

persisting changes in methylation of BDNF DNA that caused altered BDNF gene expression in the adult prefrontal cortex

BDNF DNA methylation in offspring of females that had previously experienced the maltreatment regimen
Review

Epigenetic mechanisms mediating the long-term effects of maternal care on development

Frances A. Champagne\textsuperscript{a,*}, James P. Curley\textsuperscript{b}
Profiling of childhood adversity-associated DNA methylation changes in alcoholic patients and healthy controls.

Childhood adversities could induce methylation alterations in the promoter regions of specific genes and changes in gene transcription with increased risk for substance use disorders.

(Zhang et al., 2013)
The link between trauma, HPA axis and substance use disorders vulnerability

Lower methylation of glucocorticoid receptor gene promoter 1F in peripheral blood of veterans suffering for post-traumatic stress disorder

Yehuda et al., accepted article, Biological Psychiatry
Childhood neglect
Altered response to emotions
HPA axis dysfunction
Addiction Severity

Gerra et al., 2013
Psychiatric comorbidity
Arch Gen Psychiatry. 64(5):566-76.
Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions.
Compton et al., 2007

Comorbidity of drug use disorders

- other substance use disorders
- antisocial personality disorder
- mood disorders
- generalized anxiety disorder

appears to be due in part to unique factors underlying the disorders studied.
Psychiatric disorders in adolescents often **predate** the substance use disorder.

Once the substance use disorder develops, the psychiatric disorder may be **further exacerbated**.
Pharmacogenetics

A functional polymorphism in the catechol-O-methyltransferase (COMT) gene moderated the influence of adolescent cannabis use on developing adult psychosis.

COMT *valine*158 allele
psychotic symptoms if they used cannabis

COMT *methionine* allele
no such adverse influence

Caspi et al., 2005)
Association between gene variants and response to buprenorphine maintenance treatment

Gilberto Gerra a, Lorenzo Somaini b,*, Claudio Leonardi c, Elena Cortese c, Icro Maremmani d, Matteo Manfredini e, Claudia Donnini e

<table>
<thead>
<tr>
<th>Allele no. (%)</th>
<th>10</th>
<th>9</th>
<th>11</th>
<th>6</th>
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<tr>
<td>B: DAT1 gene</td>
<td></td>
<td></td>
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<tr>
<td>Responders</td>
<td>66 (55,93)</td>
<td>39 (33,05)</td>
<td>9 (7,63)</td>
<td>3 (2,54)</td>
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<tr>
<td>Non-Responders</td>
<td>61 (64,89)</td>
<td>31 (32,98)</td>
<td>0</td>
<td>0</td>
<td>2 (2,13)</td>
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Recreational use of drugs?

Drugs to cope with:

Extreme poverty
Exploitation
Social exclusion
Hunger
Work overload
Exposure to violence
Displacement
Abuse
Early childhood trauma
Substance use prevention?
Substance use prevention? A challenging task
Just say no.
You really like it?
beauty of the DRUGS
choose not to use
SPORT

using sport for drug abuse prevention
Too Good
For Drugs
Bad enough for drugs?
International Standards on Drug Use Prevention
- International Standards of Drug Use Prevention: Science based methods
- Life skill / social skills education
- Family skills programs
- Reliable information /interactive approach
- Brief intervention

- Children social protection and support to families with problems
- Fighting inequality, reduce social exclusion and change the trajectory
- Early screening of children at risk and specific educational work
relationship between family meals frequency and adolescents' risk profile for substance use disorders

Skeer and Ballard, 2013
Family program:

Undivided time devoted to children

Monitoring and supervision

Rules in family life

Warm and supportive style

Granting psychological autonomy

Values and believes proposed

Dreaming with children about the future
Life skill education

Greenberg, Ann N Y Acad Sci. 2006
Promoting resilience in children and youth: preventive interventions and their interface with neuroscience.

by improving

- inhibitory control
- planning
- problem solving skills
- emotional regulation
- attentional/critical capacities
Adolescents' resilience

