

**Spring Semester 2018**

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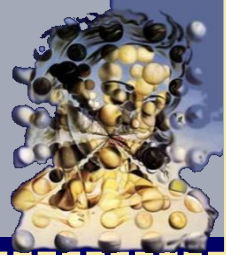
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## 7. Substance-related disorders

# Substance related disorders

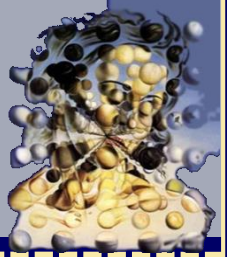


# 毒品的危害



毒品的危害可以说罄竹难书，它戕害人的身体，毒害人的心理，破坏人的家庭，残害人的生命，扰乱社会秩序，影响社会安定，危害国家经济。一句话，毒品对国家的安定、社会的进步、人民的生命安全构成了极大的威胁。





# What is a drug?



# What is a drug?



- = chemical that affects one or more biological processes
- $\neq$  common foods unless isolated and used in certain quantities
- $\Rightarrow$  fuzzy boundary, to be discussed in certain cases (cf. beer companies)

# Types of drugs



## Drugs listed in DSM-5 specifically

- Alcohol
- Caffeine
- Cannabis
- Hallucinogens
  - Phencyclidine
  - other
- Inhalants
- Opioids
- Sedatives/hypnotics/  
anxiolytics
- Stimulants
- Tobacco
- Other/Polysubstance/  
Unknown

# Main distinctive elements



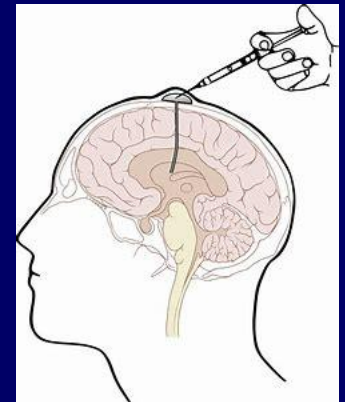
- Substance-induced mental disorders
- Substance use disorder
  - Tolerance as one symptom
  - Withdrawal as one symptom
  - Craving
- **Intoxification**
- **Withdrawal**
- New category DSM-5: gambling disorder

# Routes of administration



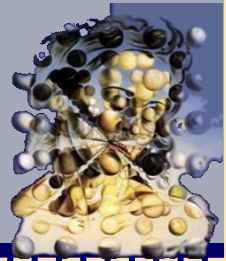
All drugs can be taken in various forms. Important is the absorption into the blood stream to finally reach the brain.

- Oral – by mouth
- Intravenous, i.v. – by injection into the blood stream
- Subcutaneous, s.c. – via skin
- Sublingual – underneath the tongue
- Intramuscular, i.m. – into the muscle
- Inhalation – via lungs
- Intracerebroventricular, i.c.v. – into the brain





# Sedative-hypnotics



- Origin of name
  - Low dosage: calming effect (anxiolytic)
  - High dosage: sleep-inducing effect
- *Examples:* alcohol, barbiturates, benzodiazepines
- Alcohol = “**bulky drug**”
  - 20-50mg per 100ml blood needed for an effect (opiates: milligrams enough)= blood alcohol content BAC 0.2-0.5‰  
(1BAC  $\cong$  1g/1000ml blood )
  - Most countries: BAC < 0.5-0.8 ‰ legal for driving

# Example: Annette



Europe:  $c = A/r \cdot m$  (Widmark formula)

- A = amount of alcohol (g)
- r = reduction and distribution constant
  - Men: 0.68–0.70
  - Women: 0.55–0.60
- m = body mass (kg)



$$c = 20\text{g} / [.57(73\text{kg})] \\ = 0.48\text{g/kg} = .48\text{‰}$$



=



=



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$$\begin{aligned} -20\% &= .28\text{‰} \\ -.10\text{‰/hour} \\ &= 20\text{g pure ethanol} \end{aligned}$$

# Characteristics of alcohol



- Small molecule = easily absorbed
- Mostly oral consumption
- High water solubility, low fat solubility
  - ⇒ females: higher rate of body fat & enzymes
  - ⇒ alcohol cannot dissolve to those body parts
  - ⇒ easier to get drunk
- Highly caloric (but no vitamins)
- Liver responsible for 90% of the metabolism

# Do Asian people have problems with metabolizing alcohol?



- Alcohol after consumption mainly metabolized by
  1. Alcohol dehydrogenase (ADH1A, B and C allele)  
⇒ acetaldehyde (toxic and carcinogenic)
  2. Acetaldehyde dehydrogenase  
⇒ acetic acid ⇒ carbon dioxide and water
- 80% of Asians have a variation of ADH1B and C (step 1)  
⇒ even more efficient in breaking down alcohol than Westerners!
- *But:*  
50% of Asians have an ALDH2 allele that does not break down acetaldehyde efficiently (step 2)  
⇒ Acetaldehyde intoxicification = “Asian flush”

# Geographic distribution of ALDH2\*504Lys

(Li et al. 2009)



