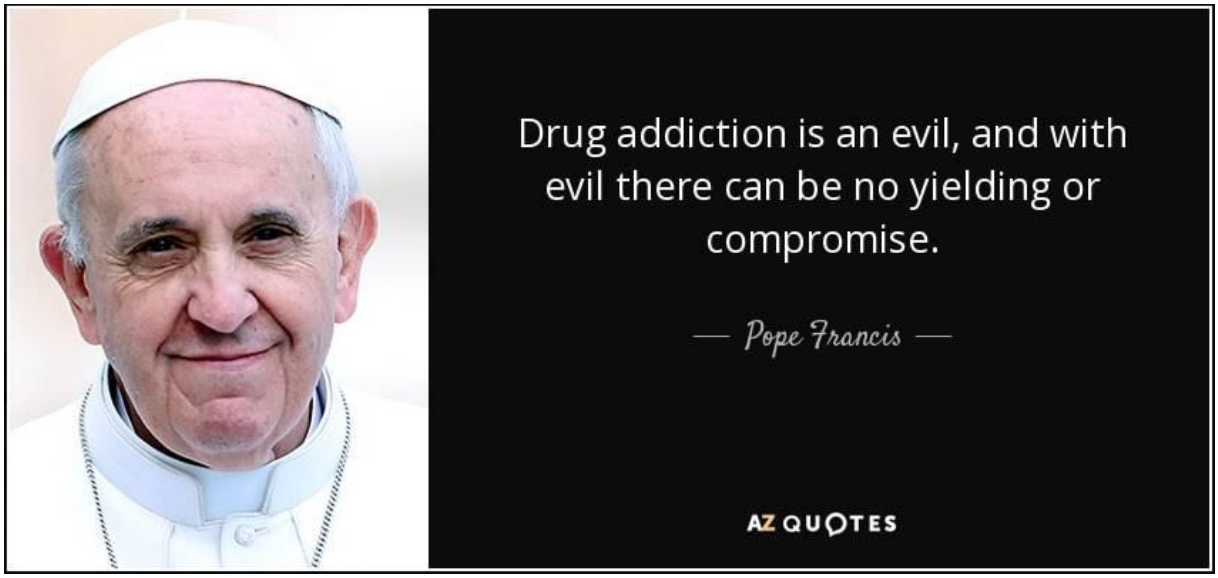
Drug-related deaths in the United Kingdom

Horst Josef Koch

Table of contents



Source: http://www.azquotes.com/quote/916667. accessed 20.06.2018

List of tables

List of figures

Abstract

The dissertation summarizes the drug-related death phenomenon in the UK emphasizing England and Wales and compares the figures with international development, particularly in the EU. Legal regulation, in particular the Misuse of Drugs Act of 1971 and its amendments strive for classifying drugs and label illicit drugs or their exceptional use. Moreover, legislation gives us a bundle of measures to investigate drugs misuse and especially drug-related deaths, allocating the duties of the police, coroner and judiciary.

Opiates, especially heroin, cocaine and stimulants are still the major drugs involved in the UK, which largely – with the exception of cocaine – reflects the situation on the continent. The distribution of age of death shows a tendency from the range of 20 to 30 years towards men in their forties during the last decades. Overall, the UK, Scandinavia and the Baltic states have leading numbers drug-related deaths. New Psychoactive Substances are a new challenge in Europe but the UK may be especially affected by this unfortunate wave. All authorities world-wide have to deal with this "hydra" of new psychoactive substances (NPS) due to infinite chemical variations and unlimited supply. Nevertheless, heroin and cocaine still belong to the most noxious drugs with regard to the fatal outcome.

The problem of drug-related deaths starts with the neurobiology of addiction including cerebral reward cycles which disinhibit prefrontal control, leading to craving and drug intake, even if severe somatic damage occurred. This fatal course does not depend on a particular drug but may be concerned as the final part the fatal reward pathway. In general, noradrenalin, serotonin and dopamine are involved, although some drugs may act on specific receptors such as

opiates or cannabinoids. Unfortunately, the pharmacology of the NPSs is often not well known, and this lack of information will increase the risk of drug-related deaths or delinquency in future.

Autonomy, paternalism and liberty form a field of tension in democracy, so that preventive measures must respect individual rights. Restrictive strategies alone show a limited success. It will be the concerted action of law, judiciary, police, science, educators, social work and medicine among others to strengthen future generations. We struggle hard against drugs and the sequelae but we should never give up.

1 Introduction

In August 2017 the BBC reported on the serious drug problem in England and Wales: "Drug deaths: Cocaine contributes to record number".[1] The BBC cited data of the ONS (Office for National Statistics) and stated that 3.774 people died due to use of legal and illegal drugs, which was the highest death rate since 1993. 371 died following use of cocaine, corresponding to a rise of 16%. Surprisingly, the major affected age groups were men between an age of 30 and 49 years. The authors suggested that the quality ("purity") of street drugs has improved in combination with the foundation of "shooting galleries" [or "crack houses"] – meeting points – and the recent promotion of the "Legal Highs" could be responsible for the evil development. New Psychoactive Substances (NPS) and fentanyl as well as hepatotoxic paracetamol were also increasingly involved in drug deaths, heroin or morphine being still on top of the list with 1.209 deaths in 2016. The article postulated treatment as the approach of choice and rejected criminalization of the persons affected.

The problem is not only virulent in the UK, but a world-wide issue, which is going to deprive a generation of their future. Nobody has the "magic pill" to solve the problem. However, it is worth thinking about the problem, discussing it with experts, offer treatments, and what is most important, never giving up to save lives. I hope that the following work mediates an idea of the problem and supports our mutual efforts to stop this awful trend.

2 Definitions and Epidemiology

Drug-related deaths are defined are deaths for which illicit drug use is the major underlying cause, although the definition may vary in the scientific literature. We talk about deaths which can be in drug misusers, addicted, suicides,

homicide, accidents and so on.[2,3] We are aware of the fact that some cases may be overseen due to uncertainities of the death certificate, but the data of the UK in comparison international data gives us an idea to cope with problem and if possible helps us to make adequate medical and political decisions. The relation between drug and death may be irrational (e.g. intoxication) or rational due to the medical use (e. g. chemotherapy, HAART). The compound may be legal (prescription, OTC, glue or thinners) or illicit (e.g. heroine, crocodile), may be taken deliberately (suicide) or accidentally (e. g. due to false dose or compound).

In a specific statistics Public Health England (2016) analyzed trend of drug related deaths between 1993 and 2004.[4] They found a tremendous increase in mortality with a peak in 2000 (summed up: 6101 men and 2055 women). Most deaths were related to drug abuse or dependence (m 48.1% or f 31.0%) and accidental poisoning (m 34.9 or f 28.9 %). Interestingly, self-poisoning was more frequent in women (22.5 %) than in men (7.5 %). In this paper the most inflicted group were men between 25 and 39 years old, but a trend to "older" age groups was already vaguely perceptible during this period. The authors calculated the Years of Life lost (YLL) before 55 years, this number increased from 11.7 to 18.9 years in men, and from 2.6 to 4.4 years in women which quite alarming. The following drugs topped the list in males: Heroin/morphine (48 %), methadone (22 %), benzodiazepines (15 %), opiates (9) and cocaine (6) with more than 700 deaths each.

The ONS (Office for National Statistics) statistics includes legal and illegal drugs – not alcohol - and recorded an increase predominantly for males aged 40 to 49 of mostly accidental deaths during the last decade in England and Wales (Fig. 1).[1] The changes were relatively constant, the rate of deaths even decreased in those aged 20 to 29 years. In 2017 (table 1) opiates (n=2038) were

the leading problem followed by benzodiazepines (n=406) and antidepressants (n=406), cocaine (n=371) or amphetamines (n=160). What is remarkable in comparison with the above study: Those dying from drug-related deaths are getting older! Could it be that preventive measures are of use in the younger generation?

Moreover, the increase of deaths due to NPS (new psychoactive substances) from 55 to 123 deaths between 2012 and 2016 is a worrying world-wide development, which did not play such a relevant role in 1990ies.

Drug related deaths are for sure a leading challenge for the country also in relation to EU-partners. What is astonishing – for me as a psychiatrist – is the high rate of deaths due to antidepressants, as modern compounds (SSRIs) should be safer than tricyclics in former times. Moreover the high numbers of deaths with regard to benzodiazepines let suspect combinations of drugs. Also cocaine, an "old stuff", obviously “celebrates” some kind of a bad revival.

The corresponding death rates of Scotland and Northern-Ireland are given in Tables 2 and 3 as well as in figure 2. We realize a substantial increase of deaths between 2006 and 2016 in Scotland. Opiates also dominate in these parts of the country, and deaths due to cocaine rise, too, although not as marked as in England and Wales. However, antidepressants, NPSs and particularly benzodiazepine derivates become more and more important. Particularly, etizolam has gained importance during the last years. Interestingly, the deaths due to paracetamol – low therapeutic index! – could be almost eliminated in Northern-Ireland.

In order to have some kind of external control, I compare the British data with those of the 3 equivalent countries: Germany, France and Italy. The European drug report 2017 allows us a comparative view on drug data.[5]

- In the **UK** we have **11.3** % users of cannabis aged 16-34 years, cocaine comes to 4 %, MDMA to 3 % and amphetamines to 0.9 %. High-risk opiate users (heroin) total up to **330446** users.

- In **Germany** – alike population – we find **13.3** % cannabis users, amphetamine 1.9 %, MDMA 1.3 % and cocaine 1.2 %. High risk opiate users total up to **160322**.

- In **France** the cannabis is consumed in **22.1** %, cocaine in 2.4 %, MDMA in 2.3 % and amphetamines in 0.7 %. **211000** users take high-risk opiates.

- In **Italy** the numbers are **19 %** for cannabis, 1.8 % for cocaine, 1 % for MDMA and 0.6 % with regard to amphetamines. **205200** use high risk opiates.

If we include the drug-related death rates in figure 3, it is really astonishing that Germany and the UK "lead" the rates, although the frequency of low risk drug consumers is lower in both countries compared to Italy and France. However, high-risk consumers are highly frequent in the UK. France and the UK, on the other side, offer more substitution treatments (i. e. 168840 and 142085 treatments, respectively) compared to Germany or Italy. We shall try to differentiate this paradoxon in the prevention section.

In table 4 the figures of different countries are summarized. The drug-related death rates of the Baltic States and Scandinavia and Scotland turn out to be ex-

tremely high compared to the average figures of the EU. On the contrary, the death rates in France, Italy or Belgium are apparently much lower than in other countries. What attracts my attention is the low number of death rates in the Netherlands, although the country is known for its liberal drug policy.

3 Legal Aspects

Laws and regulations

Several specific drug laws regulate use or misuse of drugs in the UK e.g. the Misuse of Drugs Act (MDA) in 1971, the Medicines Act in 1968 or the Psychoactive Substance Act in 1976.[6,7] However, other laws (e. g. the Road Traffic Act, Clinical trial regulations, the Medicines Act of 1968 and EU drug regulations, patent laws, the Children and Young Person Act of 1933) may have an influence on the use of drugs. The MDA classifies - and restricts possession, commerce and regulates penalties - the compounds according to 3 groups:

Class A compounds are dangerous (e. g. cocaine or MDMA, mushrooms, injected Class B drugs),

Class B compounds such as amphetamine, cannabis or codeine are legal for certain purposes (amphetamine - ADHS, severe pain-cannabis (SativexR, DronabinolR) but also widely used as illegal drugs (amphetamine = speed, cannabis = marihuana), and

Class C drugs which include anabolic steroids or ketamine, even benzodiazepines and liquid ecstasy [used as SomsanitR, a narcotic, in some countries).

The allocations of drugs may vary from time to time and is also influenced by social attitude (e. g. cannabis is now legal for treatment of severe pain in Germany (personal communication). The Temporary Class Drug Order (2011) amended the MDA of 1971 and allowed the Home Secretary to add any dangerous substance (e. g. **NPSs**) transiently to the list in order to keep in step with illegal drug labs. The penalties which can be given for drug offences are summarized in table 5. The legislation may be – in theory – a bit clearer than in Germany. Possession of small amounts of drugs alone, according to my experience, is generally not prosecuted in Germany and the influence of this philosophy remains open. The Netherlands, where cannabis is offered in coffee shops, was and is very attractive for addicted from adjacent countries.

In 2001 a more detailed classification (schedule 1-5) was introduced:
1: no medical use – LSD [except rare experimental trials in psychotherapy in Switzerland, personal communication], opium, psilocybin, coca leafs

2: possession without prescription not allowed- amphetamine, cocaine (sometimes used as local ophthalmological anaesthetic), morphine, methadone

3: prescription necessary – barbiturates, flunitrazepam, temazepam

4: a: minor tranquillizers without prescription
4: b: possession allowed, dealing forbidden: anabolic steroids

5: corresponding to OTC (over the counter) products

Should a product be used for another indication one speaks of "off-label use", which requires a special informed consent (e. g. ketamine nasal spray in depression). Compassionate-use (e. g. thalidomide in a patient with glioblastoma

some years ago – inhibition of vascularisation) is the administration of drugs under development (phases I to III/IV) or not approved drugs. These uses (to the best of the patient) demand a high standard of diligence and comprehensive information. However, unlicensed drugs for children are quite usual and they are of course ethically absolutely indicated.

