Understanding drug use disorders as a multi-factorial health problem

Policy implications

Gilberto Gerra
Drug Prevention and Health Branch
Decreased Brain Metabolism in *Drug Abuse Patient*

Control                         Cocaine Abuser

Decreased Heart Metabolism in *Heart Disease Patient*

Healthy Heart                  Diseased Heart

N. Volkow
ADDITION IS A DEVELOPMENTAL DISEASE starts in adolescence and childhood

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Stigma and discrimination

To punish … To permit…

**Denial**

Not to share suffering

To ignore responsibility

To attenuate sense of guilt
- fragile
- sensible
- suffering persons
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.
Drug addiction is often the result of an unwholesome social atmosphere in which those who are most exposed to the danger of drug abuse live.

Resolution III, 1972
(amendments to 1961 Convention)
A social atmosphere detrimental to physical, mental and moral well-being...
Emotional neglect
Abuse
Adverse childhood experiences
Household dysfunction
Emotional neglect
Abuse
Adolescent substance abuse and psychiatric comorbidities. Deas, 2006

Psychiatric disorders in adolescents **often predate** the substance use disorder. Once the substance use disorder develops, the psychiatric disorder may be further **exacerbated**.

More than 40%
Drugs to cope with:

- Extreme poverty
- Exploitation
- Social exclusion
- Hunger
- Work overload
- Exposure to violence
- Displacement
- Abuse
- Early childhood trauma
To be recognized…

- not as a criminal issue
- not as a moral issue
- not as a danger for society to be “expelled”

suffering persons affected
by a complex and chronic disease
Circuits Involved In Drug Abuse and Addiction
Reward / salience
emotional memory
screening
salient
stimuli

reward and risk
“winning, taking the risk of losing”: the conditioned emotional memory
Drug dependence

Compulsive behavior: motivational system hijacked by drugs

- strong instrumental memories linking actions to drug-seeking
- persistent stimulus-response habits
- neutral environmental stimuli associated with drug highs through Pavlovian conditioning
usurpation of emotional memory

Cocaine addicts brain is not activated anymore by monetary reward

Milton and Everitt, 2012
“unseen” (backward-masked) cocaine cues of 33 milliseconds duration in male cocaine patients

Childress et al., *PLoS ONE* 2008
Allostasis and addiction: Role of the dopamine and corticotropin-releasing factor systems

Olivier George a,*, Michel Le Moal b, George F. Koob a
Cocaine mechanism of action: epigenetic changes
Are drugs dangerous only for the brain?
Main physiological effects of Crack cocaine

Systemic:
- Increased temperature

Pupils:
- Dilation

Sense of balance:
- Vertigo

Blood vessels:
- Constriction
- Increased blood pressure

Heart:
- Increased heart rate
- Risk of cardiac arrest

Lungs:
- Risk of respiratory arrest

Muscles:
- Tremor
- Twitches
Are drugs dangerous only for the brain?

Cocaine users at risk of ‘silent’ heart attacks
Lancet

Adverse health effects of non-medical cannabis use.

The health effects most likely to occur and to affect a large number of cannabis users:

- A dependence syndrome
- Impaired respiratory function
- Increased risk of motor vehicle crashes
- Cardiovascular disease
- Adverse effects on adolescent psychosocial development and mental health

Hall and Degenhardt, 2009
Dunedin prospective study

Regularly smoking cannabis in their teens and then stopped

8 point less in IQ scale as adults
Effect of MDMA Administration on rCBF

Subject (age 21 yr)  Baseline  2 weeks post-MDMA

Ecstasy
Are substance abuse disorders starting with the first beer?
The pathogenesis of drug use disorders: experimenting with drugs or continuous use are the result of a long sequence of disadvantages

- Genetic predisposition
- Stress during pregnancy
  - Disrupted attachment
  - Lack of bonding to family
- Neglect and abuse
  - Lack of engagement in school
- Social exclusion
The pathogenesis of a complex health problem

- Genetic predisposition temperament
- Stress during pregnancy
- Disrupted attachment
- Lack of bonding to family
- Substance Use Disorders
- Neglect and abuse
- Social exclusion frustration
- Lack of engagement in school
- Early onset psychopathology
- Coping with stress
- Coping with work overload
- Coping with hunger
**Temperament and personality traits at risk: genetic vulnerability**