<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2846302/>

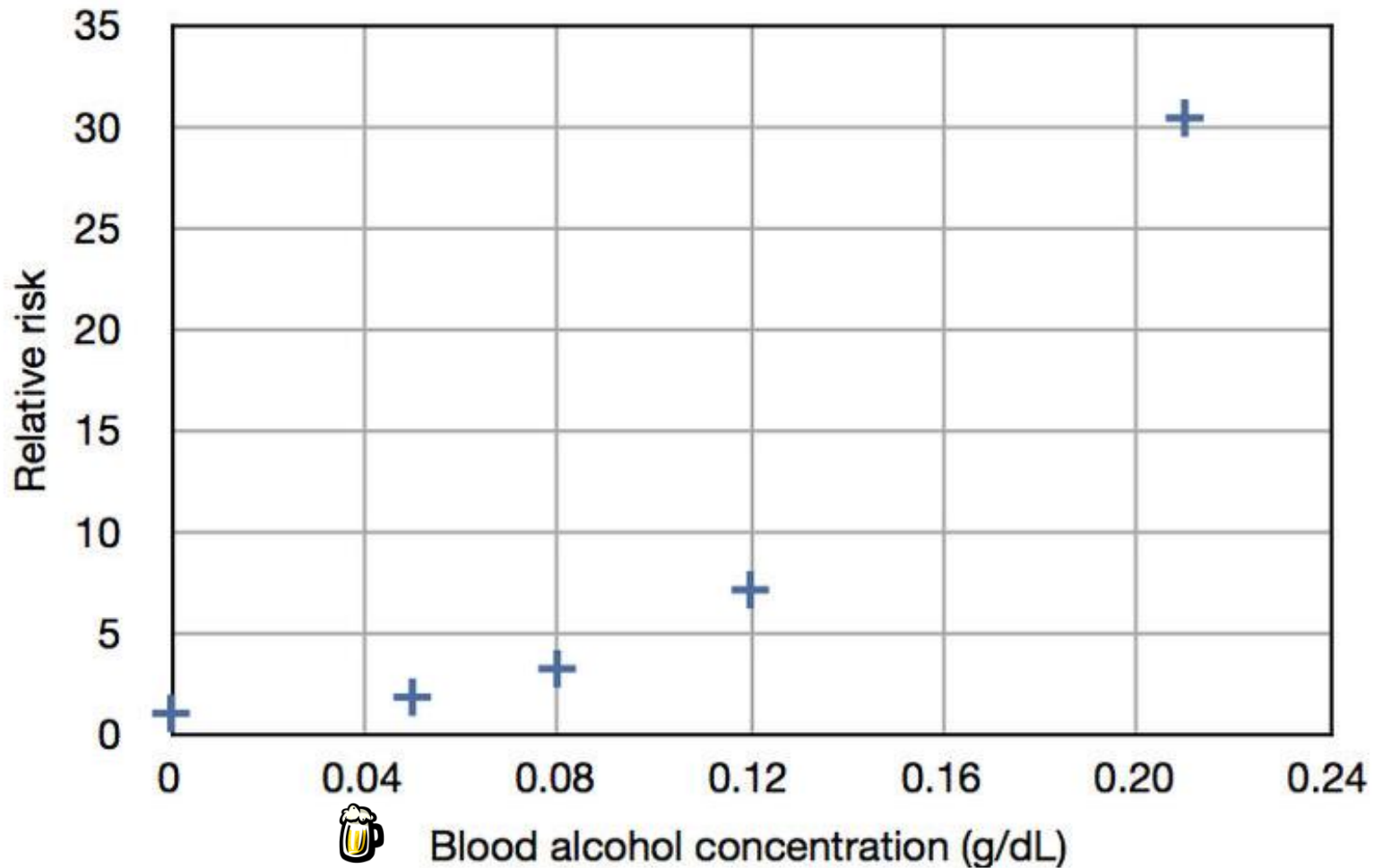


# Psychological effects (1)

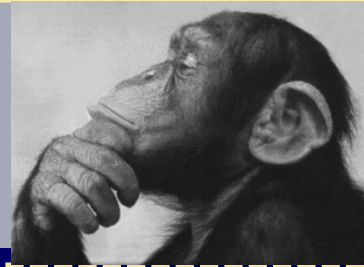


- Common belief: many positive effects
  - More active
  - Excited
  - Enhances social pleasure
  - Alcohol = stimulant (wrong!)
  - Enhances sexual performance (wrong!)
- But
  - Higher probability to engage in criminal activity
  - Family violence
  - Reckless behavior (traffic violence)
  - Diminished abilities

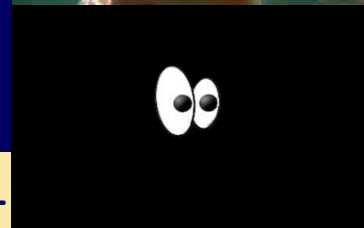
# Risk of traffic accidents based on alcohol levels (Kirklin, 2013)



# Psychological effects (2)



- Processes are inhibited in the reverse order that they were learned
  1. Complex cognitions (planning, problem solving)
  2. Fine learned motor skills (playing piano)
  3. Grossly learned motor skills (walking)
  4. Visual accommodation
  5. Unconditioned reflexes (breathing)
- Most extreme: blackouts (complete amnesia)
- Sleep inducing, but REM sleep reducing

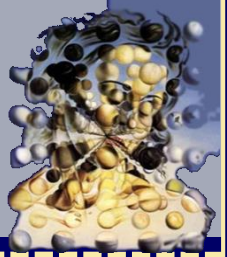


# Physiological effects (1)



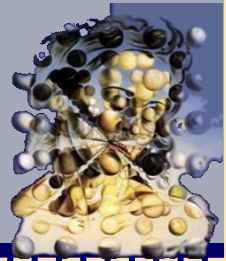
- Inhibits release of antidiuretic hormones  
⇒ dehydration of the body (lack of water)
- Reduces the rate of which the liver releases glucose and complex fats
  - ⇒ early stage: fat liver
  - ⇒ later stage: cell death, liver dysfunction, cirrhosis
- Increases the amount of enzymes (15-30%) and receptors (GABA, NMDA), sudden abstinence can cause
  - ⇒ early stage: disturbed sleep, tremor, elevated blood pressure, pulse rate, etc.
  - ⇒ later stage: irritability, headache, fever, nausea, visual hallucinations (delirium tremens)