The Coroner´s and Procurator´s Fiscal duties

The historical difference between the UK and the continent may be reflected by the coroner´s system. Even translation of famous literature (e.g. Jenny Cooper of M R Hall: "The coroner" was changed to "Death certificate - Totenschein") causes problems. The coroner [procurator fiscal in Scotland, PF] is an independent official – about 100 professionals in England and Wales – who has to answer with his staff the question about unexpected deaths – often referred by a doctor – the following questions:
Who is the person?
When, how and where did he/she die?[7]

He/She can start an inquest and order an autopsy, depending on the circum-stances (unnatural death, violence, unknown course, prison etc.). Drug-related deaths are an integral part of his duty. The inquest ["fatal accident inquiry" in Scotland] is done public – in general – and a jury with 7- 11 members may be appointed. In complex cases - mass accidents - the coroner may supported by a special "Identification Commission". The recommendations – not really legal liability since the criminal law act 1977- may lead to a judicial processing and often the verdict of the coroner is confirmed by the judge. In this regard the coroner is part of the CPS (crown prosecution service), but the coroner has also the aim, to prevent similar fatal developments. Although normally restricted to his/her region [the coroners regulation of 2013 allows the coroner to pursue a

case beyond the "borders"], the coroner may also investigate cases from abroad, which is, on the contrary, never done by the procurator fiscal. As a rule, the PF is a lawyer, whereas the coroner could also be a doctor. According to the Coroner´s and Justice Act 2009 the future coroners will be lawyers, only. The PF can, in contrast to the coroner, initiate a legal process on behalf of the Lord Advocate. Moreover, the balance of probabilities leading the coroner´s verdict is the duty of Sheriff (judge) in Scotland and not the primary duty of the PF.

4 Psychology and neurobiology of drug abuse

A lot of drug users are quite young humans, which is a tragedy, as brains in a developmental state are very susceptible for chronic harm of the brain and therefore future cognitive impairment. In adolescence especially boys have the feeling of "sensations seeking" on the one side, and boredom on the other side.[8] They look for some kind of thrill and new experiences and have difficulties to fill the time with reasonable activities. Some dysbalance of neurotransmitters, particularly noradrenaline, may be responsible. The PFC (prefrontal cortex) is not yet fully developed at an early age – integrative center with responsibility for executive foresightful thinking - and therefore teenagers, particularly lads, are not able to fully control their motivation. This age, however, is the time in which most of the addicts start.[9] In addition, the reward system, i.e. including the Ncl. accumbens, plays a major role especially for young adults with regard to risk behavior.[10]

In modern neurobiological hypotheses dopamine in the limbic regions, particularly in the Ncl. accumbens (Nac) and the ventral tegmental area (VTA) is an important issue. The following connections are relevant for the addiction process:[11, 12, 13, 14]

- Stimulants directly inhibit re-uptake of dopamine in the Ncl. accumbens (Nac) (and also in the Amygdala),
- opiates activate via interneurons the Nac, Amygdala and VTA (ventral tegmental area), the latter facilitates release of dopamine in the Nac
- alcohol acts via GABAa on the VTA, the Nac and the Amygdala, leading to release of dopamine (note: it also said to facilitate secretion of opioidergic peptides in these regions) [note: Opiate-antagonists such as naltrexone reduce craving in alcoholism]
- nicotine activates Ach-receptors in the VTA, the Nac and the Amygdala, and possibly also release of opioidergic peptides
- THC activates CB1-receptors in the VTA the Nac and the Amgydala and facilitates secretion of dopamine

Dopamine facilitates the motivation to seek the anticipated reward and conditional learning, e.g. the salience of special trigger factors or environments. In case of addiction, these mechanisms cause long-term habituation of the dopamine effect, longer than they do after natural positive stimulations -e. g. moments of happiness-, which also need lower concentrations of dopamine. If this is the case, some kind fatal addiction circle – *craving* →*binging* → *withdrawal* →*conditional response* - is initiated. The most important structures involved in this neurocircuit are given in Figure 4. One distinguishes 3 separate stages of addiction:[14]

- Preoccupation/anticipation: The PFC (prefrontal cortex) is impaired, glutamate concentrations increase, and impulsive craving behavior is facilitated as the PFC does not "stop" sufficiently impulses

- Withdrawal/negative affect: Stress neurotransmitters are activated (Corticotropin, dynorphin) in the Amygdala. The addicted longs for the drug to get rid of the negative feelings

- Binge/intoxication stage: The reward circuit (Nac) with dopamine and endogenous opiates is upregulated and triggers craving and substance seeking.

This model explains the effects of alcohol and other drugs on the brain and useful to understand that the addicted has a lot difficulties to withstand further intake of the drug.

5 Toxicology and Drug-effect relation

In order to classify the risk potential of a drug, several measures have been introduced.[15] The LD50, i. e. the dose which leads to death in 50% of the animals (or analogously the ED50, i. e. the dose where 50 % of a population come at a wished effect) has been a popular measure to characterize the dose-mortality-relation of a drug in animal tests. Table 6 gives us a hint that intoxications with diazepam or THC may be less dangerous than heroine or even nicotine. The principle of the method to determine the LD50 is shown in figure 5 using clinical routine data of extrapyramidal side effects of antipsychotics. The ED50 informs us about the dose which provokes a specific wished event. The OECD (OECD guidelines) has classified acute oral toxicity of compounds based on LD50 values as follows:[16]
LD50 <=25mg/kg – very toxic,
LD50 26 mg/kg <= 200 mg/kg – toxic,
LD50 201 mg/kg <=2000, and
LD50 > 200 mg/kg – unclassified

We are aware that illegal drugs may be very toxic indeed, especially if no data are available such as in NPSs. Meanwhile, the acute toxic class method - or alternatives- has replaced LD50 classification, as the sequential testing methods reduce the number of animals in the EU and USA.[17]

In clinical terms, the ratio ED50/TD50 (TI, therapeutic index) is used as a measure of drug safety in practice.[15] E. g. the ED50 for morphine (pain) is roughly 10 mg, the TD50 for respiratory depression is 60 mg (for human, 70 kg), corresponding to a TI of 6, which is quite acceptable. Many more characteristics have been introduced in clinical toxicology - especially for long-term use - e. g. NOEL, NOEC which characterize toxicity of chronic and subchronic administration but are beyond the scope of the dissertation.[18] Table 6 summarizes some LD50-values to get a "feeling" for the toxicity of some compounds.[19]

Lachenmeyer et al. used the MOE approach (margin of exposure) – European research project - to assess the risk of a drug, which is not identical to toxicity.[20] Briefly, the method uses toxicological threshold doses in relation to (supposed) human intake rates and integrates animal MLDs (mean lethal doses) in a Monte-Carlo model. High risk drugs for individual users are alcohol, cocaine, nicotine and heroine, "mean" risk drugs are stimulants, opiates or benzodiazepines. Cannabis was assessed as a low risk drug. Alcohol and nicotine have a tremendous prevalence indeed. In other words, the overall predominant risk for a citizen to die from a drug remains very high for alcohol and nicotine.

6 Pharmacokinetics – routes of administration

As a clinician I see every – even peculiar – ways to administer illicit drugs (via urethra e. g) including abstruse methods to hide the intake, exchange of urine

or passports. The coroner and toxicologist need a lot of imagination to distangle the way of drug consumption.

Three ways are rather common: oral intake, intravenous injection and inhalation.[21,22] Sometimes, subcutaneous/intramuscular administration or from time to time rectal and nasal spray applications, and - as an exception- transdermal systems (e. g. fentanyl) are used by consumers. LADME (Liberation, Absorption, Distribution, Metabolism, Elimination) is the acronym, which is important to understand how the drug reaches body compartments to become effective. Liberation means that the formulation must be disintegrated before it can be absorbed. The extreme variant is body packing (or stuffing), in which the drug (e. g. cocaine from South America) is – deliberately - not set free. No liberation, no drug in the body. But this may be a fatal deception for the "bodystuffer", if the container rips.

Absorption then can take place depending on the site and physicochemical properties of the stuff. Intravenous administration may be an exemption, as the drug directly enters the blood compartment. Very rapid absorption is observed after inhalation (e. g. THC joints) or nasal (e. g. ketamine) administration with latencies of some minutes. After oral or rectal (or vaginal) application 30 to 60 minutes may be a rule of thumb until the effect starts. However, liposolubility or pk-values (acid-base-property) can alter absorption dramatically. KCN (potassium cyanide) is lethal (HCN!) within minutes in acidic stomach, but not in case of anacidity as potash lye (KOH) is formed.

Distribution depends very much on liposolubility. A good example is cannabis which can be distributed into fat tissue from which it can be released for several months onward. A clinical example is diazepam, which is re-distributed in

fat tissue after intravenous injection causing a very short fictive half-life of 10 to 20 minutes.

Metabolism depends on the structure of the molecule (e.g. N2-groups, -SH-groups, OH-groups) or whether specific enzymes exist.[23] Phase I metabolism adds such functional groups. Phase II reactions often bind endogenous substrates (conjugates) to the polar compounds such as glucuronic acid, sulfuric acid or acetic acid, in order to accelerate elimination. Phase I reactions are often mediated via Cytochrome P450 isoenzymes (e. g. 2D6, 3A4 etc.) which can be induced or inhibited. A practical example was a man taking oxycodone who also obtained paroxetine with an overwhelming effect. Due to inhibition of 2D6 due to paroxetine the oxycodone concentration increased up to toxic levels. Such interactions can be fatal and it is important to ask anybody whether he is taking illicit drugs as well (personal experience).

Alcohol (in normal doses) is degraded by the ADH via a linear zero-order kinetics, however, MEOS (microsomal ethanol oxidizing system) can be induced following chronic abuse. Other compounds such as THC are hydroxylated, glucuronidated or carboxylated usually following Michael-Menton kinetics. Some metabolites are active, others are inactive.[24] Sometimes prodrugs must be metabolized to become active; a relevant example may be codein, which has to be demethylated to morphine. One metabolism is clinically extremely important: the combination of alcohol and cocaine. The metabolite cocaethylene is highly toxic with lethality rate some 20 times increased compared to cocaine and leads to seizures and liver damage.[25]

Elimination is the final process to excrete the compound from the body.[24] The kidney may be the most important organ, but exhalation via the lungs, excretion via bile or feces, even via skin (sweat, hair) or salivary may suitable for

diagnostic of illegal drugs. Excretion often follows an exponential decrease (first order kinetics), so that half-life can characterize excretion, i.e. after 5 half-lives the drug may be roughly considered as eliminated. Of course, physicochemical properties are substantial especially for renal excretion: Acids such as barbiturates are better excreted in alkaline environment and, vice versa, amphetamines are better excreted in acidic milieu. In Table 7 basic metabolic and kinetic data of some drugs are summarized.

7 Some notes concerning drug detection

A very simple test for drugs is the DrugWipe-Test, which detects cannabis, cocaine, opiates and amphetamine derivatives in saliva or sweat.[26] It is based on an antibody-antigen (drug) reaction. A analogous mechanism characterize drug screening tests in urine, which in general also include barbiturates and sometimes PCB.[27] With regard to alcohol the breath test is in use since the 1950ies and was developed by Mr. Borkenstein, a police captain from Indiana.[28] The principle has remained the same, i. e. the degradation of potassium dichromate K2Cr2O7- measured via a spectrophotometer - correlates with the amount of alcohol, which is itself oxidized to acetic acid (HAc). Many color tests exist (for cocaine, stimulants, barbiturates, Marquis-test for opiates, van Urks test for psilocybin and psilocin), which could be completed by thin-layer chromatography, gas chromatography or UV-spectroscopy and IR-spectroscopy. Very sophisticated procedures are the Gaschromatography-Mass spectroscopy (GC/MS) or the HPLC (high pressure liquid chromatography for real quantitative analysis.[28,29] The toxicologist has an arsenal of methods to support the forensic team.

Some pitfalls can nevertheless arise. After intake of THC the metabolite 9-carboxy-THC is relevant in urine, not the mother compound. Heroin is rapidly

metabolized to monoacetyl-mophine and morphine, therefore heroin disappears quickly. So both metabolites prove the intake of morphine. In case of doubt, vitreous humor can be analyzed, where monoacetyl-mophine is degraded remarkably slower.[28] For particular purposes drugs can be looked for in stomach, organs (e. g. talc crystals or cotton fibers after use of heroin), bile, stool, hair (time of intake can be estimated), intraocular fluid or even in insects or their maggots.