<table>
<thead>
<tr>
<th></th>
<th>LL</th>
<th>SL</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abstinent</strong></td>
<td>37.73%*</td>
<td>50.54%</td>
<td>11.83%</td>
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<tr>
<td><strong>Experimenters</strong></td>
<td>23.19%</td>
<td>50.72%</td>
<td>26.09% *</td>
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</table>
Temperament and personality traits at risk: genetic vulnerability

<table>
<thead>
<tr>
<th></th>
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<th>SL</th>
<th>SS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOVELTY SEEKING</td>
<td>15.72</td>
<td>19.41</td>
<td>21.75*</td>
</tr>
<tr>
<td>BDHI DIRECT AGGRESSION</td>
<td>51.03</td>
<td>55.70</td>
<td>59.58*</td>
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</tbody>
</table>

*Indicates significant difference.
Association Between Low-Activity Serotonin Transporter Genotype and Heroin Dependence: Behavioral and Personality Correlates.


<table>
<thead>
<tr>
<th></th>
<th>LL%</th>
<th>LS%</th>
<th>SS%</th>
<th>L%</th>
<th>S%</th>
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<tbody>
<tr>
<td>Heroin addicts</td>
<td>26.73</td>
<td>43.56</td>
<td>29.70</td>
<td>48.51</td>
<td>51.49</td>
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<tr>
<td>Controls</td>
<td>33.66</td>
<td>50.50</td>
<td>15.84</td>
<td>58.91</td>
<td>41.09</td>
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<tr>
<td>Sign.</td>
<td></td>
<td>p&lt;0.05</td>
<td></td>
<td></td>
<td>p&lt;0.03</td>
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</table>
A dopamine transporter gene functional variant associated with cocaine abuse in a Brazilian sample

Guindalini et al., 2006
<table>
<thead>
<tr>
<th>Genotypes</th>
<th>9-9</th>
<th>10-10</th>
<th>9-10</th>
<th>9-11</th>
<th>10-11</th>
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</thead>
<tbody>
<tr>
<td><strong>Offenders</strong></td>
<td>17.3%</td>
<td>42.3%</td>
<td>36.5%</td>
<td>0%</td>
<td>3.8%</td>
</tr>
<tr>
<td><strong>Non-offenders</strong></td>
<td>3.8%</td>
<td>48.1%</td>
<td>44.3%</td>
<td>5.8%</td>
<td>0%</td>
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<tr>
<td>$\chi^2 = 4.39$</td>
<td>n.s.</td>
<td>n.s</td>
<td>n.s</td>
<td>n.s</td>
<td>n.s</td>
</tr>
<tr>
<td></td>
<td>$p = 0.04$</td>
<td></td>
<td></td>
<td></td>
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</table>

Gerra et al., Addiction Biology, 2005
GENE VARIANTS: risk or protection?
Prenatal stress affects 3,4-methylenedioxy methamphetamine pharmacokinetics and drug induced motor alterations in adolescents female rats

Morley-Fletcher S., Puopolo M., Gentili S., Gerra G., Macchia T. and Laviola G.
Parenting moderates a genetic vulnerability factor in longitudinal increases in youths' substance use. 5-HTTLPR status SS linked with increases in substance use over time. The association was greatly reduced by involved-supportive parenting.
Perceived Parenting Behavior in the Childhood of Cocaine Users: Relationship With Genotype and Personality Traits

G. Gerra,1* A. Zaimovic,1 L. Garofano,2 F. Ciusa,1 G. Moi,1 P. Avanzini,3 E. Talarico,3 F. Gardini,4 F. Brambilla,1 M. Manfredini,5 and C. Donnini5
PARENTS CARE PERCEPTION

**RISK % OF DRUG DEPENDENCE IN THE ADULT**

- 10% less risk
- 20% less risk
- 90% less risk

PBI SCORE
short version (S) of the 5-HTTLPR

secure attachment  →  agreeable autonomy

insecure attachment  →  hostile autonomy

Zimmermann et al., 2009
reduced maternal care perception was found to represent a key intermediate factor of the association between SS polymorphism and drug use
Childhood neglect
Altered response to emotions
HPA axis dysfunction
Addiction Severity

Gerra et al., 2013
Monkeys who suffer maternal deprivation in childhood tend to be fearful, more aggressive, less exploratory, and subject to binge drinking on exposure to alcohol.