# Liver cirrhosis





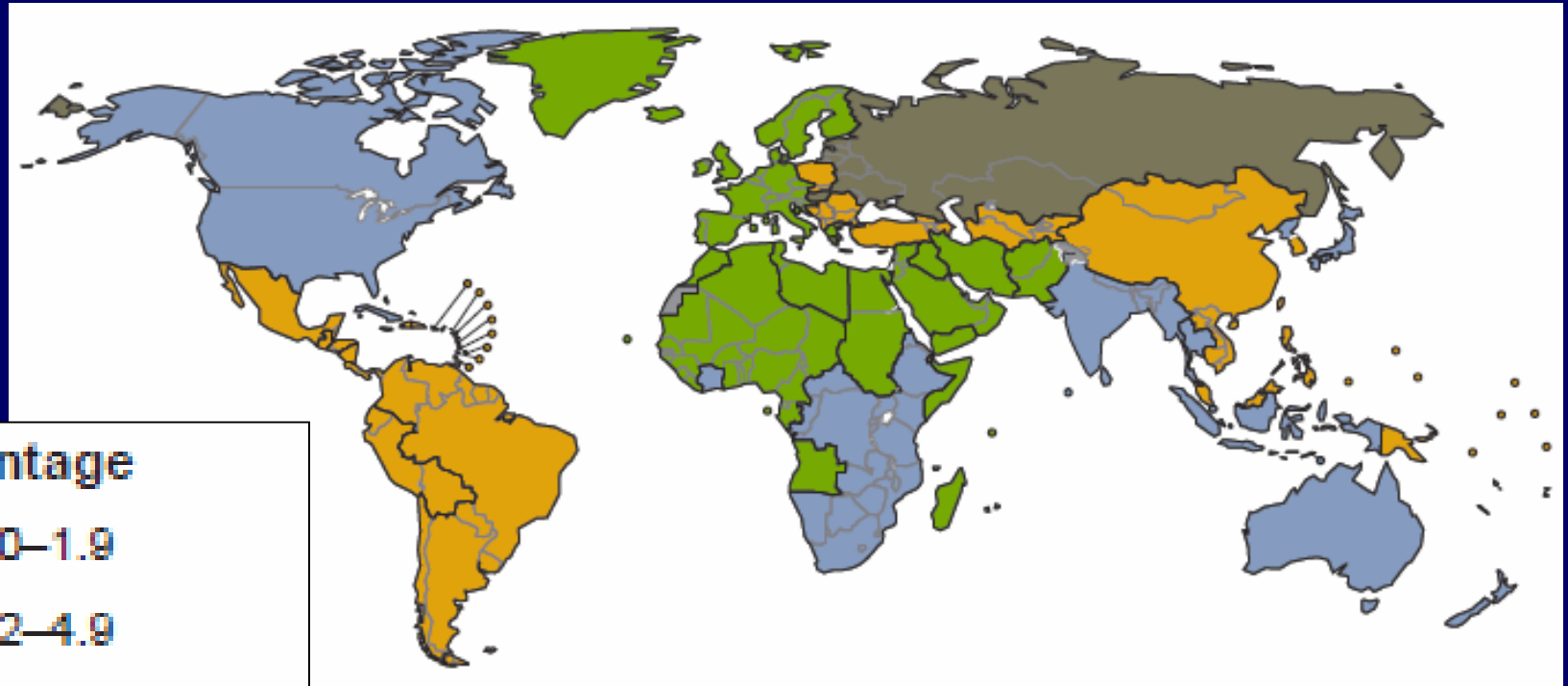
# Physiological effects (2)



- Constant rate of metabolism: 15ml/hour
- Lethal dosage: BAC = 0.5% (not ‰!)  
(about 23 drinks in a 80kg male)
- Protective mechanisms of the body
  - Vomiting: BAC > 0.12%
  - Passing out: BAC  $\cong$  0.35%
- Long-term chronic usage: brain shrinkage

# Alcohol attributable deaths

(WHO, 2004)



## Percentage



0-1.9



2-4.9



5-9.9



10-14



Not applicable

# Average worldwide alcohol consumption



Men: 7.6l/yr (10.9l [2014])  
Women: 0.6l/yr (2.2 [2014])

WHO Member State

Recorded  
consumption<sup>\*a</sup>

Unrecorded  
consumption<sup>\*b</sup>

Total consumption<sup>\*c</sup>

Beer<sup>d</sup>

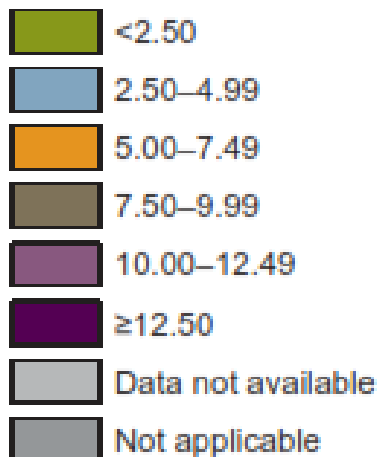
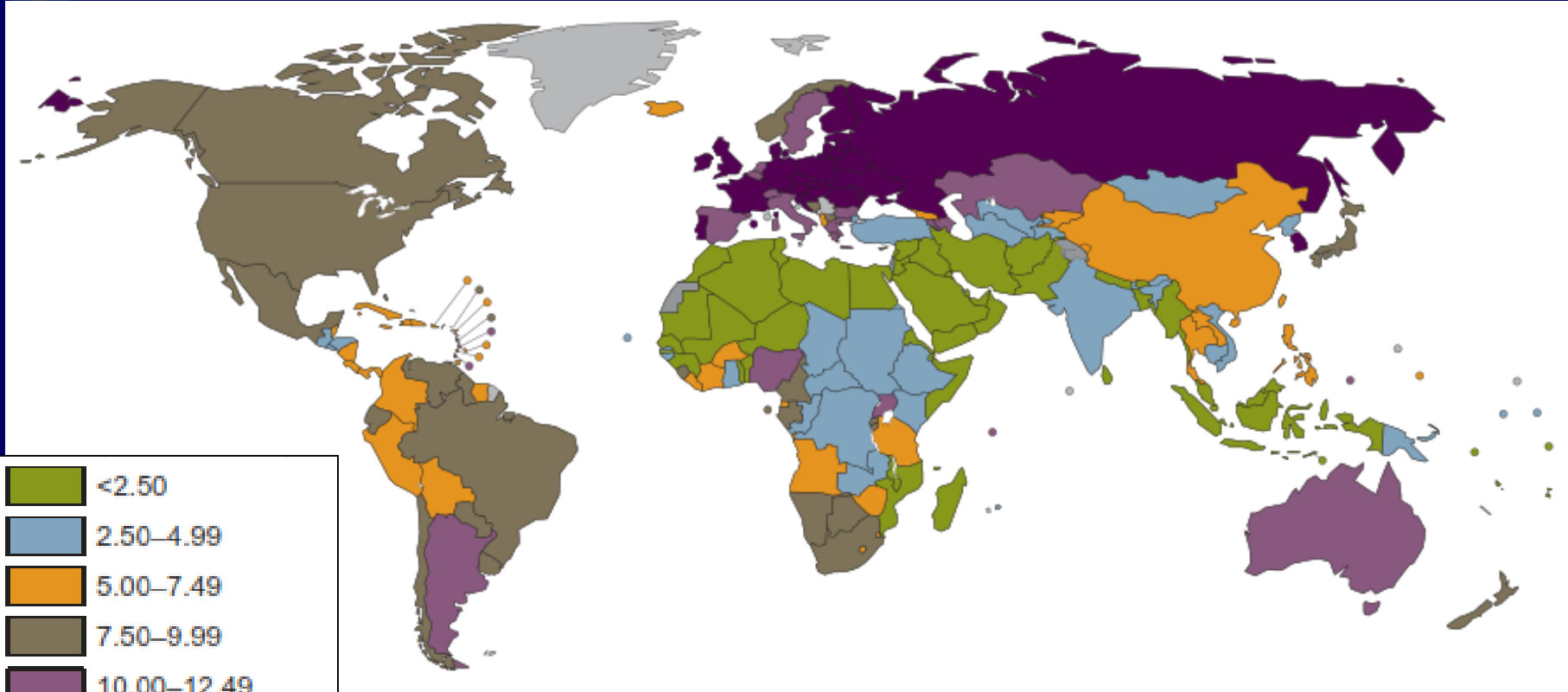
Wine<sup>e</sup>