Very important is to consider – on duty - the short half-life of "liquid ecstacy" (GHB gamma-OH-butyric acid).[27,30] After 12-24 hours the samples were 100 % below the limit of detection. The samples (plasma, urine) should be collected as soon as possible, as the drug is metabolized an intruded into the Krebs-cycle. Perhaps a glucuronide may improve – will be longer detectable- the analysis in future.[31] As it paramount importance, some critical detection limits in urine drug screening tests, the following paragraphs gives us the approximate latencies for some frequent drugs in urine tests.[27]

- Amphetamines 2-5 days, Methamphetamine 5-7 days
- Ecstacy 5-7 days
- Barbiturates 3-4 weeks (long acting compounds)
- Benzodiazepines 7-10 days (midazolam 0.5 days!)
- Cannabinoides 5-60 days (the detection latency increases with time of use. 5 days after single use, up 60 days after 6 weeks daily use)
- Cocaine 1-4 days (metabolites)
- PCP (phencyclidine) 2-4 days
- LSD 7-10 days
- Ketamine 5-7 days

We learn from this simple data to take urine as soon as possible without hesitation in the emergency room - when feasible.

8 Drugs and Mechanisms of Action

Opiates

Opiates such heroin or morphine bind to classical opioid receptors on the surface of cells (e. g. CNS and spinal neurons, smooth muscle) μ [exactly: μ1 presynaptical and μ2 postsynaptical], δ and κ [note: recently also orphan receptors and ε-receptors have been found].[32,33] The binding on receptor site is followed by an activation of pathway (cascade) including Gi-proteins ("transducer) and cAMP (inhibition of adenylate cyclase) or ion channels and neurotransmitters. All receptors reduce calcium currents and μ-receptors increase additionally potassium current. Physical addiction is predominantly mediated via μ-receptors and to a lesser extent via κ-receptors. Tolerance is an important issue as especially the central euphoric effect needs increasing doses of an opiate to maintain a constant effect. A δ-receptor-agonist would be a relatively selective analgesic, which unfortunately does not yet exist. However, noscapine (used as an antitussive) lacks activation of μ-receptors.
Heroine is very dangerous with an extremely high toxicity and addiction potential. It is rapidly metabolized to 6-mono-acetylmorphine and morphine and some other metabolites. Usual doses are 75-200 mg, but deaths were already observed with 10 mg (in drug-naive persons). Therapeutic doses - in special substitution programs - start with 5 mg.[34] The user pays about 50 Euro per g heroine (middle quality of brown heroine). White heroine may be more expensive (personal information). As in general young people with low or even no income are affected by drug dependence, this fact may warrant special programs to reduce concomitant life threatening risks such as HIV or promiscuity.

In routine clinical use many patients benefit from the analgesic or antitussive effect, sedation, reduction of gut peristalsis in case of diarrhea or even improvement of dyspnea in palliative care. However, respiratory failure in overdose is life-threatening which needs immediate ventilation or administration of naloxone (non-selective, competitive antagonist; note: repeated doses may be necessary due different half-lives). Withdrawal can cause vital complications due to the excessive secretion noradrenaline and may require sedation and/or clonidine. It is important to know that naïve patients and drug users a quite different. To illustrate this: a patient with pain needs buprenorphine in a dose of 0.2 mg sl. However, drug addicted get 2 to 4 mg, even up to 24 mg per day.[35] It can be dangerous to dose naïve patients with doses adequate for chronic consumers. Harold Shipman used high doses of heroine – in addition to other opioids - to kill his patients, which is 2 to 3 times more potent with the regard to morphine and especially dangerous when applied intravenously. Even 30 mg iv – starting doses are 2.5 or 5 mg per os – can be lethal. However, the detection of opioids in the buried corpses was a real challenge.[36]

Major toxicological risks: respiratory depression, overdose in drug naïve patients

Stimulants

Amphetamines and derivatives including modern designer drugs act via secretion of neurotransmitters such as noradrenaline, serotonine or dopamine.[37] They antagonize tiredness, cause euphoria or improve self-confidence ("uppers or pushers") and reduce appetite. Some derivatives are in clinical use for obesity, narcolepsia or ADHS (e. g. methylphenidate or dexamphetamin). Although small doses of "speed" or similar drugs do not cause a serious toxicological problem – apart from psychosis, which occurs in up to 30% of users -, high

doses ("binges") can result in life threatening cardiovascular sequelae such as arrhythmia, especially in non-adapted users.[38] Doses of 100 mg up to 1000 and more – therapeutic doses of dexamphetamine for narcolepsia or ADHS are 2.5 to largely 20 mg! - can be considered as dangerous, particularly when given iv.

Withdrawal symptoms (predominantly psychic addiction) are generally mild but long-term use can lead to depravation and social decline. Indirect vital threats are hypoglycemia or exsiccosis due to somatic exhaustion. One should not forget the risk of depression after cessation of stimulant effects which increase the risk of suicide. An important drug interaction is the combination with SSRIs or MAOIs, as both classes of drugs may increase the serotonin level in the synaptic cleft.
Major toxicological risk: Psychosis including associated accidents, depression after cessation, serotonin syndrome.

Ecstacy

Ecstacy (MDMA) and other amphetamine-related designer drugs affect particularly serotonine and noradrenaline secretion, which explains their hallucinogenic properties ("entactogen, empathogen"). It was already synthetisized in 1922, when a local hemostyptic was looked for.[38] Since the 60ies it has become more popular and a common rave drugs in young people. In "normal" doses of 50 to 200 mg hyperthermia, exsiccosis and sometimes aggression are the most important side effects.[39] However, higher doses and impurities can also lead to fatal heart failure or arrhythmia. One should not forget that combination with drugs elevating serotonin (such as SSRIs or Monoaminooxidase inhibitors, even opiates such as tramadol) can cause serious serotonin syndromes.
Major toxicological risks: exsiccosis, hyperthermia, hypertension, interaction, serotonin syndrome

Cocaine

Cocaine also possesses stimulant effects but is chemically and pharmacologically different from amphetamine.[38] Cocaine predominantly inhibits reuptake of catecholamines and has local anaesthetic effects similar to procaine (blocks Na+-channels). Already 50 mg systemically applied can cause epileptic fits or respiratory failure. Bad adverse events due to its constrictive properties are nasal necroses, stroke and heart attacks even in young people. The addictive potency is quite higher compared to other stimulants, notably for crack (cocaine plus baking powder). Chronic use leads to depravation, social decline, change of personality or even psychosis.

Renal failure, rhabdomyolysis, liver impairment or even cardiovascular crises including arrhythmia often require ICU treatment. Lethal oral doses for beginners are approximately 0.5 to 1.3 mg per day, chronic users may tolerate daily intakes up to 5 mg.[40] The price for the addict is approximately 90 Euro per gram (personal information).

Withdrawal is much more severe compared to amphetamines including tachycardia, exhaustion, transpiration or psychosis as well as depression with increased rates of suicide.
Major toxicological risks: drug-induced psychosis, heart failure, stroke, septum necrosis, withdrawal, psychosis

Cannabis (Cannabinoids)

The major active compound in cannabis (Cannabis sativa, hemp) preparations is tetrahydrocannabinol (TCH). Usually, hashish derives from the resin of fe-

male blossom and contains 2 -10 % THC, marihuana from dried blossoms ("gras") and contains up to 30% of THC.[41,42] THC (and endogen agonists such as anandamide) can stimulate cannabinoid receptors - CB1, CB2-, CB1 affecting mainly the nervous system and CB2 the immune system.

CB1 stimulation increases Ca-channel activity influencing associative learning and neuronal plasticity. The minimal dose of THC in normal "use" is about 5 mg, a cigarette ("joint") may have about 1g marihuana containing 25 mg of THC with an absorption of 60% .[42] Cannabis is not harmless. 2g injected iv in 70 kg person can be lethal.

Agonists have been developed, such as rimonabant for overweight or addiction [no longer on the market], SativexR spray (THC and cannabidiol; usual dose: one puff contains 2.7 mg THC and 2.5 mg Cannabidiol, maximum: 12 puffs per day, expert information), which alleviates spasticity in patients with multiple sclerosis, or dronabinolR (THC solution) in the treatment of severe pain (normal dose 2.5 to 15 mg, maximum about 50 mg).[43]

"Spice" contains synthetic cannabinoids which bind to the CB-receptors; examples are JWH-019 or JWH 073 (note: JWH stands for J. W. Huffman, the inventor of the chemicals, sometimes allocated to the NPSs) and were sold as incense material.[44] However, spice preparations (mixture of cannabinoid agonists) were forbidden in the UK in 2009 and – due to the number of alternatives - the government initiated the Psychoactive Substance Act in 2016, which bans all spice variations.

The effect of the cannabinoids depends very much on personal factors and emotions.[45] The drug can be smoked (joints) or taken orally (tea, cookies). Rare but dangerous is the intravenous administration of a cannabis broth which

leads to the serious "intravenous marihuana syndrome" with fever, myalgia, nausea and vomiting.[46] Inhalation is effective within minutes and lasts up to 5 hours, after oral intake the effect is delayed. The users feel relaxation, well-being, euphoria, altered perception as well as a altered sensation of time and slight tachycardia, conjunctivitis, slurred speech and ataxia or nystagmus. After chronic use an amotivational syndrome with self-neglect provokes social decline. Although the toxicity is low and withdrawal syndromes are mild, schizophrenia-like severe psychosis may occur in chronic users and drug-induced hubris may be fatal; the drug also facilitates a switch to "hard" drugs, although the majority of the users will not switch. Moreover "bad trips" or flashbacks (even weeks after intake) may impend. What should never be forgotten: Smoking risks of joints do not differ from cigarettes and likewise the unborn child can be affected.[45]

Major toxicological risks: psychosis and faulty actions, high intravenous doses can cause renal failure, switch to "hard" drugs.

Hallucinogens

Hallucinogens are a heterogeneous group of compounds, often phytotoxins from plants, which more or less facilitate serotonin effects.[47] The most known representatives are LSD (claviceps purpara), mescalin (ingredient of cactus), psilocybin (fly aminita) or phencyclidin (PCP, synthesized from ketamine, a NMDA-receptor blocking narcotic, some, see below). The initial effects are vertigo, palpitation, mydriasis or tremor. Then affect may sway up and down and is followed by predominant visual hallucination with intensive perception of colour, hubris and loss of reality. Flashbacks can be very inconvenient. "Normal" doses of LSD (formerly DelysidR from Sandoz) are 20 to 200 mg, the effect starting 2-3 hours after oral administration. The half-life is about 2.6

hours, the effect lasts up 8 hours with a 100 mg dose. Although it has a low addiction potential, action slips are a real - even vital- danger.[48]
Major toxicological risks: faulty actions due schizophrenia-like psychopathology

Sedatives and Hypnotics

Sedative or hypnotic drugs are a heterogeneous group used clinically widely to facilitate sleep, to calm down ("downers"), to reduce excitation, muscle spasms or withdrawal symptoms. Some of these drugs play a major role in anesthesia or as antiepileptics (e. g. clonazepam or primidone).

Benzodiazepines

The most popular group of sedatives are the benzodiazepines which on the market since the early 60ies. They affect the GABA-chloride-channel-complex - influx and hyperpolarisation - leading to a reduced excitability of neurons.[49]

There are compounds with very short HL (midazolam, 2-3 hs, active metabolite), mean HL (lorazepam, 10-20 hs, no active metabolite, dose 1 to 4 mg per day) or long HL (diazepam ,up to 100 hs!, including active metabolites, dose 5 to 30 mg per day). Common side-effects are dizziness, coordination problems, addiction or ataxia (risk of falls). However, toxicologically they are considered as relatively safe, although respiration failure, especially when combined with drugs or alcohol may cause vitally dangerous complications. Fortunately, the effect of benzodiazepines can be antagonized by flumazenil (0.5 to 1 mg initially, but the half-life of 40 to 80 minutes may shorter than that of the benzo-

diazepine). The withdrawal can cause delirium and must be done very slowly over weeks due to the risk of fits.
Major toxicological risks: accidents, respiratory failure, withdrawal fits

Barbiturates

Barbiturates were popular before the benzodiazepine era in 1960ies. They – like the benzodiazepines – bind to the GABAa-receptor but another site of the complex. In higher doses they cause coma and respiratory failure, which make them extremely dangerous in contrast to benzodiazepines. Occasionally, one can observe barbiturate blisters (personal experience). ICU-treatment is generally necessary to warrant ventilation; moreover, forced alkaline diuresis – barbiturates are derivatives of the barbituric acid – promotes renal excretion of barbiturates. Therefore, they are no longer used as sedatives but derivatives such as thiopental and methohexital or phenobarbital (approximately oral dose of 30 to 200 mg per day) fulfill a purpose in anesthesia or as antiepileptics, respectively.[49,50] The lethal dose may be 2 to 10 g, but is much lower in combination with alcohol.[51]
Withdrawal can be complicated by vomitus, collapses or vegetative reactions or even delirium and fits. Therefore, the dose must be tapered carefully.
Major toxicological risks: respiratory failure, hypotonia, withdrawal, alcohol interaction

Planttoxins and fungal toxins

A plenty of plants or mushrooms are used from time to time from addicted, may be accidental or deliberately. Some of them have quite regularly relevance in clinical toxicology, although "general unkown diagnostics" is necessary.[52]
Popular plants are the angel trumpet, belladonna, henbane or mad apple. They

exert an atropine-like effect such as atropine itself (LD50 90 mg after iv-administration in mice[19]; already 10 berries of banewort may be fatal!) or scopolamine, leading to tachycardia, mydriasis, urinary retention, hyperthermia, hallucinations or delirium. Physostigmin may be an adequate antidote for such emergencies. Cardiac problems can be a vital threat as could be hyperthermia. Fatal accidents or self-mutilation can occur. There is no clear dose-response-relationship which make the toxic effects hardly predictable.