Early maternal deprivation reduces serotonin transporter

Ichise et al., 2006
Isolation and Social Status Can Change Neurobiology

Individually Housed

Becomes Dominant
No longer stressed

Group Housed

Becomes Subordinate
Stress remains

Brain DA D2 Receptors

Abnormal brain structure implicated in stimulant drug addiction.
University of Cambridge, Cambridge, UK.
Alpha-1- and 2-adrenoceptor sub-sensitivity in siblings of opioid addicts with personality disorders and depression.


Centro Studi Farmaco-tossicodipendenze, SER.T., Parma, Italy.

The Growth Hormone (GH) and beta-endorphin responses to clonidine were blunted in the siblings of heroin addicts affected by concomitant personality disorders.
Adverse childhood experiences

neglect

abuse
Review

Childhood neglect and parental care perception in cocaine addicts: Relation with psychiatric symptoms and biological correlates

G. Gerra\textsuperscript{a,b,*}, C. Leonardi\textsuperscript{c}, E. Cortese\textsuperscript{c}, A. Zaimovic\textsuperscript{d}, G. Dell’Agnello\textsuperscript{a}, M. Manfredini\textsuperscript{e}, L. Somaini\textsuperscript{f}, F. Petracca\textsuperscript{d}, V. Caretti\textsuperscript{g}, M.A. Raggi\textsuperscript{h}, C. Donnini\textsuperscript{e}

Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Coeff.</th>
<th>$p$-Value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>$-0.234$</td>
<td>0.906</td>
</tr>
<tr>
<td>Years of dependency</td>
<td>$0.181$</td>
<td>0.492</td>
</tr>
<tr>
<td>Antipathy mother</td>
<td>$-0.548$</td>
<td>0.009</td>
</tr>
<tr>
<td>Antipathy father</td>
<td>$-0.362$</td>
<td>0.054</td>
</tr>
<tr>
<td>Neglect mother</td>
<td>$-0.641$</td>
<td>0.001</td>
</tr>
<tr>
<td>Neglect father</td>
<td>$-0.392$</td>
<td>0.090</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.345</td>
<td></td>
</tr>
</tbody>
</table>
Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum

Martin H. Teicher*{a,b,1,2}, Carl M. Anderson*{a,b,c,1}, and Ann Polcari*{a,b,d}

Adverse Childhood Experience Score

Percent Variance Explained by Maltreatment

Subfields

Proceedings of the National Academy of Sciences of the United States of America (PNAS), 2012
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
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)
Review

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

Frances A. Champagne\textsuperscript{a,}\textsuperscript{*}, James P. Curley\textsuperscript{b}
A functional polymorphism
in the catechol-O-methyltransferase (COMT) gene
moderated the influence of adolescent cannabis use
on developing adult psychosis

COMT valine158 allele
psychotic symptoms
if they used cannabis

COMT methionine allele
no such adverse influence
Addiction and premorbid psychiatric disorders:

- social phobia
- bipolar affective disorder
- depression
- anxiety
- conduct disorder
- oppositional defiant disorders

were strongly associated with the subsequent development of substance dependence (attributable risks ranging from 44 to 86%)

Merikangas and Avenevoli, 2000
Socioeconomic vulnerability

Poverty
Social exclusion
Instability/migration
Coping with stress
Hunger
Work overload
Exposure to violence
Victims of human trafficking
Vulnerability conditions for substance use disorders
44% of households with a member living abroad are caring for at least one child left behind.

This proportion is higher in rural than in urban areas: 47% respectively.

*Moldova, UNICEF 2009*

- Maternal deprivation
- A grandparents society
- Social exclusion
What is the response to complex health disorders?

Building an articulated and comprehensive response is a long lasting process.
Drug use disorders are preventable and treatable
PREVENTION

Early screening of temperaments at risk and help to the parents/teachers

Improved parenting and strengthening family skills

Protection of children and adolescents from adverse childhood experiences
PREVENTION

Life skills education in schools

Reliable and science-based information in school

Orientation to health lifestyle, values and positive believes

Youth mobilization and engagement in their schools
Piloting E B programme Life Skills Education Programme (UNPLUGGED) in Brazil

Relative difference (Δ%) 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
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
UNODC youth initiative

- Mobilization
- Empowerment
- Volunteering
- Dissemination of values

- Drugs are not a way of life
- Adolescents do not accept to be submitted to psychotropic substances
Help for psychological and social problems

Break social exclusion
Selected-indicated prevention
Family-based prevention

Family-strengthening approaches for the prevention of youth problem behaviors.