Spirits<sup>f</sup>

Germany	11.81	1.00	12.81	6.22	3.15	2.30
China	4.21	1.70	5.91	1.50	0.15	2.51
Ireland	13.39	1.00	14.41	7.04	2.75	2.51
Czech Republic	14.97	1.48	16.45	8.51	2.33	3.59
United States	8.44	1.00	9.44	4.47	1.36	2.65

liters of pure alcohol per year (WHO, 2011)

# Worldwide alcohol consumption liters/capita/year (WHO, 2005)



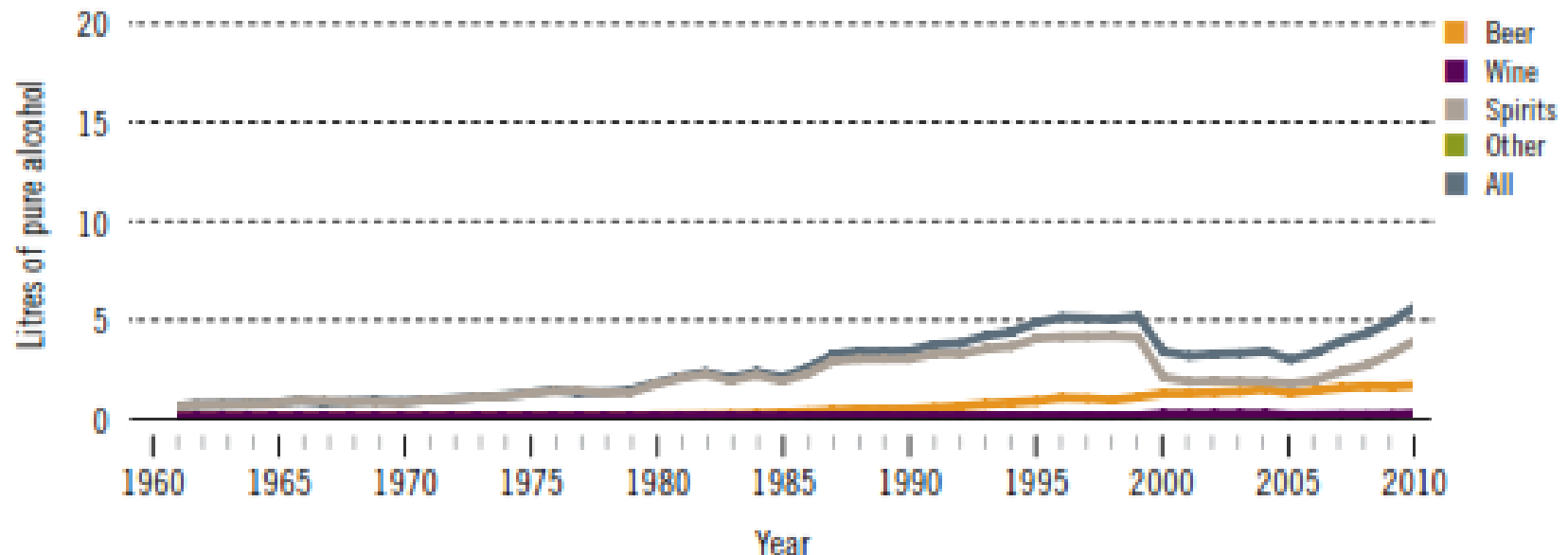
# Profile over time (WHO, 2014)

## China – “rising tendency”



### Recorded alcohol per capita (15+) consumption, 1961–2010

Data refer to litres of pure alcohol per capita (15+).