Chronic use can lead to some kind of dependence relatively mild withdrawal symptoms such as nausea, vomitus or transpiration.
Major toxicological risks: hyperthermia, cardiac problems, accidents due to delirium.

The toxicological "mirror image" of atropine-like drugs are inhibitors of the cholinesterase or agonists of acetylcholine such as muscarin, physostigmin or arecolin. Such alkaloids are found e. g. in betel nuts or calabar bean. Here, atropine is the usual antidote. Such intoxications, however, may be fortunately very rare.

Thinners and sniffers (volatile compounds)

Simple and complex hydrocarbons such as benzene, acetone, butane or xylene, toluol, amylnitrite ("Poppers") and chloroform are widely available. The compounds are used in the industry (clue, solvents, petrol, nail varnish remover, propellants etc.) and comparably cheap [personal experience: sniffing teenagers in Sao Paulo is a catastrophy]. They can be inhaled from bags with the fluid or just from a cloth soaked with the thinner. [53] They non-specifically increase unit membrane permeability leading to euphoria, confusion, slurred speech and blurred vision or misperception.[54] Very dangerous can be cardiac arrhythmias,

laryngeal edema or acute suffocation due to hypoxia if only the oxygen deficient contents of the plastic bags is inhaled. Long-term use can cause encephalopathies, polyneuropathy and liver or kidney impairment. Multi-organ failure is possible with sudden death. Withdrawal similar to alcohol can occur. *Major toxicological risks: acute hypoxia, polyneuropathy, cardiac arrhythmia*

9 New Psychoactive Drugs

Designer drugs - also called “Legal Highs, New Psychoactive drugs (NPD), New Psychoactive Substances (NPS) or Research Chemicals”- can be easily synthesized in labs, like the name already indicates "tailor-made".[55] The concept of Legal Highs is very delusive and the law may lag behind the scene and the illegal inventive talent of drug labs. Some NPSs are summarized in table 8.

Startung from a basic structure, e.g., amphetamine, morphine or LSD, are generated using relatively simple reaction steps and an almost infinite variety of new drugs can be produced. With regard to amphetamine derivatives, a back room might be sufficient as a rule. Probably, there exist more than 1000 variations („chemical hydra“) and per year more than 50 new psychoactive substances flood the “drug market”.[56,57]

Designer drugs in the narrower sense are not new as one might think. Some were synthesized in the 1920s, some were forgotten and re-discovered some years ago (e.g. mephedrone). Loi and coworkers have analyzed fatalities in teenagers and young adults (16-24 years) after use of mephedrone between 2009 and 2013 in the UK.[58] 30 young people died (73% male), all being of white ethnicity, and 85 % had a history of drug use. 63 % of the cases were considered as accidental poisoning and other drugs may be involved in some 60% of the deaths.

Because many of these substances of this group of the stimulants are assigned as "recreational drugs", it seems very tempting to consume this stuff as doping agents – especially in young adults![59] Unfortunately, the effect of NPSs cannot always be foreseen, the structure does not correlate with the effect. E. g. the synthetic cannabinoides in Spice differ structural-chemically from Tetrahydrocannabinol in the marihuana, so that no real analogical conclusion is possible.[55] My personal experience with “Flakka” is as follows: fully awake at 3 a.m., wide pupils, massive aggression and force (6 officers necessary), no chance of even basic communication and screaming, optical hallucinations and paranoid thoughts (absolute misinterpretation of environment, transpiration and fever (39 C°), flush, duration of about 6 hours, slight response to benzodiazepines and antipsychotics.

The chemical hydra impedes the work of the legislation and authorities, as the imagination of the adulterators is endless. The Internet contributed substantially to the spreading of these substances, partly in disguise as "research molecules", "plant food" or "bath salts" with a professional appearance and nice names like "Bromo-DragonFly" or "China White".

The high rate of new substances contribute massively to the vital danger of consumers, because no scientific experiences with the substances are given. The easy production of the NPDs lowers their price – partly cheaper than alcoholic beverages in an order of 10 Euros for a “line” - what leads, in addition, to a financial incentive for potential drug consumers.[60]

Substances

No unique definition of NPS exist and the lists vary from source to source. As almost every week new NPSs are produced, one should not be surprised. However, I used the information of EU und WHO as a guideline and added information from literature.[61]

Effect and pharmacology

We know only the exact pharmacology from some new NPSs, from some poisons not even the exact ingredients, what still raises the hazard potential. Bath salts resemble pharmacologically to the amphetamines and the effects change according to composition of the stuff and the penetration through the blood brain barrier.[62] Methylendioxypyrovaleron (MDPV), methylon or mephedron (class of the cathinones) can hide behind the false mask of bath salts. Common to all compounds is a considerable addiction potential. The concentrations of the mono- amines (serotonin, noradrenalin, dopamine) in the synaptic gap rise after intake of bath salts.

“Flakka”, also called "zombie's drug", (MDPV, see above) inhibits mainly the re-uptake of noradrenalin and dopamine and causes especially heavy hyperactive psychoses with faulty actions, mostly aggressive assaults ("exited delirum"), which may continue several hours.[63] A compound with similar structure and effect is alpha-Pyrrolidinopentiophenon (alpha-PVP) [sometimes also called Flakka]. Bromo-DragonFLY is a derivative of the DOB (2,5-Dimethoxy-4-bromamphetamin) which itself is to be classified as the potent psychodelic hallucinogenic. Like LSD it works mainly as a serotonin agonist.[64,65]

To the same group of hallucinogenic chemicals belongs the "N-bombs" (25I-NBOMe), which was synthesized recently in 2003.[66] Probably, this drug has to

be classified as psychodelic hallucinogenic with is more dangerous and has the risk of fatal cardiac complications as a result of vasoconstriction.[67] Another hallucinogenic is Demethyltryptamin (DMT).[68,69] In particular, after oral intake DMT is in praxi often combined with natural occurring MAO-inhibitors such as passion flower or ayahuasca extracts which reduces the metabolic capacity of the liver, in order to slow down elimination of DMT

A hallucinogenic of "special kind" is Jenkem which is inhaled for usual. It is won from human excrements after a fermentation process and was "discovered" in Zambia, where it threatens the welfare of the youth. The pharmacological knowledge is rare. Some investigations state that it resembles to the sewage gas or decayed gas. The gas works for approximately 1 hour intensely as an auditory and optical hallucinogenic. As we know from thinners ("inebriantia"), the vital risk of the acute hypoxia exists, too, when it is inhaled from plastic bags.[70,71]

"Crocodile" or "Krok" (desomorphine) was already synthesized in 1932 and was first destined for a potent a quick and effective opiate.[72] However, in the synthesis process, among other compounds, the combination of pseudoephedrin beside phosphorus and iodine leads to an extremely toxic mixture. The results are horrible phlebitides, thromboses, osteomyelitis, muscle and skin ischemia and complicated organ damages with gangrenes liable to amputation.[73]

Kratom, a plant essence of the Kratom plant (ingredient mitragynin), played a role already in 19th century in Indo-China, shows an effect similar to codeine and, in the past, was used as an analgesic in Asia. it can cause severe withdrawal syndromes. The sage of deviners ("magic mint") stimulates opioid receptors (kappa). The ingredients (salvinorines, orignally from central America)

are supposed to be the strongest natural (biological) hallucinogenic compounds.[74. 75]

The list of NPSs is by far not complete – some sources add new benzodiazepines or ketamine-derivatives as well as spice to the list - , it is just a first step to understand the danger of this terrible development. Further information on NPSs are e. g. available at the WHO (United Nations Office on Drug and Crime or The DrugWise homepage).[76,77]

10 Legal compounds for illegal use

Some drugs which are in clinical use can be nonetheless used in an illegal way by drug addicts. One common example is ketamine or sometimes its enantiomer esketamine- also used in veterinary medicine- , which is twice as potent. It has some structural similarities with pethidine and PCP. It is used as an anesthetic but has a hallucinogenic and a dissociative property, and is therefore combined with benzodiazepines.[78] Recently, it gains importance in the treatment of depression [personal experience: can be given successful as nasal spray]. It is a NMDA-receptor antagonist with some effect on catecholamine re-uptake. Dissociative anesthesia using ketamine (combination with benzodiazepine due to bad dreams) means spontaneous breathing, good analgesia without hypotonia and maintenance of preventive reflexes. What makes the drug "interesting" is of course its larger therapeutic index and that ketamine could be sniffed nasally, given orally or into muscle or vein and even sublingually. After administration the effects lasts up to 2 hs, after oral intake up to approximately 5 hs. Unfortunantely, ketamine has gained importance as a party drug under names such as K, Kate, Special K, Fiction or Kitty. However, horror trips, bad tunnel visions and near death experiences – and hypertension with the risk of cardiovascular events - limit its illicit use.

Gamma-hydroxy-butyric (GHB) acid belongs to the group of oxybates and is known in the drug scene as "liquid ecstasy, fantasy etc.". It is often misused as “date rape drug”, and you should be cautious on parties with drinks.[79] GHB works both as an intrinsic neurotransmitter and a partial agonist of the GABA-A-receptor, being structurally related to GABA. It is metabolized very rapidly – the active metabolite is OH-crotinic acid - so that it can be detected in urine only up to 12 hs and in blood up to 8 hs, which must kept in mind in emergency situations. Moreover, it causes amnesia, which makes it often impossible for the victim to remember the felony. It is, however, used as a narcotic (SomsanitR) and in narcolepsia with a good effect for cataplexia (XyremR) - doses 4, 5 to 9 g per day - in some countries (patient information sheet). However, Xyrem contains a lot of sodium!

Etizolam (EtilaamR) and phenazepam (developed in Russia) or flunitrazeapam (RohypnolR, “forget-pill, R2, ruffies”) are benzodiazepines with affinity to the GABAa receptor and a relatively high addiction and withdrawal potential. The compounds are used in some countries as anxiolytics, antiepileptics or anaesthetics. The compounds have a very high addictive potential compared to usual benzodiazepines.[80] The drugs were allocated to Class C according to British law and generally are not used in clinical practice.

Caffeine – a methylxanthine - in very high doses is an inhibitor of the phosphodiesterase (PDE) and inhibits adenosine receptors. Therefore, it is related to the asthma therapeutic theophyllin and can be used for this purpose. Many of us use caffeine-containing beverages “to wake up” in morning. However, if one admits that a cup of coffee contains about 50 to 80 mg of caffeine, largely 75 to 100 cups of coffee – or the equivalent dose of caffeine administered - can cause serious cardiac problems, approximately 10 g being really a

toxicological threat. We must add that caffeine powder is also sniffed by abusers and is then faster effective and more bioavailable compared to oral intake.[81,82]

11 Dying from drugs – A clinical view

How can drugs kill humans? First of all, the drug can kill a human being directly such as an overdose of heroin or barbiturates leads to respiration failure or a thinner to cardiac arrhythmia. Secondly, the use of a drug can facilitate complications such as an epileptic seizure after intake of amphetamines or high doses of caffeine. In the third place, withdrawal may lead to fatal cardiovascular failure or a serious fit after stopping alcohol. In the fourth place, physical mechanisms such as squeezing out oxygen from a bag with thinner can cause hypoxia. In the fifth place, fatal accidents due to ataxia or paranoia ("I can fly") or hubris may cause death. In sixth place, long-term complications such as lung cancer (not only tobacco but all smoked stuff) or liver cirrhosis or HIV (risk of promiscuity) or cerebral bleeding or heart attacks (cocaine) can lead to death. One should not forget that suicide rates are higher in addiction compared to normal population. Another source of deaths are pharmacological interactions – e. g. AntabusR (disulfiram) effect or serotonin syndrome – when users combine drugs or patients on tramadol take an SSRI. Occasionally, preexisting diseases (e. g. diabetes or coronary heart disease) may be a substantial factor such as death due to ketoacidosis or acute heart attack and arrhythmia due to long QT-syndromes. Some addicted die from traffic accidents or even due to action slips or confusion, e. g. if they consume methanol instead of ethanol or fatal contamination. Finally, one must be aware of the fact that those who suffer from addiction have a higher risk of becoming a victim of fatal assaults. One should also not forget the children who suffer or even die, if the drug-affected parents are no longer able to care for them. So the question of

death caused by drugs is complex and not always easy to answer. It is however always important that drugs can lead to a false premature diagnosis of death and intoxications should be excluded or technical devices be used. Among others, it is the duty of the coroner or procurator fiscal in Scotland to unravel this bundle of questions.

12 Prevention strategies

It is not the purpose to review therapeutic interventions as excellent textbooks with detailed standard procedures exist, e.g. the work of Ries and colleagues, which I cited repeatedly. I must underline that the efforts against all statistics were successful in the last 20 years. For years, police, judges, coroners, social workers, educators or doctors try to improve the self-efficacy of generations and make young people resilient against any fatal temptations. The struggle was not all in vain, however, many consumers do not get rid of the drug.