Effective parenting is the most powerful way to reduce adolescent problem behaviors.

Kumpfer and Alvarado, 2003
Undivided time
Warm child-rearing style
Rules
Supervision
Granting psychological autonomy
Managing aggressiveness
Dreaming with the children
relationship between family meals frequency and adolescents' risk profile for substance use disorders

Skeer and Ballard, 2013
to change the trajectory of children at risk
<table>
<thead>
<tr>
<th>Treatment elements</th>
<th>1) Initial stage</th>
<th>2) Treatment services development</th>
<th>3) Consolidated treatment network</th>
</tr>
</thead>
<tbody>
<tr>
<td>N. of patients/service</td>
<td>Tens</td>
<td>Hundreds</td>
<td>Thousands</td>
</tr>
<tr>
<td>Infrastructures</td>
<td>Deteriorated buildings</td>
<td>Refurbished large buildings</td>
<td>New clinics easy to reach</td>
</tr>
<tr>
<td>Professional teams</td>
<td>Volunteers</td>
<td>Medical doctor / nurses / social workers / counsellors</td>
<td>Multidisciplinary team: addiction / mental health / infectious diseases</td>
</tr>
<tr>
<td>Managed by…</td>
<td>Police / Ministry of Interior</td>
<td>Ministry of Social Affairs</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>Knowledge and science</td>
<td>Empirical and basic knowledge</td>
<td>Knowledge transfer from abroad</td>
<td>Science based knowledge consolidated</td>
</tr>
<tr>
<td>Discipline involved</td>
<td>Education / re-education</td>
<td>Social science</td>
<td>Medicine and psychiatry</td>
</tr>
<tr>
<td>Setting</td>
<td>Long term residential</td>
<td>Outpatients / outreach</td>
<td>Outpatients / inpatients</td>
</tr>
<tr>
<td>Decision for treatment</td>
<td>Compulsory</td>
<td>Voluntary-based</td>
<td>Therapeutic alliance</td>
</tr>
<tr>
<td>Training for personnel</td>
<td>Episodic training</td>
<td>Systematic training</td>
<td>University training</td>
</tr>
<tr>
<td>Pharmacological tools</td>
<td>Used for a minority / wrong dosages - methods</td>
<td>Used extensively without control</td>
<td>Used extensively / tailored / under control</td>
</tr>
<tr>
<td>Psychosocial tools</td>
<td>Self made psychosocial: ergo-therapy</td>
<td>Vocational skills and social protection</td>
<td>Cognitive behavioural – family therapy</td>
</tr>
<tr>
<td>Costs</td>
<td>Expensive - ineffective</td>
<td>Cheap – partially effective</td>
<td>Cost-effective</td>
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<tr>
<td>Services integration</td>
<td>Ignoring each other</td>
<td>Competition and conflicts</td>
<td>Integrated in a system</td>
</tr>
</tbody>
</table>
What we do in drug dependence treatment with 1 $?

We save 7.2 $ in health and crime costs

SAMSHA, US, 2009
Cost per patient per year: outpatient in Germany: EUR 3460

Saving:
Cost for crime/security
Cost of social care
Cost of health care

Treatment is cost-effective

EMCDDA, EU, 2011
Costs of drug abuse treatment in the USA per person, per year
(United States dollars)

- Outpatient treatment (cocaine): $2,722
- Methadone maintenance (heroin): $3,500
- Residential treatment (cocaine): $12,467
- Probation: $16,691
- Incarceration: $39,600
- Untreated addiction: $43,200

United States of America, Department of Health and Human Services, Centers for Disease Control, *Policy Issues and Challenges in Substance Abuse Treatment*, 2002
Nothing less than what is expected for any other disease.
1) Training: good practice – science based methods dissemination

2) Low cost integrated treatment centers (multidisciplinary)

3) Services accessible and appealing: large numbers of patients

5) Data collection and research
Moving from social exclusion and loneliness…

…to acceptance, - treatment - recovery - rehabilitation
Moving from a sanction-oriented approach ... to a health-oriented approach.
The Convention indicates that States Parties may provide measures for treatment, education, aftercare, rehabilitation or social reintegration as an alternative to conviction or punishment.