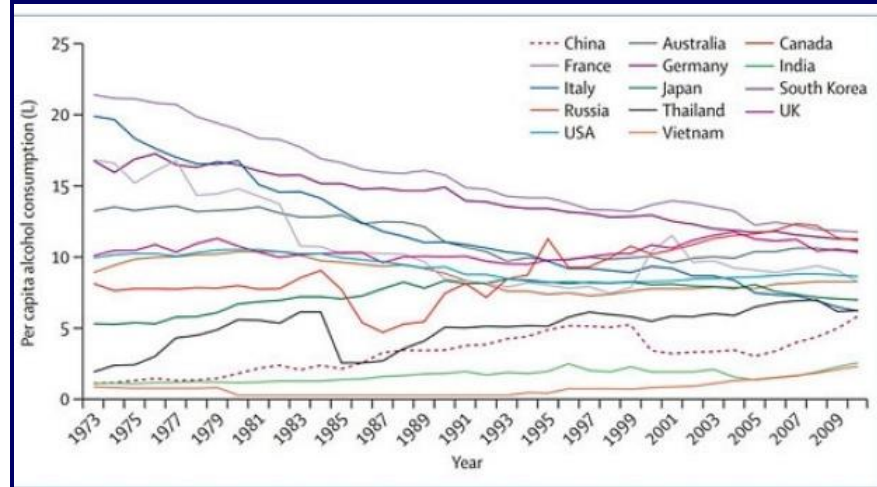


# Per capita alcohol consumption

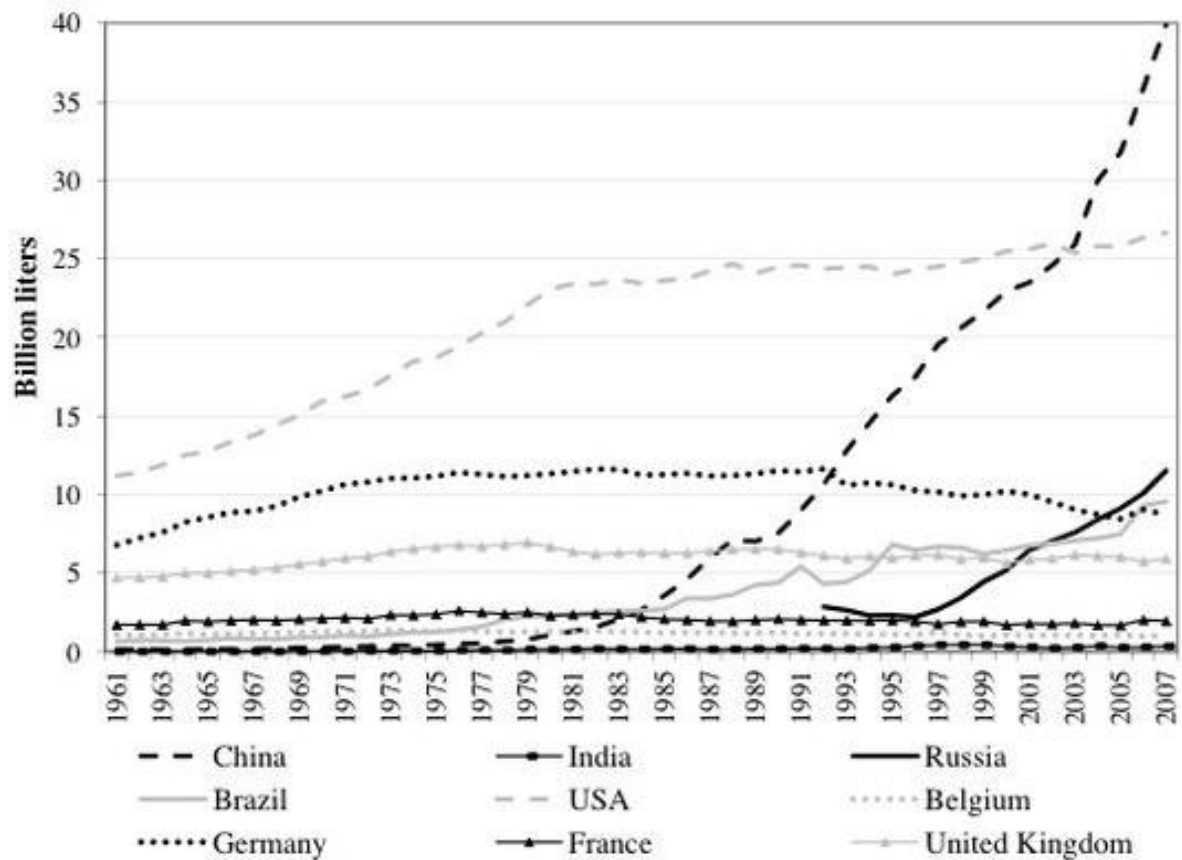
Jiang et al. (2015, The Lancet, p. e190)



parts of the world (figure). Although the population drinking level in China used to be far lower than in many high-income and middle-income countries, per capita alcohol consumption has risen from 2.5 L in 1978 to 6.7 L in 2010.<sup>2</sup> However, more than half of the Chinese population aged 15 years and older are alcohol abstainers—42% of men and 71% of women in 2010.<sup>2</sup> So the alcohol consumption level of those who actually drink was 15.1 L in 2010, which is higher than the equivalent figure in the UK, the USA, Sweden, Germany, Australia, New Zealand, and many other countries.<sup>2</sup> Furthermore, there is a great disparity in alcohol consumption and rates of dependence between the sexes: the rates of alcohol use disorder are 9.3% among men and 0.2% among women, with the male-to-female ratio of 47:1 being substantially higher than in most other countries in the world.<sup>2,5</sup> The Global Burden of



# Absolute beer consumption around the world



Source : FAOstat (2010)

Retrieved from: <http://www.theworldofchinese.com/2014/08/ganbei-changes-in-chinas-drinking-habits/>

# Prevalence rates alcohol dependence



- Point prevalence China:
  - 3.4% (Cochrane et al. 2003)
  - 5% (Phillips et al. 2009)
    - Men: 6.6%
    - Women: 0.1%
- Lifetime prevalence
  - North Germany (Meyer et al., 2000)  
3.8% (OR males 4.3)
  - Germany (National Survey, 1997): 3.8%
    - Men: 6%
    - Women: 1.5%

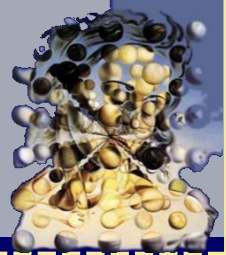
# Drinking patterns in China (1)

Li et al. (2011)