If somebody accepts treatment – and this is a real obstacle – he has a chance of about 50 % to live abstinent from alcohol or drugs. The data are slightly worse for illegal drugs compared to alcohol, but comparable in developed countries. In praxi, we often get them out of criminal milieus, too. But this is not enough, the struggle must go on. To have stricter laws, does that help? In the UK in 2016 128260 offences had been documented, in Germany 229227, in Italy 61145 offences (EU-report).[83] Obviously, laws or "war against drugs" cannot solve the problem alone. A British study is dubious about the role of laws or repression with regard to control of consume of hard drugs, particularly.[84] Italy has the lowest substitution rate but also the lowest death rate due to drugs. Simple answers do not exist. A wise measurement is the Drug Arrest Referral Scheme of police, which is encouraged by PACE.[7] It offers drug users low threshold and confidential drug program in the custody unit.

When I think of my patients, they are young, they have problems to become adults, to learn a profession, they have problems with their relationships and they have no real aim for their live or "common sense". Approximately 2/3 may be male. Modern communication – which is in realiter no personal communication – alienate the young generation from each other. They mostly have no idea that drugs can hurt and they tend to trivialize the risk. In general, they have no idea, what a risk is. What is more evil, air pollution or smoking habits? Of course, smoking habits The answer is scientifically clear, but even politicians ignore the facts, although I support the struggle for better air.

The author suggests that the relevance of the core family has changed. A plenty of young adults lack intact family structures. Why does Italy cope with the problem better than the UK or Germany? May be that the joint family gives self-confidence and emotional protection. In conjunction with this dilemma, I got the impression that activities in the local football club or other community based groups has diminished in the last 20 to 30 years also in my country.

What was surprising for me is the fact that more rural regions – Bavaria in Germany and Wales in the UK – have very high drug related death rates (Figures 6 and 7, table 9).[85,86] London or Berlin are not so much affected than rural regions? Good air, silence or a nice landscape do apparently not exert a preventive effect. However, if you look on the table of German states, eastern Germany has a significantly lower rate of drug-related deaths compared to the western part? What does that mean? Even the Czech Republic with its drug laboratories – SN (Saxony) is in the neighborhood of the Czech Republic- does not increase the death rate, but the Netherlands with their liberal drug politics (neighborhood or NW (Northrhine-Westafalia) do? Or is it the real purchase power which is still better in the western states? However, I doubt that Wales

has more purchase power than London. What is the difference between the East Midlands and two northern regions of England? What is the reason for the high rates in the North East and North West counties? Many questions remain open and the data base is too weak in order to jump into conclusions.

Last but not least, ethical considerations are important. All those engaged in prevention walk a fine line between autonomy of the consumer, paternalism, beneficence and moral duty. In a liberal democratic society the struggle against drugs is always related to a supreme level of responsibility with regard to an individual person.

References

1. BBC News 2 August 2017. http://www.bbc.com/news/uk-40800288. Accessed 04.03.2018

2. Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations. Accessed 20.03.2018

3. DrugWise. How many people die from drugs. http://www.drugwise.org.uk/how-many-people-die-from-drugs/. Accessed 03.03.2018

4. Public Health England. Trends in the deaths related to drug misuse in England and Wales 1993-2004.

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/669620/Trends_in_drug_misuse_deaths_in_England_from_1999_to_2014.pdf. Accessed 03.03.2018

5. European Monitoring Center for Drugs and Drug Addiction http://www.emcdda.europa.eu/stats07/DRD/methods. Accessed 03.11.2017

6. DrugWise. What are the UK drug laws: http://www.drugwise.org.uk/what-are-the-uk-drug-laws/. Accessed 03.03.2018

7. Wyatt J, Squires T, Norfolk G, Payne-James J. Oxford Handbook of Forensic Medicine. Oxford. Oxford University Press. 2011

8. Hwang H, Park S: Sensation seeking and smoking behaviours among adolescents in the Republic of Korea. Addict Behav 2015; 45: 239-244

9. Gerra G, Avanzini P, Zaimovic A et al.: Neurotransmitters, neuroendocrine correlates of sensation seeking temperament in normal humans. Neuropsychobiology 1999; 39: 207-213

10. Hawes SW, Chahal R, Hallquist MN, Paulsen DJ, Geier CF, Luna B. Modulation of reward-related neural activation on sensation seeking across development. Neuroimage 2017; 147: 763-771

11. Koob GF, Volkow ND: Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry 2016; 3: 760-773

12. Koob GF, Everitt BJ, Robbins TW. Reward, motivation, and addiction. In: Squire LR, Berg D, Bloom F, du Lac S, Ghosh A, Spitzer NC (eds). Fundamental Neuroscience Chapter 43. Elsevier. Amsterdam 2008, pp 987-1016

13. Dobrin CV, Roberts DCS: The anatomy of addiction. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 27-38

14. The Surgeon General report on alcohol, drugs, and health – Facing addiction in America. Washington DC 2016. https://www.ncbi.nlm.nih.gov/books/NBK424857/pdf/Bookshelf_NBK424857.pdf. Assessed 04.03.2018

15. Hodgson E: Introduction to toxicology. In: Hodgson E (ed.). A Textbook of Modern Toxicology. Wiley and Sons, New Jersey 2004, pp. 3-12

16. OECD guidelines for testing of chemicals section 4: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788. Accessed 07.03.2018

17. Schlede E, Geschow E, Spielmann H, Stropp G, Kayser D. Oral acute toxic class method: a successful alternative to the oral LD50 test. Regul Toxicol Pharmacol 2005; 42: 15-23

18. Baynes RE: Human Health Risk Assessment. In: Hodgson E (ed.). A Textbook of Modern Toxicology. Hoboken. 2004. Pp.423-438

19. Spector WS: Handbook of Toxicology Vol I: Acute toxicities of solids, liquids and gases to laboratory animals. Saunders Company, Philadelphia- London 1956

20. Lachenmeier DW, Rehm J: Comparative risk assessment of alcohol, tobacco, cannabis and other illicit drugs using the margin of exposure approach. Scientific Reports 2015; 5: 8126

21. Holford NHG: Pharmacokinetics and pharmacodynamics: Rational dosing the time course of drug action. In: Katzung BG, Masters SB, Trevor AJ (eds.): Basic and Clinical Pharmacology. McGraw Hill, New York 2009, pp. 37-51

22. Nierenberg DW, Melmon KI: Introduction to Clinical Pharmacology. In: Melmon KI, Morrelli HF, Hoffman BB, Nierenberg DW: Clinical Pharmacology. Basic principles in therapeutics. New York. McGraw-Hill. 1992. Pp. 1-51

23. Corriera MA: Drug biotransformation. In: Katzung BG, Masters SB, Trevor AJ (eds.). Basic and Clinical Pharmacology. McGraw Hill. New York 2009, pp. 53-66

24. Dasgupta A: Pharmacology of commonly abused drugs - Beating drug tests and positive results. A toxicologists perspective – Chapt 2. Springer 2010, pp. 11-28.

25. Sharma P, Murthy P, Bharath MM. Chemistry, metabolism, and toxicology of cannabis: clinical implications. Iranian J Psychiatr 2012; 7,4: 149-156

26. Securtec Detektionssystem. Drug test – at a glance. https://www.securetec.net/en/drug-test. Accessed 08.03.2018

27. Drug Testing network 2018. https://drugtestingnetwork.com/urine-testing. Assessed 04.03.2018

28. Lyle DP: Forensics for Dummies. Wiley Publishing Inc.. New York. 2004

29. OECD guideline for testing chemicals. https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd_gl423.pdf. Accessed 05.11.2017

30. Haller Chr, Thai D, Jacob P 3rd, Dyer JE. GHB urine concentration after single-dose administrations in humans. J Anal Toxicol 2006; 30: 360-364

31. Petersen IN. Identification of new metabolite of GHB. Gamma-hydroxybutyric acid glucuronide. Analytical Toxicology 2013; 37: 291-297

32. Lüscher Chr. Drugs of abuse. In: Katzung BG, Masters SB, Trevor AJ (eds.). Basic and Clinical Pharmacology. McGraw Hill. New York 2009, pp. 553-568

33. Borg L, Kravets I, Kreek MJ. The pharmacology of long-acting as contrasted with short-acting opioids. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 117-131

34. Diamorphine: http://www.inchem.org/documents/pims/pharm/pim261f.htm. Accessed 04.03.2018

35. Payk TR, Brüne M: Checkliste Psychiatrie und Psychotherapie. 7th ed. Thieme. Stuttgart 2018

36. Pounder DJ: The case of Dr Shipman. Am J Forensic Med Pathol 2003; 24: 219-226

38. Gorelick DA. The pharmacology of cocaine, amphetamines, and other stimulants. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 133-157

39. Badon LA, Hicks A, Lord K, Ogden BA, Meleg-Smith S, Varner KJ. Changes in cardiovascular responsiveness and cardiotoxicity elicited during binge administration of ecstasy. J Pharmaol Experim Therap 2002; 302: 898-907

40. Cocaine: http://www.inchem.org/documents/pims/pharm/pim261f.htm. Accessed 04.03.2018

41. Welch SP. The pharmacology of cannabinoids. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 193-214

42. Cannabis sativa L. http://www.inchem.org/documents/pims/pharm/pim261f.htm. Accessed 04.03.2018

43. THC-Pharm: http://www.thc-pharm.de/wp-content/uploads/2017/08/DAC-NRF-2017-%C3%96lige-Dronabinol-Tropfen-25-mg-22.8..pdf. Accessed 04.03.2018

44. Lapoint J, Nelson LS. Synthetic Cannabinoids: The Newest, Almost Illicit Drug of Abuse. Emergency Medicine 2011; 43(2):26-28

45. National Institute on Drug Abuse. Marihuana: https://www.drugabuse.gov/publications/research-reports/marijuana/where-can-i-get-more-scientific-information-marijuana-abuse. Accessed 04.03.2018

46. Brandenburg D, Wernick R. Intravenous marihuana syndrome. Western J Med 1986; 145: 84-96

47. Glennon RA: The pharmacology of classical hallucinogens and related designer drugs. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 215-230

48. Dolder PC, Schmid Y, Steuer AE et al. Pharmacokinetics and pharmacodynamics of Lysergic Acid Diethylamide in healthy subjects. Clin Pharmacokin 2017; 56: 1219-1230

49. Circaulo DA, Knapp CM: The pharmacology of non-alcohol sedative hypnotics. . In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 99-115

50. Trevor AT, Way WL: Sedative-hypnotics drugs. In: Katzung BG, Masters SB, Trevor AJ (eds.). Basic and Clinical Pharmacology. McGraw Hill. New York 2009, pp. 371-386

51. Singh V. Survival after fatal pentobarbital ingestion. Indian J Anaesth 2014; 58: 55-86

52. Seeger R. Giftpflanzen und Pflanzengifte. In: Gloxhuber Chr (ed.) Toxikologie. Thieme. Stuttgart 1994, pp 358-449

53. Bulster RL. The pharmacology of inhalants. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 241-249

54. Campos-Ordonez T, Gonzales-Perez P: Cyclohexane, a potential drug of abuse with pernicious effects on the brain. Frontiers in Pharmacology 2016; 6: Article 291

55. Rech MA, Donahey E, Cappiello Dziedzic JM, Oh L, Greenhalgh E. New drugs of abuse. Pharmacotherapy 2015; 35: 189-197

56. Baggaley K: Designer drugs hit dangerous lows to bring new highs. ScienceNews 2015; 185: 22-25

57. Mrav N. The challenges of designer drugs. http://www.euronews.com/2013/11/06/the-new-challenges-of-designer-drugs/.30.09.2015

58. Loi B, Corkery JM, Clardige H et al. Deaths of individuals aged 16-24 years in the UK after using mephedrone. Hum Psychopharmacol 2015; 30: 225-232

59. Teale P, Scarth J, Hudson S. Impact of the emergence of designer drugs upon sports doping testing. Bioanalysis 2012; 4: 71-88

60. McCandless D. Goodbye ecstasy, hello 5-Meo-DMT: new designer drugs are just like a click-away. The Guardian 02/2004. http://www.theguardian.com/society/2004/feb/16/drugsandalcohol.drugs.30.09.2015

61. European Monitoring Center for Drugs and Drugs Addiction. New psycho-active substances in Europe. Lisbon 2015. www.gov.uk/government/publications/controlled-drugs-list--2/list-of-most-commonly-encountered-drugs-currently-controlled-under-the-misuse-of-drugs-legislation. Accessed 08.03.2018

62. Coppola M, Mondola R. Synthetic cathinones: chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as “bath salts” or “plant food”. Toxicol Letters 2012; 211: 144-149

63. Aarde SM, Creehan KM, Vandewater SA, Dickerson TJ, Taffe MA. In vi-vo potency an efficacy of the novel cathinon α-pyrrolidinopentiophenone and 3,4-methylenedioxypyrovalerone: self-administration and locomotor stimula-tion in male rats. Psychopharmacology (Berl.) 2015; 232: 3045-55

64. Andreasen MF, Telving R, Birkler RI, Schumacher B, Johannsen M. A fa-tal poisoning involving Bromo-DragonFLY. Forensic Science International 2009; 183: 91-96