The Conventions do not require conviction and punishment for possession, purchase or cultivation for personal use.

Art. 3, para. 4. (d) of the 1988 Convention
From coercion to cohesion
Treating drug dependence through health care, not punishment
DISCUSSION PAPER
Unconditioned measures to protect health and reduce the consequences of drug use

9 interventions to protect from HIV included needle exchange and opioid agonists

naloxone for overdose prevention

measures for prevention of car accidents
One stop shop

Pharmacotherapy for stimulants users
Detoxification
Naltrexone
Methadone maintenance
Buprenorphine maintenance

Self-help groups
AA - NA

Mental health care
Counselling
Health care
Dentist
Psychotherapy
CBT
Family therapy
Vocational skills and reintegration
Follow up in prison

Measures to prevent HIV and Hepatitis
Antiretroviral therapy
Social assistance
Outreach and home visiting
Overdose prevention

Mental health care
Counselling

Antiretroviral therapy
Social assistance
Outreach and home visiting
Overdose prevention

One stop shop

Pharmacotherapy for stimulants users
Detoxification
Naltrexone
Methadone maintenance
Buprenorphine maintenance

Self-help groups
AA - NA

Mental health care
Counselling
Health care
Dentist
Psychotherapy
CBT
Family therapy
Vocational skills and reintegration
Follow up in prison
Detoxification protocols:
Short term pharmacological treatment of withdrawal and intoxication

Long term pharmacological interventions
- agonists
- antagonists
- anti-withdrawal
- anti-craving
- anti-reward
Non-pharmacological treatment modalities:
- brief intervention
- individual psychotherapy
- group psychotherapy
- family psychotherapy
- cognitive-behavioural interventions
- therapeutic community
- motivational interviewing and motivational enhancement
- contingency management
- self-help groups
- job skills education

Treatment of co-occurring substance use and mental health disorders
Treatment of co-occurring HIV/AIDS Hepatitis TBC cardiovascular liver diseases
opioid medications for addiction treatment wrongly considered as “state drugs” instead of “street drugs”
The differences

**Kinetic**

**Drug liking/reinforcing effects**

**Effects on HPA axis**

**Effects on the immune system**
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
Promising medication for stimulants dependence treatment

Topiramate
Adderall
Methylphenidate
Modafinil
Baclofen
Buprenorphine/naltrexone
SRNI antidepressants
Buprenorphine and methadone maintenance treatment of heroin addicts preserves immune function.

No differences in socio-demographic conditions between heroin addicts and patients in treatment.

Paola Sacerdote, Silvia Franchi Gilberto Gerra Vincenzo Leccese Alberto E. Panerai Lorenzo Somaini
Supervised daily consumption, contingent take-home incentive and non-contingent take-home in methadone maintenance

G. Gerra a,* E. Saenz a, A. Busse a, I. Maremmani b, R. Ciccocioppo c, A. Zaimovic d, M.L. Gerra e, M. Amore e, M. Manfredini f, C. Donnini f, L. Somaini g

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c Department of Experimental Medicine and Public Health, University of Camerino, 62032 Camerino, Italy
d "Programma Dipendenze “ Ser.T, AUSL Parma, 43100 Parma, Italy
e Division of Psychiatry, Dept. of Neurosciences, University of Parma, Parma, Italy
f Dipartimento di Genetica, Biologia dei Microrganismi, Antropologia, Evoluzione, University of Parma, Parma, Italy
g “Dipartimento Dipendenze” Health Local Unit Bl, 13900 Biella, Italy
Combination of Olanzapine With Opioid-Agonists in the Treatment of Heroin-Addicted Patients Affected by Comorbid Schizophrenia Spectrum Disorders

Gilberto Gerra, MD,* Gilberto Di Petta, MD,† Antonio D’Amore,‡ Pasquale Iannotta, MD,‡ Francesco Bardicchia, MD,¶ Fabio Falorni, MD,¶ Alessandro Coaci, MD,¶ Giovanni Strepparola,|| Giuseppe Campione, MD,|| Alfio Lucchini, MD,|| Giuseppina Vedda, MD,§

![Graph showing the proportion of surviving patients over time for two groups, Group 1 and Group 2. The x-axis represents the weeks from baseline to week 12, and the y-axis represents the proportion surviving.]
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