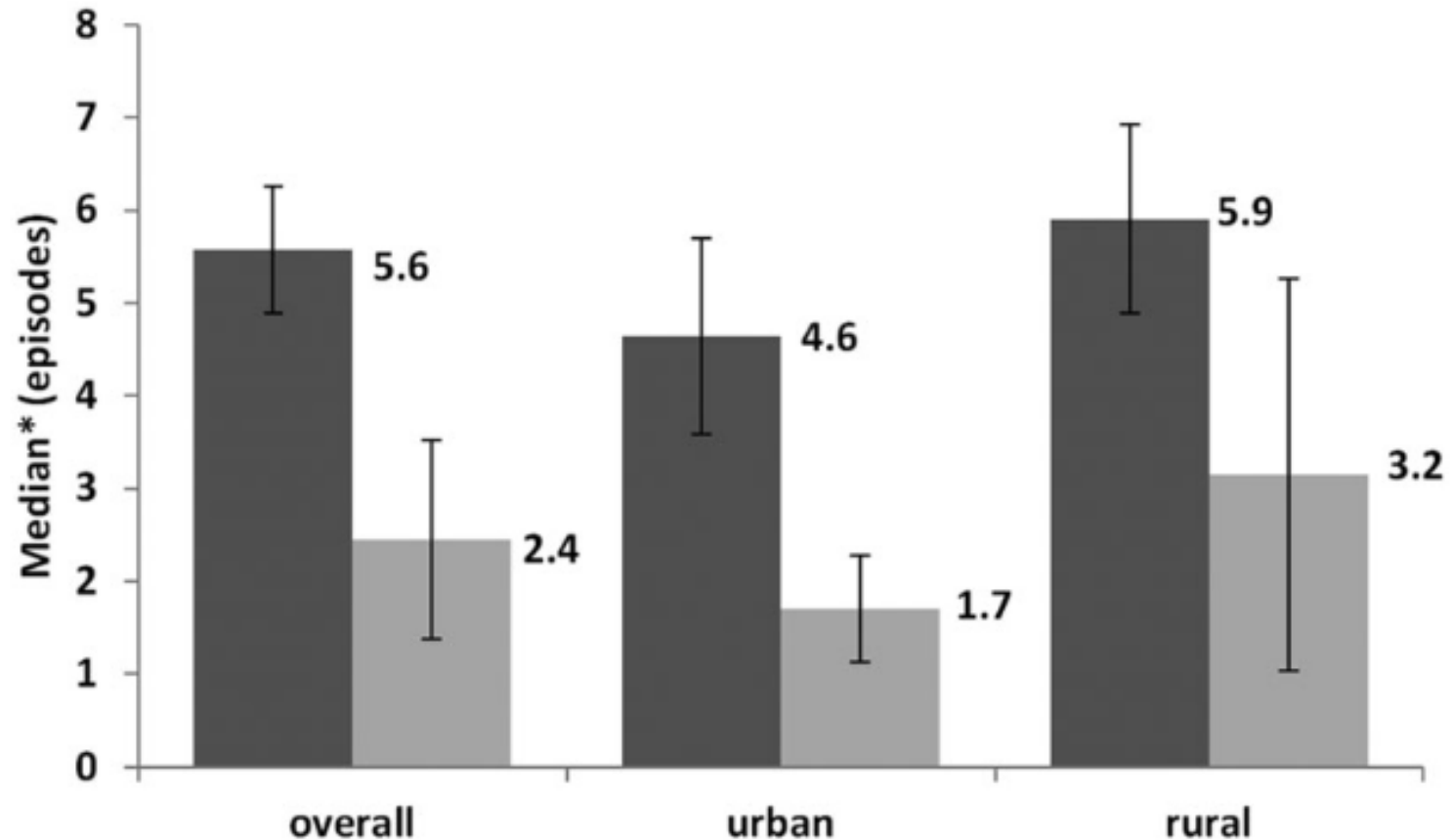


- Age group: 15-70
- $\cong$  50% of men, and 15% of women drink alcohol
- Highest prevalence between 25- to 55-year-old males
- Average daily quantity
  - Males: 48g
  - Females: 19g

# Drinking patterns in China (2)



median annual binge drinking episodes (m/f)





# Etiology and treatment



## Etiology

- Genetic basis
- Positive peer/family attitudes to alcohol
- Role models
- Addictive beliefs

## Treatment

- Goals: complete abstinence (Alcoholics Anonymous) vs. controlled drinking
- Drug therapy: antabuse (low acceptance)
- Different psychotherapies:  
voluntary commitment of patient crucial to success
  - 12 step approach by AA, CBT, brief therapies
  - Challenge: extreme denial of the problem

# Other drugs - Summary



- Psychostimulants
  - Coffee, tea
  - Nicotine
  - Amphetamines (synthesized drug; e.g. XTC - ecstasy)
  - Cocaine (coca leaf in South America); crack = crystalline form of the compound
- Opioids/narcotics (narke = Greek for stupor)
  - Heroin
  - Morphine (from opium poppies)
  - Methadone
  - Antagonist: Naloxone
- Psychedelics/hallucinogens
  - Cannabis (Marijuana)
  - LSD
  - Phencyclidine (PCP) (“Angel’s dust”)



# Drug schedules

DEA (US Drug Enforcement Agency)



		<i>Addictive potential</i>		
		<i>High</i>	<i>Moderate</i>	<i>Low</i>
<b>Medical use</b>	<i>High</i>	<b>Schedule II</b> e.g. : cocaine methadone morphine	<b>Schedule III</b> e.g.: nalorphine codeine- containers	<b>Schedule IV</b> e.g.: diazepam  <b>Schedule V</b> most drugs
	<i>Low</i>	<b>Schedule I</b> (locked behind 3 barriers) e.g.: heroin, LSD		

# Nicotine 尼古丁



# Psychostimulants (1)

## Nicotine



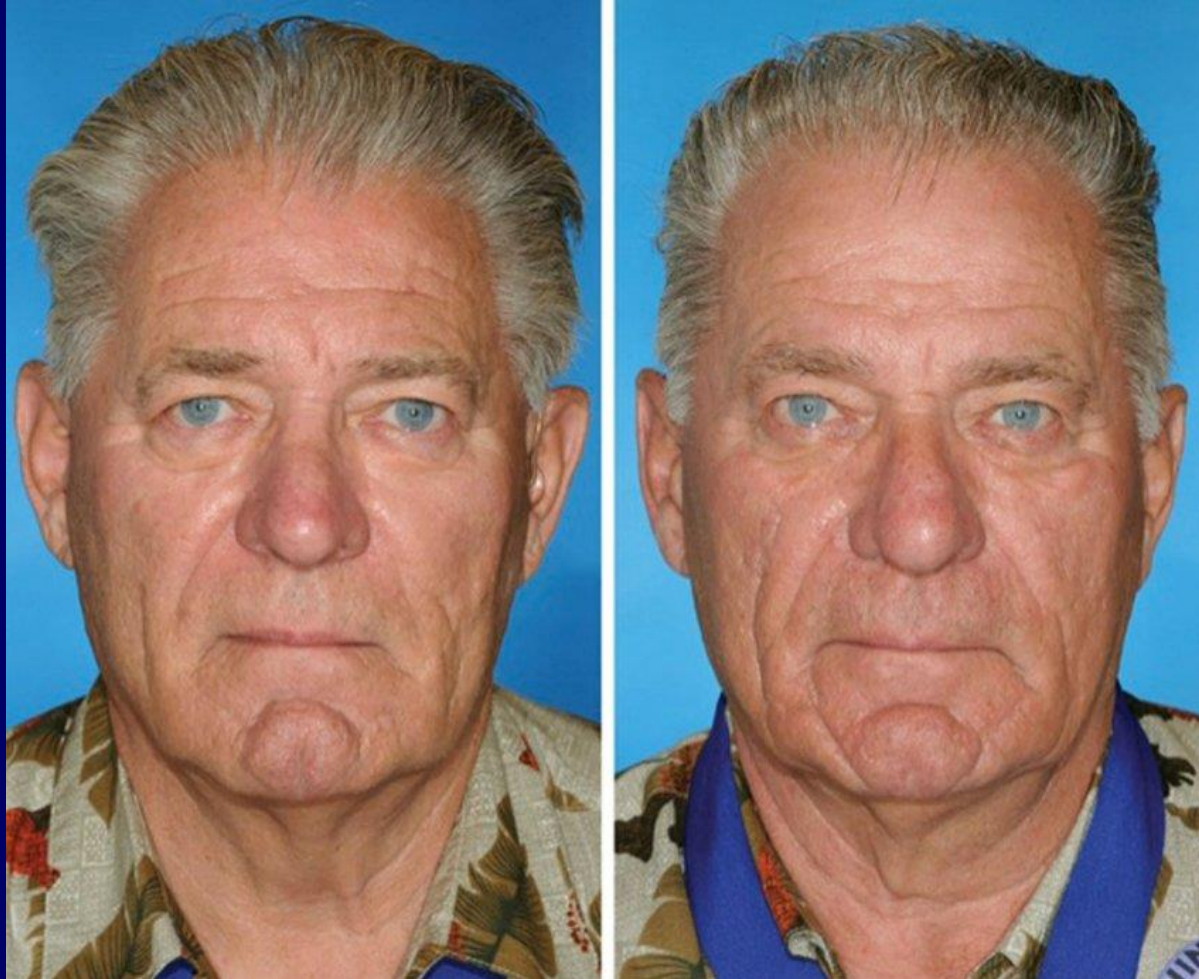
- *Effect:*  
“good” reinforcer, but people do not claim they feel good
- *Amount:*
  - 5% of tobacco
  - 9mg in one cigarette
  - 1mg absorbed in lungs
  - 25% of 1mg reaches brain in 7 seconds  
= faster than i.v. => the “**hit**” most important
- *Withdrawal:*  
irritability, hunger, insomnia, decreased heart rate
- High relapse rate after quitting:  
60-65% in first month, 90% first year