65. Corazza O, Schifano F, Farre M et al. Designer drugs on the internet: a phenomenon out of control? The emergence of halluzinogenic drug Bromo-DragonFLY. Current Clinical pharmacology 2011; 6: 125-129

66. National Institute on Drug Abuse: N-Bomb (2013) https://www.drugabuse.gov/drugs-abuse/other-drugs

67. Science Daily (April 2015): Poison center warns against designer drug "N-Bomb". http://www.sciencedaily.com/releases/2015/ 04/150409162230.htm.30.09.2015

68. Shenberg EE, Alexandre JF, Filev R. Acute biphasic effects of ayahuasca. PLoS One 2015; 10: 1-27

69. National Institute on Drug Abuse (2015): Emerging Trends. http://www.drugabuse.gov/drugs-abuse/emerging-trends.30.09.2015

70. Wikipedia the free encyclopaedia: Jenkem. https://en.wikipedia.org/wiki/Jenkem.30.09.2015

71. African children high on sewage. BBC July 30 1999. http://news.bbc.co.uk/2/hi/africa/406067.stm. Accessed 08.03.2018

72. Alves EA, Soares JX, Afonso CM et al. The harmful chemistry behind "krokodil": Street-like synthesis and product analysis. Forensic Science International 2015; 257: 76-82

73. Gahr M, Freudenmann RW, **Hiemke** C, Gunst IM, Connemann BJ, Schönfeldt-Lecuona C. Desomorphine goes „crocodile". J Addict Dis 2012; 31: 407-412

74. Maqueda AE, Valle M, Addy PH. Salvinorin-A induces intense dissociative effects, blocking external sensory perception and modulating interoception

and sense of body ownership in humans. International Journal of Neuropharmacology 2015; 1-14

75. White,CM: Pharmacological and clinical assessment of kratom. Am J Health Syst Pharm 2018: 75: 261-267

76. DrugWise: New Psychoactive Substances. http://www.drugwise.org.uk/tag/nps/.08.03.2018

77. United Nations Office on Drugs and Crime. The Challenge of Synthetic Drugs in East and South-East Asia - Trends and Patterns of Amphetamine-type Stimulants and New Psychoactive Substances. https://www.unodc.org/unodc/en/scientists/trends-and-patterns-of-ats-and-nps-2017.html. Accessed 08.03.2018

78. Domino EF, Miller SC. Pharmacology of dissociatives. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 231-240

79. Wilkins JN, Danovitch I, Gorelick DA. Management of stimulant, hallucinogen, marihuana, phencyclidine, and club drugs. Intoxication and withdrawal. In: Ries K, Fiellin DA, Miller SC, Saitz R (eds.). Wolters Kluver-Lippincott Williams and Wilkins. Philadelphia 2009, pp 607-628

80. Nakamae T, Shinozuka T, Sasaki C et al. Case report: Etizolam and its major metabolites in two unnatural death cases". Forensic Sci Int 2008; **182** (1–3): e1–6.

81. Pflaum N. Koffeinpulver schnupfen: So stark wie 200 Tassen Kaffee. Augsburger Allgemeine, 17. Januar 2012

82. Party Safe for Parents (2014): New drug trend, powdered caffeine. http://supportiveparent.com/2014/07/14/new-drug-trend-powdered-caffeine/.30.09.2015

83. European Drug Report 2017. Lisbon 2017 https://ec.europa.eu/unitedkingdom/news/european-drug-report-2017-uk-leads-sad-statistic-drug-overdose-deaths-europe_en- . Accessed 05.11.2017

84. Reveal: How drugs war failed. The Guardian International Edition, 2005. https://www.theguardian.com/uk/2005/jul/05/drugsand alco-hol.freedomofinformation. Accessed 11.03.2018

85. Bossert A. Drogentote in Deutschland. http://ixd-hof.de/blog/2014/02/12/dokumentation-drogentote-in-deutschland/. Accessed 03.03.2018

86. Office for National Statistics. Deaths related to drug poisoning in England and Wales: 2016 registrations. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations. Accessed 08.03.2018

87. https://www.gov.uk/penalties-drug-possession-dealing. Accessed 03.03.2018

88. Gov.UK controlled drug list (update 2017) https://www.gov.uk/government/publications/controlled-drugs-list--2/list-of-most-commonly-encountered-drugs-currently-controlled-under-the-misuse-of-drugs-legislation. Accessed 05.11.2017

89. Vree TB, Wissen V. Pharmacokinetics and metabolism of codeine in humans. Biopharm Drug Dispos 1992; 13: 445-460

90. Jufer RA, Wstadik A, Walsh SL, Levine BS, Cone EJ. Elimination of cocaine and metabolites in plasma, saliva, and urine following repeated oral administration to human volunteers. J Anal Toxicol 2000; 24: 467-477

91. Drogenbeauftragte der Bundesregierung (23.07.13): Neue psychoactive Substanzen. http://www.drogenbeauftragte.de/drogen-und-sucht/illegale-drogen/heroin-und-andere-drogen/neue-psychoaktive-substanzen.html.30.09.2015

92. http://ixd-hof.de/blog/2014/02/12/dokumentation-drogentote-in-deutschland/. Accessed 03.03.2018

93. European Drug Report, Lisbon 2017: http://www.emcdda.europa.eu/edr2017_en. Accessed 03.03.2018

94: https://de.wikipedia.org/wiki/Vereinigtes_K%C3%B6nigreich. Accessed 03.03.18

95: Coroner: https://www.cps.gov.uk/legal-guidance/coroners. Accessed 18.03.2018

96: National Records of Scotland. https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2016. Accessed 23.03.2018)

Appendix – Tables and Figures

Tables

Table 1: Number drug-related deaths in England and Wales between 2012 and 2016 according to death certificates. Source: ONS: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations.Accessed 03.03.2018[86]

Number of deaths

	2012	2013	2014	2015	2016
All drug poisoning deaths	2,597	2,955	3,346	3,674	3,744
Any opiate[4]	1,290	1,592	1,786	1,989	2,038
- Heroin and/or morphine	579	765	952	1,201	1,209
- Methadone	414	429	394	434	413
- Tramadol	175	220	240	208	184
- Oxycodone	37	51	51	51	75
- Fentanyl	22	22	40	34	58
Cocaine	139	169	247	320	371
Any amphetamine	97	120	151	157	160
Any new psychoactive substance	55	63	82	114	123
Any benzodiazepine	284	342	372	366	406
Pregabalin	4	33	38	90	111
Gabapentin	8	9	26	49	59
All antidepressants	468	466	517	447	460
Paracetamol[5]	182	226	200	197	219
Propranolol	39	46	54	55	45

Source: Office for National Statistics

Table 2: Drug-related deaths in Scotland according to the ONS between 2006 an 2016 (source: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2016. Accessed 23.03.2018)[96]

Drugs [1, 2]	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
All drug-related deaths (on the 'wide' definition)	**577**	**630**	**737**	**716**	**692**	**749**	**734**	**685**	**743**	**813**	**997**
Alprazolam	0	0	1	1	0	1	0	0	0	2	24
Amitriptyline	29	24	41	32	41	37	44	60	41	47	54
Amphetamines	11	12	12	7	3	24	18	27	22	17	26
Anti-depressants [3]	93	84	101	97	123	116	121	120	103	132	130
Anti-psychotics [4]	21	26	25	19	21	32	35	29	23	30	29
Benzodiazepines [5]	94	109	150	158	124	187	198	149	125	192	431
Buprenorphine	0	2	0	2	4	10	8	11	29	25	40
Cannabis	3	8	1	0	0	0	0	0	2	7	5
Citalopram	25	22	19	20	26	22	18	13	11	18	11
Cocaine	33	47	41	33	34	36	31	45	45	94	123
Codeine or a compound thereof [6]	38	30	40	46	20	48	41	46	45	40	45
Delorazepam	0	0	0	0	0	0	0	0	0	1	21
Dihydrocodeine or a compound thereof [7]	45	55	74	65	65	87	86	81	72	95	115
Diazepam	78	79	116	120	94	124	161	106	85	122	154
Diclazepam	0	0	0	0	0	0	0	1	6	9	75
Ecstasy-type	12	12	5	2	0	9	9	17	14	15	29
Etizolam	0	0	0	0	0	0	1	8	37	43	225
Fluoxetine	8	11	6	7	16	11	13	9	10	11	16
Gabapentin	0	0	3	2	4	10	24	51	67	102	154
Heroin/diamorphine or Morphine [8]	260	291	327	326	256	207	222	221	312	349	477
Heroin / morphine, Methadone or Buprenorphine [9]	328	372	449	440	400	431	403	383	454	497	656
Methadone	96	115	171	177	177	275	241	216	216	252	366
Mirtazepine	5	8	12	14	9	18	24	26	20	39	35
Olanzapine	5	10	8	6	7	9	14	8	5	11	11
Opiate or opioid [10]	403	451	550	540	480	558	531	499	553	619	776
Oxycodone	0	1	8	6	3	12	11	9	7	12	17
Paracetamol or a compound [11]	53	56	55	43	48	45	37	38	43	36	41
Phenazepam	0	0	0	0	0	14	20	34	6	8	8
Pregabalin	0	0	0	0	1	1	5	12	26	42	71
Propranolol	4	8	4	9	5	11	15	18	17	13	15
Sertraline	5	2	4	2	6	3	6	7	11	13	16
Temazepam	9	4	7	9	3	8	6	4	4	8	8
Tramadol	17	26	32	40	40	34	48	64	38	53	64
Zopiclone	1	4	5	9	12	14	16	16	9	20	22
Alcohol	151	181	196	187	151	148	136	129	116	123	135

Table 3: Drug related deaths in Northern-Ireland between 2006 and 2016 according to death certificates (source: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2016. Accessed 23.03.2018)[96]

Substance	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	Total (2006-2016)
All Opioids	41	35	35	37	52	54	67	71	63	88	90	**633**
Heroin/Morphine*	12	10	6	9	16	17	24	25	11	27	25	**182**
Methadone*	2	1	1	1	3	4	5	5	8	6	8	**44**
Tramadol	11	11	11	8	13	17	31	20	22	28	33	**205**
Codeine not from compound formulation*	9	16	14	8	17	15	22	22	19	13	17	**172**
Dihydrocodeine not from compound formulation*	14	9	11	17	10	9	8	5	8	13	18	**122**
Oxycodone	1	4	1	4	9	6	2	9	8	12	10	**66**
Fentanyl	1	2	-	1	6	3	7	4	1	15	13	**53**
Cocaine*	1	3	6	4	3	5	4	1	8	8	3	**46**
All amphetamines*	2	5	4	4	2	4	4	1	11	7	8	**52**
MDMA/Ecstasy*	2	5	3	3	1	2	4	1	7	4	7	**39**
Any psychoactive substance**	-	-	-	4	2	2	2	4	19	16	7	**55**
Cathinones (includes Mephedrone)	-	-	-	-	1	2	2	3	8	7	1	**24**
All benzodiazepines*	26	29	35	28	40	36	47	47	45	63	65	**461**
Temazepam*	4	8	6	1	3	1	4	-	1	4	2	**34**
Diazepam*	20	21	28	22	35	34	42	40	42	58	60	**402**
Pregabalin	-	-	-	-	-	-	-	1	5	7	8	**21**
All antidepressants	25	20	27	27	22	20	28	27	30	38	39	**303**
Mirtazapine	4	3	5	2	6	4	6	5	11	11	13	**70**
Tricyclic antidepressants (TCA)	15	11	15	18	10	10	11	11	13	19	17	**150**
Dothiepin	4	4	6	5	2	3	6	3	-	3	1	**37**
Amitriptyline	9	7	8	9	8	4	4	9	12	17	15	**102**
Selective serotonin re-uptake inhibitors (SSRI)	5	7	6	5	7	6	10	7	6	7	8	**74**
Paracetamol (includes dextropropoxyphene or propoxyphene mentioned without paracetamol)	14	8	4	4	4	5	4	8	3	2	1	**57**

Table 4: Comparison of drug-related death rates in different countries aged 15 to 64 years – latest statistics.