- normative education
- social adjustment
- self-regulation
- peer interactions and relationships
- social problem solving
- communication

social-affective and cognitive-executive processes

Yeates et al., 2007, Dishion and Connell, 2006, Kumpfer and Summerhays, 2006
Piloting E B programme Life Skills Education Programme (UNPLUGGED) in Brazil

Relative difference ($\Delta\%$) of last year use of different substances
Adolescents (13-15 years old)

Experiment vs. Controls
(16 schools, 5000 students)

Source: Avaliação de processo e de resultados do Programa Unplugged/ #tamojunto, 2014
Is this treatment of drug dependence?
Is this treatment of drug dependence?
Most medical professionals who should be providing addiction treatment are not sufficiently trained to diagnose or treat the disease.

Most of those providing addiction care are not medical professionals.

Misunderstandings about the nature of addiction among professionals.

Disconnection of addiction medicine from mainstream medical practice.
UNODC-WHO Joint Programme on drug dependence treatment and care

The vision
Effective and humane treatment for all people with drug use disorders. Nothing less than what would be expected for any other disease.
Psychosocial science based interventions:

Brief intervention
Cognitive behavioural therapy
Self-help group therapy
Motivational interviewing
Family therapy
Job skills education

Pharmacological science based interventions

Opioid agonist (methadone, buprenorphine)
Opioid antagonists (naltrexone/slow release)
Clonidine/lofexidine
Antidepressants
Neuroleptics
Disulfiram

Integrated comprehensive multidisciplinary services
Accessible
Appealing
One stop shop
Promising Medications for Cocaine Dependence Treatment

Methilphenidate
Adderal
Topiramate
Baclofen
Modafinil
MAO inhibitors
SNRI
Neuroleptics
Buprenorphine

Subtypes of stimulants users
Unanswered questions

How many patients are attending your program every year?

How many patients/relatives are entering the service building every day?

Which percent of drug use: urine analyses?

Relapse rate / retention in treatment rate

Which rate of psychiatric comorbidity
Steps: sequence in building treatment services

Outreach: low threshold intervention and basic health care/social protection

An open door 12 hours a day in the outpatient centre

Personnel happy/passionate to see hundreds of patients

Pharmacological interventions / social incentives

Competent personnel

Integration with the public health care system

Treatment for psychiatric comorbidity

Integration with mental health care department

Short term residential treatment

Long term residential treatment
Services dimension: 300 patients per year

Outpatient service

2 doctors

2 nurses

1 social worker

1 psychologist
What we do with a patient?

Diagnosis / Assessment

Urine controls

Psychometric scales

DSM interview

Menu of services showed

Prognosis shared

Personalized integrated program proposed (psychosocial/pharmacological)

Negotiation / Engagement in a therapeutic alliance

Engagement of the family

Monthly evaluation and team discussion

Re-negotiation with the patient
opioid medications for addiction treatment wrongly considered as “state drugs” instead of “street drugs”
Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance

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Extended-Release Intramuscular Naltrexone (VIVITROL®): A Review of Its Use in the Prevention of Relapse to Opioid Dependence in Detoxified Patients

Syed and Keating, 2013

Abstinence: negative urines

24 months

Naltrexone

Placebo
Combination of Olanzapine With Opioid-Agonists in the Treatment of Heroin-Addicted Patients Affected by Comorbid Schizophrenia Spectrum Disorders

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What are the motivations of passion in responding to substance use disorders?

A complex, unexplored, patho-plastic chronic disease devastating the young generation: exciting/urgent research

Patients affected by a disease and being considered guilty/discriminated

Recovery process: the recovery of the amount of love they have been deprived during their life
Epigenetic processes are potentially reversible, pointing to epigenetic therapeutics in psychotherapy/care giving.
World mobilization for prevention and treatment of substance use disorders

A public health and human rights approach

Nothing less than what is provided for any other chronic disease
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