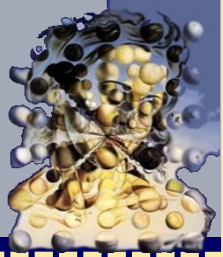
# Smoking vs. non-smoking twins

Okada et al., 2013, doi: 10.1097/PRS.0b013e3182a4c20a





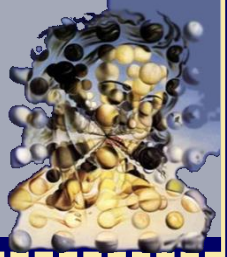
# Smoking vs. non-smoking twins



# Smoking vs. non-smoking twins



# E-cigarette





# Amphetamines

安非他命/苯丙胺



# Psychostimulants (2)

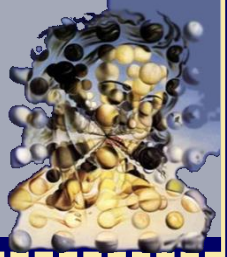
## Amphetamines



- Completely synthesized, slow absorption
- *Effects:*
  - Alertness
  - Anorexia
  - Increased respiration
  - *Hyperthermia*
  - If “on a run”: > 3-6 days of complete alertness without the need to eat or sleep
- After that:
  - exhaustion
  - possibly amphetamine psychosis
- Withdrawal: only mild



# Opiates 鸦片制剂





# Opiates/narcotics (1)

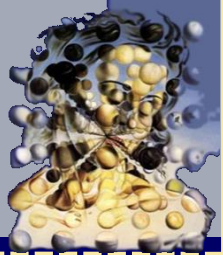


- = all kinds of drugs that are similar (structure and function) to opium
- *Effects* (“drowsiness”)
  - Analgesia (pain relief)
  - Suppressed respiration
  - Euphoria
  - Relaxation
  - Tranquilization
  - Decreased blood pressure
  - Constipation
  - Pupillary constriction
  - Hypothermia
  - Reduced sex drive



# Opiates/narcotics (2)

## Addictive potential: context-dependent



- Hardly any addictions if used for pain relief:
  - only 10-15% of people who took cocaine once or twice became abusers
  - Only 1% of the 40% heroin-consuming American soldiers during the Vietnam War continued after the war
- *But:*  
if self-administered humans and animals **crave for it at expenses of other aspects of life**, even though – after several administrations, they do not like it anymore

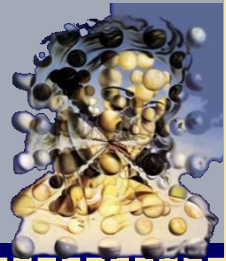
# Reading recommendation

Eitan et al. (2017) doi: 10.1016/j.neubiorev.2017.05.017



# Reading recommendation

<http://www.cedro-uva.org/lib/cohen.empress.html>



“In the field of addiction I know of no neuroscientist who is interested in ‘addicts’. They are interested in the brain and in as far as they study brains or brain tissue they study mice and rats. The labor rats are willing to do to procure drugs under different circumstances is taken as valid information about ‘addiction’ and human brains.”

*Cohen, J. (2009)*

*The naked empress –  
Modern neuroscience and the concept of addiction*

# Opiates/narcotics (3)

## Example: Heroin

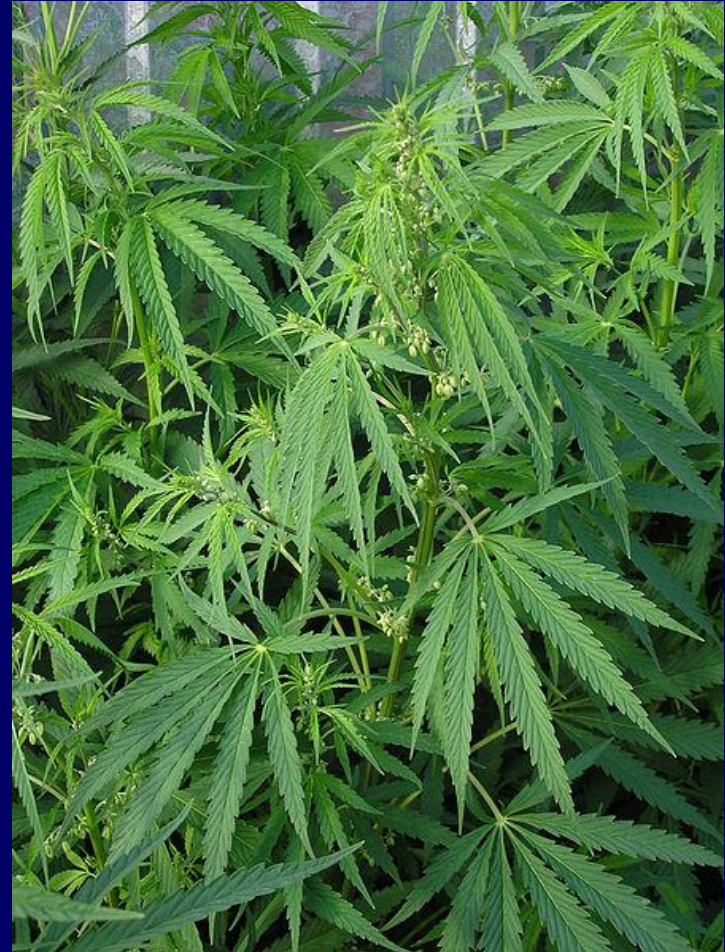
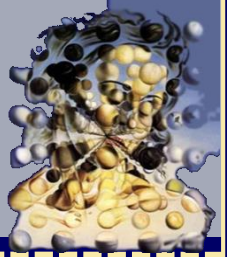