(Source: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2016. Accessed 23.03.2018)[96]

	"Drug-induced" deaths[1] aged 15-64	
	Number reported for latest year[2]	per million population[2]
Belgium	67	9
Bulgaria	17	4
Czech Republic	39	6
Denmark	210	58
Germany	1,185	22
Estonia	88	103
Ireland	213	71
Greece	..	..
Spain	455	15
France	294	7
Croatia	54	19
Italy	304	8
Cyprus	9	15
Latvia	18	14
Lithuania	115	59
Luxembourg	12	31
Hungary	25	4
Malta	8	28
Netherlands	182	16
Austria	152	26
Poland	249	9
Portugal	39	6
Romania	21	2
Slovenia	30	22
Slovakia	27	7
Finland	150	43
Sweden	618	100
United Kingdom[3]	2,528	60
European Union	7,109	21.3
Turkey	533	10
Norway	257	76
EU, Turkey and Norway	7,899	20.3
Scotland[3]	563	160

Table 5: Maximum penalties for possession, supply or production of different types of drugs in the UK. Source: Drug penalties: https://www.gov.uk/penalties-drug-possession-dealing. Accessed 03.03.2018[87,88]

Class	Drug	Possession	Supply and production
A	Crack cocaine, cocaine, ecstasy (MDMA), heroin, LSD, magic mushrooms, methadone, methamphetamine (crystal meth)	Up to 7 years in prison, an unlimited fine or both	Up to life in prison, an unlimited fine or both
B	Amphetamines, barbiturates, cannabis, codeine, ketamine, methylphenidate (Ritalin), synthetic cannabinoids, synthetic cathinones (eg mephedrone, methoxetamine)	Up to 5 years in prison, an unlimited fine or both	Up to 14 years in prison, an unlimited fine or both
C	Anabolic steroids, benzodiazepines (diazepam), gamma hydroxybutyrate (GHB), gamma-butyrolactone (GBL), piperazines (BZP), khat	Up to 2 years in prison, an unlimited fine or both (except anabolic steroids - it's not an offence to possess them for personal use)	Up to 14 years in prison, an unlimited fine or both
Temporary class drugs*	Some methylphenidate substances (ethylphenidate, 3,4-dichloromethylphenidate (3,4-DCMP), methylnaphthidate (HDMP-28), isopropylphenidate (IPP or IPPD), 4-methylmethylphenidate, ethylnaphthidate, propylphenidate) and their simple derivatives	None, but police can take away a suspected temporary class drug	Up to 14 years in prison, an unlimited fine or both

*The government can ban new drugs for 1 year under a 'temporary banning order' while they decide how the drugs should be classified.

Table 6: Comparative acute toxicological data of some common drugs.[19,20]
Note 1: Ricin was added for comparison. It was used in the cold war to kill regime critics with primed umbrellas; LD lethal dose. Note 2: No data are available about Nowitshok. However, acc. to Wikipedia it has the toxicity (AchEI) of about 1/7 of VX poisons, i.e. about 1 ug/kg after iv-administrations in rats [source: https://de.wikipedia.org/wiki/Nervengift. assessed 04.04.2018)

Drug	Route	LD50 [mg/kg BW]	Species
Heroine	Intraven	21.8	Mouse
Methadone	Oral	70.0	Mouse
Cocaine	Intraven	16.0	Mouse
THC	Oral	482.0	Rat
Nicotine	Oral	3.34	Mouse
Ethanol	Oral	3450.0	Mouse
Diazepam	Oral	500	Mammal
Pentobarbital	Oral	280 100	Mouse Cat
Amphetamine	Oral	21.0	Mouse
MDMA	Oral	325.0	Rat
Caffeine	Oral	200	Rat
Ricin	Intramusc	0.0008 (LD)	Guinea Pig

Table 7: Examples of half-lives and metabolites.[25,89,90] Abbreviations: 2-Ethylidene-1,5-dimethyl-3,3-diphenyl pyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrrolidine (EMDP)

Drug	**Half-life [hs]**	**Metabolites**
Amphetamine	6-12 hs	-
Metamphetamin	6-12 hs	Amphetamine
Cocaine	Approx. 0.5-1 hs Cocaethylene 5 hs	Benzoylecgonin, Nor-cocaine, Ecgonin-methyl-ester
Diazepam	35-55 hs ; Nordiazepam up to 8 days!	Oxazepam, nordiazepam
Gamma-OH-butyrate	40-60 minutes	Succinic acid, ß-oxidation
Heroin	2-8 minutes	6-Mono-acetyl-morphine, morphine
Morphine	2-3 hs	glucuronide
Codein	1,5, Codein-6-glucoronide: 2,75 hs	Morphine, glucuronide
Methadone	15-55 hs	EDDP, EMDP
THC	Infrequent: 1,3 d Chronic: 5-13 d	TCH-COOH Infrequent: 2-7 days Chronic: up to 25!

Table 8: Sample of „New Psychoactive substances on the European „market“ (sources: see text and 91). Further new psychoactive drugs are listed in the National Records of Scotland (source: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2016. Accessed 23.03.2018 [96])

Drug	**Class**	**Effects and major risks**
JWH-019, „Spice“	Cannabinoid	Similar to cannabis products (THC) with elation, intensive perception und experience, paranoid psychose-like symptoms
JWH-073, „Spice“	Cannabinoid	
Bath salts	Cathinone: z. B. Mephedron, Methylon, α-PVP	Powerful stimulants, which resemble cocaine or ecstasy: hallucinations, Panic, delusions; sympathomimetic (BP and HR may rise)
Flakka	MDPV	
Naphyrone	Triple-reuptake Inhibitor	Derivative of alpha-PVP with similar effects
A-Methyl-tryptamine	5-HT-agonist, MAOI	Antidepressive, psychedelic similar to LSD, stimulant
Diviner´s sage (Salvia divinorum)	κ-Agonists (Salvinorine)	Hallucinogenic effect with dissociative complications (e. g. detachment of emotion and perception)
Bromo-DragonFLY	Agonist of Serotonin	Resembles LSD; Duration of action up to 96 H, risk of gangrene

Table 8 continued		
N-Bomb	Agonist of Serotonin	Resembles to LSD effects. Much higher cardiovascular risk
Ayahuasca (DMT)	Agonist of Serotonin (+ MAOH)	Hallucinogen compound without development of tolerance
5-(2-Aminopropyl-indol) 5-API	Isomer of α-methyl-tryptamine	Powder with primarily hallucinogenic effects. 20 mg suffice to cause an action for 12 hours
Kratom	Mitragynin (κ- u. μ-Agonist)	Resembles effects of codeine. Risk of serotonin-syndrome (MAOH), Pigment depositions on cheeks. Aphrodisiac agent
Jenkem	Fermentation gas	Powerful inhalative hallucinogen; risk of hypoxia
Crocodile	Opioide (Desomorphin)	Risk of gangrene, thrombosis, pneumonia, phlebitis or sepsis
Etizolam	Benzodiazepin	Benzodiazepine with high addiction potential, interaction
Phenazolam	Benzodiazepin	
Nasal caffeine	Phosophdiesterase-inhibitor	High doses with risk of epilepsia, arrhythmia or cardiovascular decompensation

Table 9: Distribution of drug related deaths in Germany according to states and free cities in 2013. Important is the "Gesamtzahl der Todesfälle" i. e. the total number of deaths. Northrhine Wesfalia (Ruhr-region NRW) and Bavaria (BY) have the highest frequency of deaths, Berlin (Be) has much lower figures. Source: http://ixd-hof.de/blog/2014/02/12/dokumentation-drogentote-in-deutschland/. Accessed 03.03.2018[92]

Überdosis von	SH	HH	NI	HB	NW	HE	RP	BW	BY	SL	BE	BB	MV	SN	ST	TH	Gesamt
Heroin	5	1	19	11	78	26	12	40	73	2	4	1	--	5	–	2	**279**
Heroin i.V.m. sonst. Drogen	7	3	12	3	83	46	9	28	34	7	56	–	1	1	–	--	**290**
Kokain	--	3	3	--	6	1	--	1	1	--	5	–	1	1	–	–	**22**
Kokain i.V.m. sonst. Drogen	1	1	6	--	22	3	--	4	1	1	21	–	1	--	1	–	**62**
Amphetamin	1	1	--	--	3	–	--	1	6	2	2	–	–	--	--	1	**17**
Amphetamin i.V.m. sonst. Drogen	--	–	3	--	12	1	1	5	14	--	12	–	–	--	1	–	**49**
Ecstasy	--	1	–	--	--	–	--	--	–	–	1	--	–	--	--	–	**2**
Ecstasy i.V.m. sonst. Drogen	--	--	–	--	7	–	--	--	–	–	1	--	–	--	--	–	**8**
Substitutionsmittel	4	16	5	--	6	–	3	6	6	–	6	--	–	--	1	–	**53**
- davon Methadon / Polamidon	4	16	4	--	5	–	3	6	6	–	6	--	–	--	1	--	**51**
- davon Subutex	--	--	1	--	1	--	–	--	--	–	--	--	–	–	--	--	**2**
Substitutionsm. i.V.m. sonst. Drogen	8	13	5	–	39	2	4	25	18	–	44	--	2	–	--	--	**160**
- davon Methadon / Polamidon	7	10	5	–	37	--	4	23	18	–	44	--	2	–	--	--	**150**
- davon Subutex	–	3	--	–	2	--	–	2	--	–	–	--	--	–	--	--	**7**
Sonstige BtM / Drogenart nicht bek.	2	1	9	–	--	11	6	15	39	--	20	1	--	2	--	5	**111**
Suizid	1	1	2	–	10	4	4	7	9	1	14	--	--	–	2	3	**58**
Langzeitschäden	4	10	19	3	19	10	--	6	105	10	20	--	--	2	3	--	**211**
Unfall / Sonstige	2	6	1	–	–	76	2	1	2	1	5	--	--	1	1	1	**99**
Gesamtzahl der Todesfälle*	**35**	**57**	**52**	**17**	**216**	**90**	**41**	**139**	**177**	**12**	**114**	**2**	**5**	**12**	**9**	**8**	**986**
Obduktion (%-Anteil)	69	47	62	35	35	89	95	34	88	100	99	100	100	100	78	88	**65**

Figures

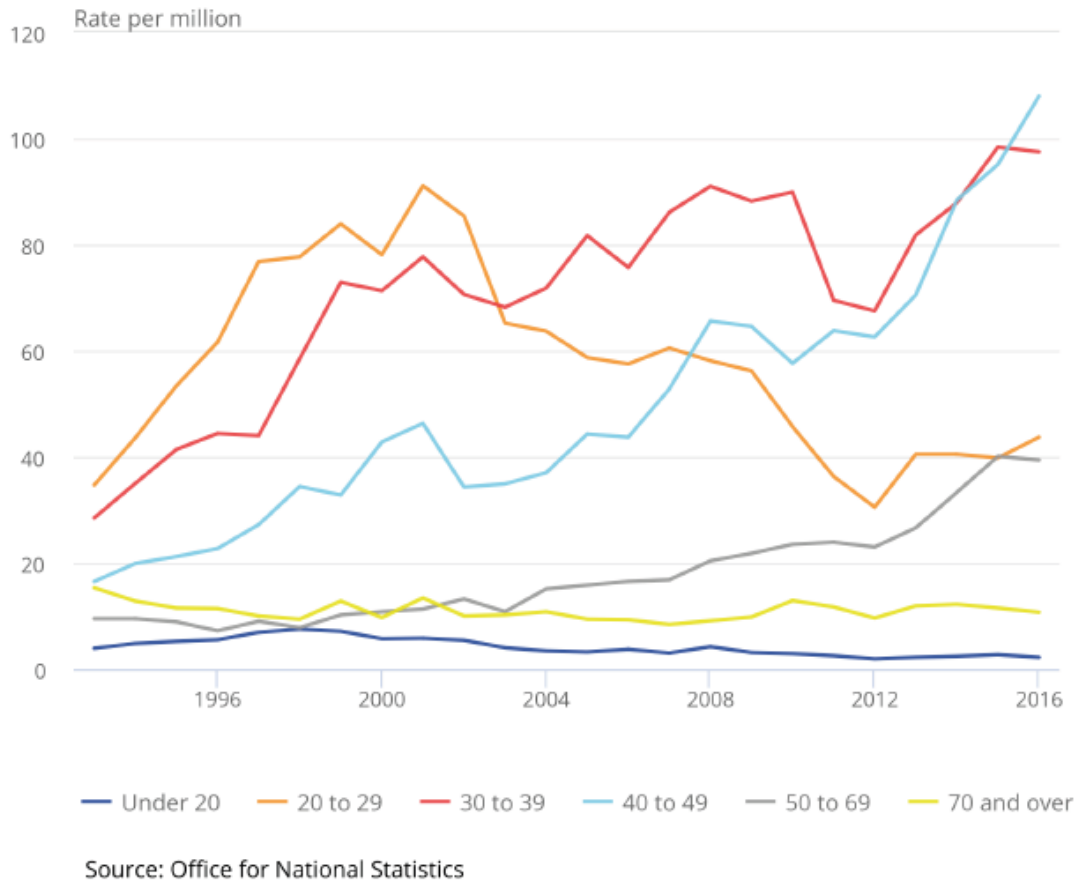


Figure 1: Age-specific mortality rates for deaths related to drug misuse between 1993 and 2016. Increase is almost entirely due male deaths, female deaths being largely constant. The total absolute figure of drug-related deaths in 2016 was 3744. Source ONS: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations. Accessed 03.03.2018[2]

