Tuberculosis in 2017: Searching for new solutions in the face of new challenges

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Substance and Alcohol Use Disorders - Pathogenesis and Significance in Clinical Practice

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Care for People Who Use Drugs

Part 1: What is substance use disorder?

Part 2: Significance

Part 3: An example of an answer to the challenge
Substance use is not a disorder.
Natural course of substance use and substance use disorder
(rates including alcohol/nicotine)

- **No use**: 80-95%
- **Recreational use (pleasure/reward driven)**: 10-30%
- **Impulsive use (habit driven)**: 2-15%
- **Compulsive use**: 2-15%
- 5-20%
- 50-80%
- 10-30%

Flowchart showing the progression from no use to recreational to impulsive to compulsive use with respective percentages.
Substance use disorder is a disorder.
“Harmful Use”: clear evidence of physical or psychological harm caused by substance use.

“Dependence”: \[ \geq 3 \text{ of } 6 \], simultaneously for at least 1 month in one year

1. Strong desire or compulsion to consume
2. Loss of control
3. Withdrawal (physical)
4. Tolerance
5. Loss of interest in alternative joy
6. Continued use despite known harm

“Recreational Use”: Use of psychotropic substances to experience joy, pleasure and/or relaxation at adequate times and amounts, not causing significant risk for social, mental or physical health. (obviously not ICD-10 defined)
“Substance Use Disorder”: maladaptive pattern of substance use leading to \( \geq 2 \) of 11, occurring at any time in one year

“Dependence”:

1. Loss of control
2. Desire or unsuccessful efforts to decrease/stop
3. Great deal of time is spent in substance consumption
4. Failure to fulfill major role obligations
5. Continued use despite social or interpersonal problems
6. Loss of interest in alternative joy
7. Recurrent use in physically hazardous situations
8. Continued use despite known physical problems
9. Tolerance
10. Physical Withdrawal
11. Craving

Severity:
- 2-3 criteria: Mild
- 4-5 criteria: Moderate
- \( \geq 6 \) criteria: Severe
Rewarding
Reinforcing
Pleasurable

Laboratory animals volitionally self-administer them

- Barbiturates
- Ethanol
- Opioids
- Benzodiazepines
- Nicotine
- Cocaine
- Amphetamines
- Cannabinoids
Dopamine is the crucial neurotransmitter in the 2\textsuperscript{nd} neuron of the brain’s reward circuit (VTA >>> Nacc)
This system is essential to survival as it is – through „reward“ – pushing motivation:

food intake, smells, sexual behaviour, parental behaviour, social interactions

But also physical exercise, music...

The system is also involved in attention, reward expectation, disconfirmation of reward expectancy, incentive motivation and anti-reward
Substance Use Disorder

is a disorder of the brain’s reward circuit
Dopaminergic N. acc-Neurons encode receipt of reward, but...

No expectation – surprising reward

Sensitized expectation by conditioning

“disappointed” expectation

Can be **acquired or inherited**.

Genetics account for 40-60% of cases of SUD

D2/D3-receptor deficiency

Atrophy of the neurofillamental transport system for tyrosine hydroxylase in DA-Axons
Animal studies:
Individual characteristics predicting enhanced drug seeking behaviour:

1. High reactivity to stress
2. High novelty induced locomotor reaction
3. High novelty seeking behaviour
4. High trait impulsivity
5. Intrauterine exposure to maternal stress
Reward deficiency syndrome (RDS)

Human studies:
Individual characteristics predicting enhanced vulnerability to SUD:

1. High reactivity to stress
2. Antisocial conduct disorder
3. DEPRESSION
4. TRAUMA
5. ADHS
6. High novelty seeking behaviour
7. High trait impulsivity
1. Humans with high baseline dopamine levels at N.acc. experience methylphenidate as displeasurable, while humans with low dopamine levels at N.acc. experience methylphenidate as pleasurable.
1. Single housed alpha-monkeys have higher N.acc.-dopamine levels than single housed submissive monkeys
2. Submissive monkeys show more drug seeking and drug taking than alpha-monkeys
3. This finding is accentuated when socially housed.
1. Cocaine- or amphetamine experienced rats, cats and monkeys have lower dopamine levels at N.acc.

2. Trait impulsive rats have lower D2/D3-binding at N.acc.
Reward deficiency syndrome (RDS)

Summary of possible causative factors:

1. Genetics
2. Behavioural traits (e.g. novelty seeking, impulsivity)
3. Transgenerational mother to child
4. Social factors (submissive vs dominant)
5. Trauma, Depression
6. Prior drug exposure
Eliot L. Gardner:

“if this be so, then our goals are really two-fold: first, to rescue addicts from the clutches of their addictions, and second, to restore their reward systems to a level of functionality that will enable them to ‘get off’ on the real world.”
“compulsive substance use” and “physical withdrawal” are neuroanatomically and neurobiochemically completely different phenomena!
Avid self-injection. No physical withdrawal.

Opioid microinjections in animal brain:

- **opioid induced analgesia:**
  - Periaqueductal grey (brain stem)
  - Lateral neospinothalamic pathway

Avid self-injection. No physical withdrawal.

No self-injection. Severe physical withdrawal.
“Harmful Use”: clear evidence of physical or psychological harm caused by substance use.

“Dependence”: ≥3 of 6, simultaneously for at least 1 month in one year

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“Recreational Use”: Use of psychotropic substances to experience joy, pleasure and/or relaxation at adequate times and amounts, not causing significant risk for social, mental or physical health. (obviously not ICD-10 defined)
Failure rate of simple detox is so high that it must be called medical malpractice.
CRAVING is the essence of Substance Use Disorder.
Craving and Relapse

Classical triggers:

• Re-exposure to drug
• **Stress**
• Environmental cues

Induce craving and relapse into substance use
Relapse to drug seeking behaviour triggered by re-exposure is mediated by
1. VTA and N.acc. (Dopamin)
Craving and Relapse

Relapse to drug seeking behaviour triggered by stress is mediated by
1. lateral tegmental nucleus A2 (Noradrenalin)
2. central amygdala (CRF)
Relapse to drug seeking behaviour triggered by environmental cues is mediated by
1. Ventral subiculum (Glutamate)
2. Basolateral amygdala (Glutamate)
3. Prefrontal cortex (Glutamate)
Craving and Relapse

Response (1 h)

Withdrawal period (d)

Baseline

Cues available

* Indicates significant difference from baseline.
What if the difference between not being addicted and being addicted...

...was the difference between seeing the world as your park...

...and seeing the world as your cage.
Substance Use Disorder
Prevalence (age 15-64 y)

• Nicotine Use Disorder ... up to 50%
  (Eastern Europe, Western Europe, Asia)

• Alcohol Use Disorder ... up to 16%
  (Eastern Europe, Americas, South East Asia, West Pacific)

• Cannabis Use Disorder ... 250.000.000
  (North America, Western Europe, Oceania)

• ATS Use Disorder... 50.000.000
  (Estern Europe, SE-Asia)

• Cocaine Use Disorder ... 20.000.000
  (Americas/Europe)

• Opioid Use Disorder ... 20.000.000
  (Central Asia, Europe, North America)
Significance

In 2010, the three leading risk factors for global disease burden were

1. high blood pressure (7.0% [6.2–7.7] of global DALYs)
2. tobacco smoking (6.3% [5.5–7.0])
3. alcohol use (5.5% [5.0–5.9])

x. “Illicit” drug use (0.8% [0.6–1.0])
http://thelancet.com/gbd/gbd-compare-visualisation
Age standardized DALY: weighting system reflects society's interest in productivity and receiving a return on its investment in educating children.