- Lethal dosage (in 50% of cases):
  - 1-5mg/kg body weight
  - = 60-300mg for 65kg person
  - $\cong$  2g of pure opium
- Metabolism:  
heroin  $\rightarrow$  6MAM (6min)  $\rightarrow$  morphine (25min)
- Fat-soluble:  
crosses brain blood barrier more quickly than morphine
- Rapid development of tolerance and severe withdrawal





# LSD 人工致幻剂 & Cannabis 大麻





# Hallucinogenes (1)



- Variety of drugs that are “mind-altering”
- Except for PHP: no voluntary administration in animals
- Concrete example: LSD
  - Very potent: 50µg/kg body weight enough for an effect
  - Effects
    - Changed perception: amusing or threatening depending on the context
    - Hallucinations
    - Synesthesia = crossing of sensory stimuli (e.g. “touching sound”)
    - Anxiety, panic, paranoia
    - Different view of the self



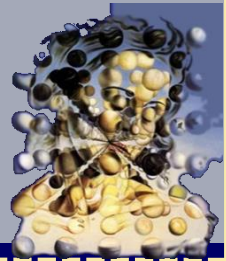
# Hallucinogenes (2)



- Concrete example: cannabis (THC)
  - Very fat-soluble: works for a long time
  - Little tolerance and little withdrawal (still under debate)
  - Long-term effects on memory and concentration (if smoked excessively)
  - Effects: being “stoned”
    - Increased appetite
    - Mild euphoria
    - Loosening of associations
    - Increased sex drive
    - Cognitive impairment
    - Anxiety, panic attacks, paranoia



# World Drug Report



## United Nations

<http://www.unodc.org/wdr2016/>

[http://www.unodc.org/doc/wdr2016/WORLD\\_DRUG\\_REPORT\\_2016\\_web.pdf](http://www.unodc.org/doc/wdr2016/WORLD_DRUG_REPORT_2016_web.pdf)

## Alternative drug report by “Count the costs”

<http://www.countthecosts.org/sites/default/files/AWDR-exec-summary.pdf>

# Withdrawal heuristics



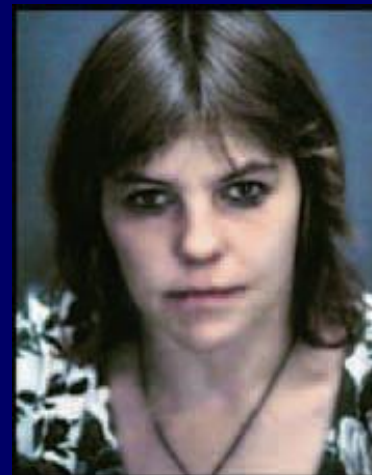
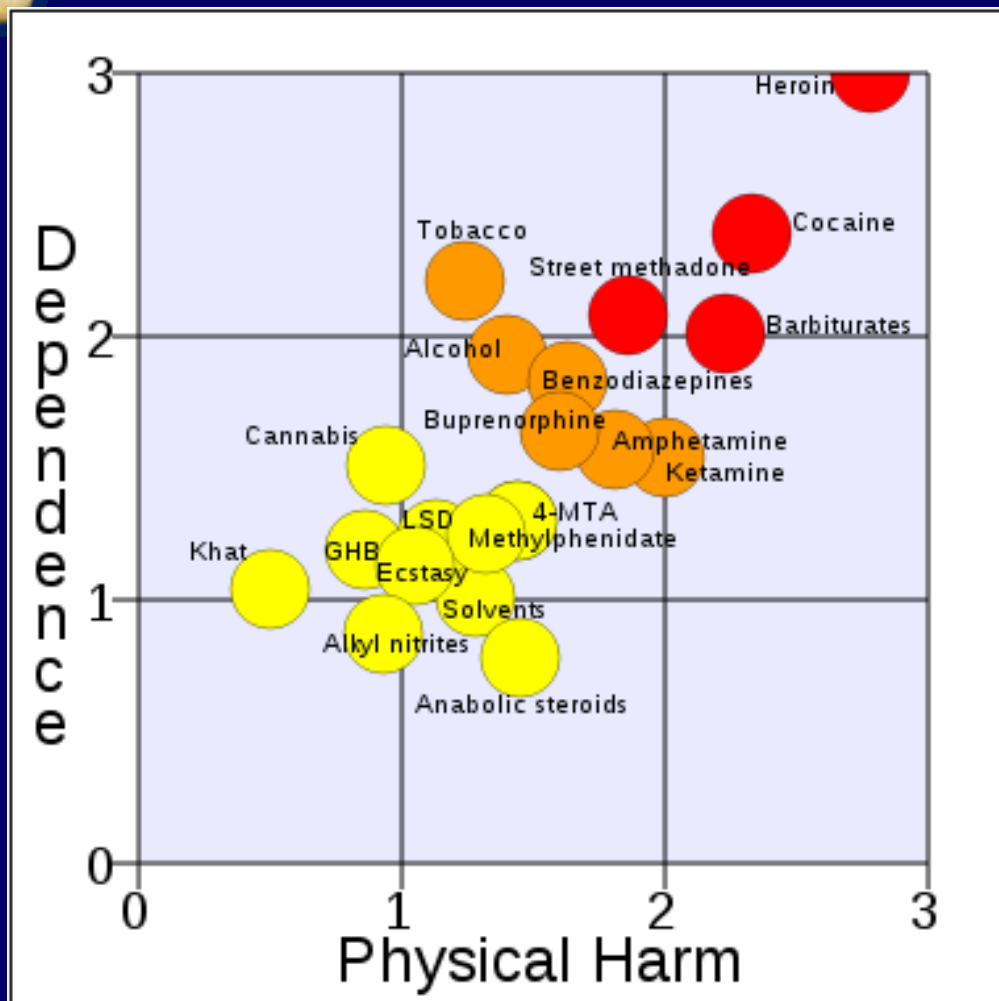
- Withdrawal effects are usually the opposite of the effects after administration, e.g. opiates:

Administration	Withdrawal
hypothermia	hyperthermia
constipation	diarrhea
euphoria	depression
relaxation	sleeplessness

- Overdose effects occur relatively seldom, most lethal incidents are effects of **mixing different kind of drugs**.

# Harm of drugs by type

## Nutt, et al. (2007)





# VIPs with substance-related problems