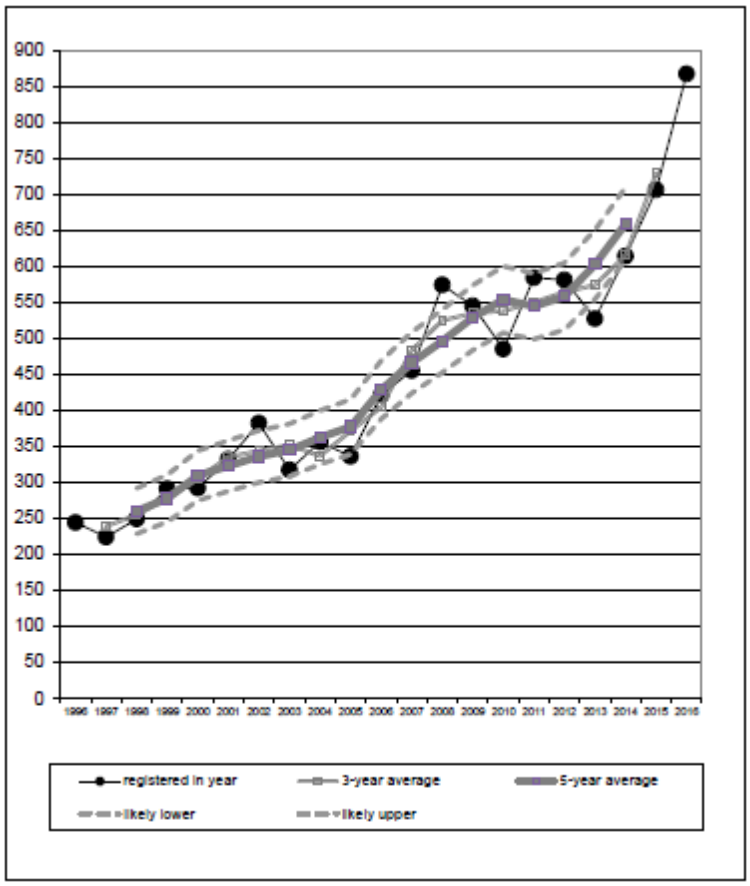
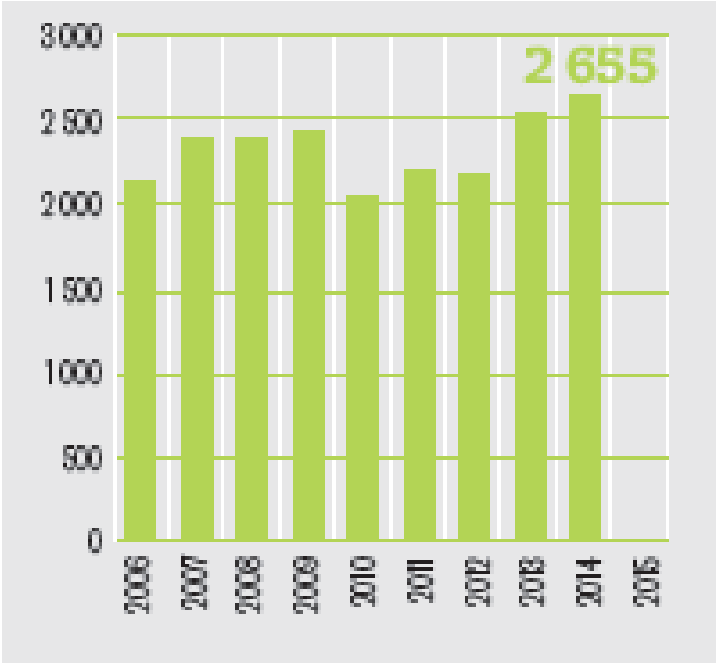
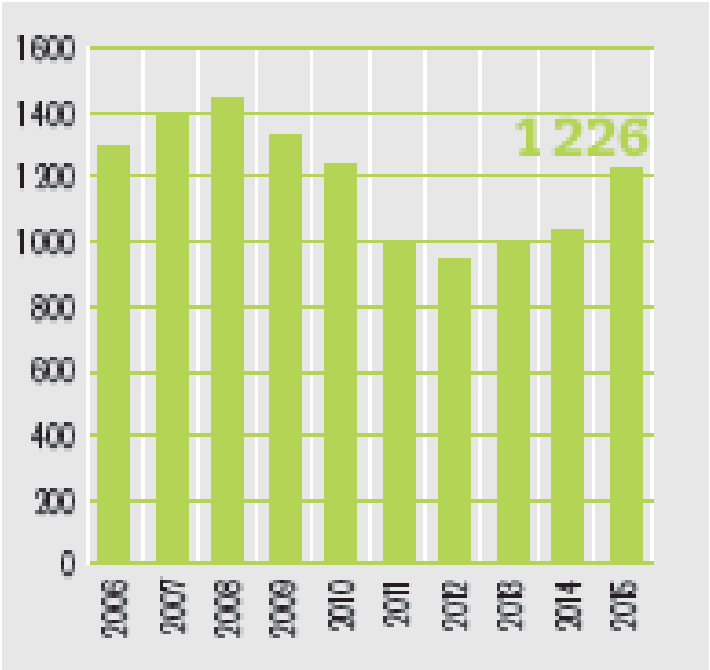


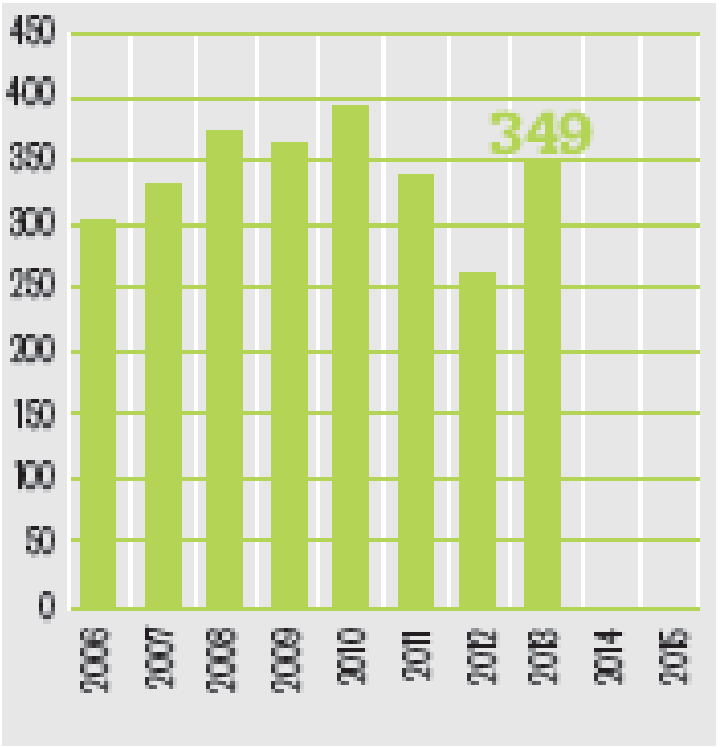
Figure 2: Trend of drug-related deaths in Scotland given as 3- and 5-year moving averages including likely range values around 5-year averages. (Source: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/deaths/drug-related-deaths-in-scotland/2016. Accessed 23.03.2018)[96]


3000
2 500
2000
1 500
1000
500
0
2 655
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

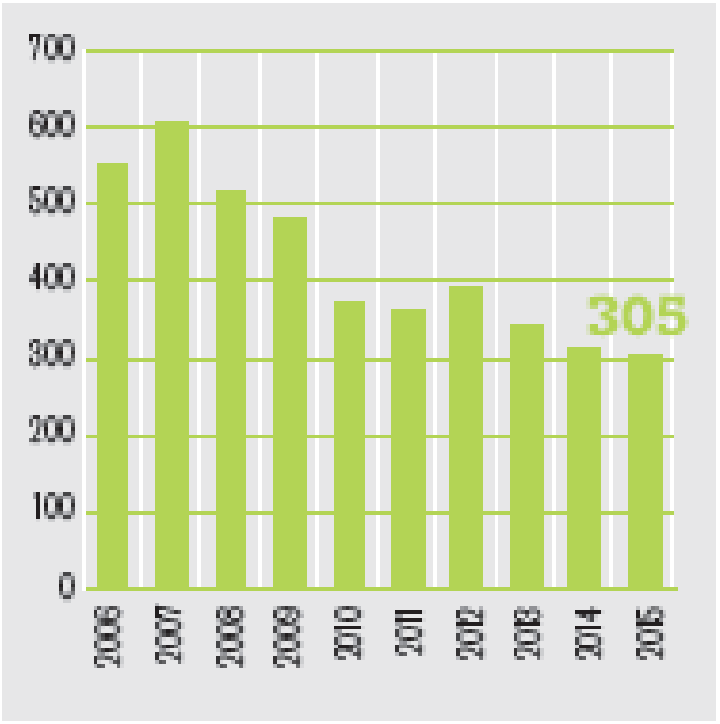
3a


1600
1400
1 200
1000
800
600
400
200
0
1 226
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015

3b



3c



3d

Figure 3 a-d: Mortality rates up to 2016 top down in the UK, Germany, France and Italy. Obviously, Germany and the UK have similar problems, whereas France has much lower figures and Italy a reduction of drug related deaths (see

text). Source: European Drug Report, Lisbon 2017: http://www.emcdda.europa.eu/edr2017_en. Accessed 03.03.2018[93]

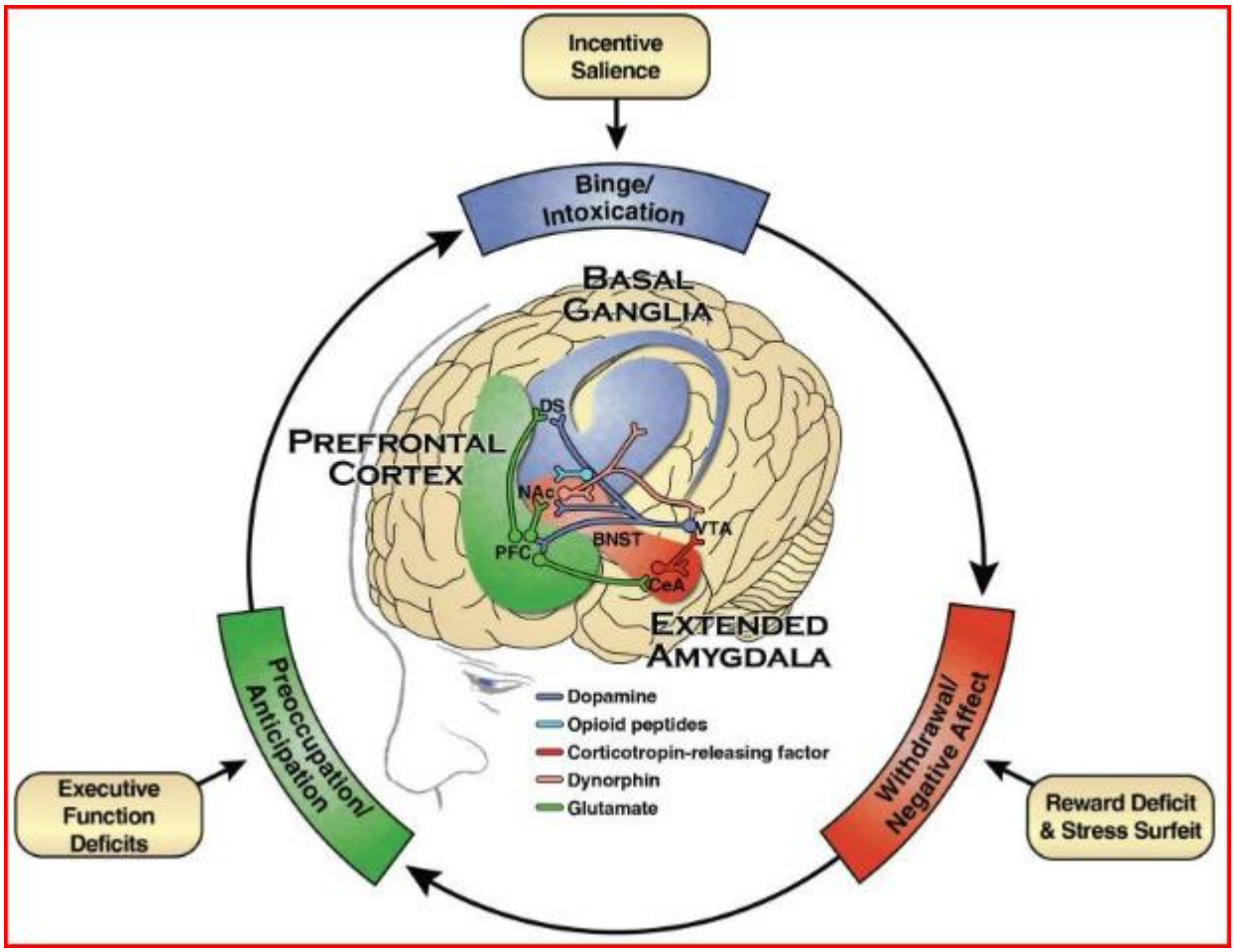


Figure 4: The figure summarizes the neurotransmitter systems involved in intoxication, preoccupation and withdrawal, the 3 stages of addiction. The neurotransmitter noradrenaline is not shown but secreted in the amygdala in case of withdrawal.

Note: Blue represents the basal ganglia involved in the Binge/Intoxication. Red represents the extended amygdala involved in the affect and withdrawal. Green represents the prefrontal cortex involved in the preoccupation/anticipation stage. Abbreviations: PFC - prefrontal cortex, DS - dorsal striatum, NAc - nucleus accumbens, BNST - bed nucleus of the stria terminalis, CeA - central nucleus of the amygdala, VTA - ventral tegmental area. Source: Surgeon General Report 2016 (US) page; 2.15https://www.ncbi.nlm.nih.gov/books/NBK424857/pdf/Bookshelf_NBK424857.pdf. Assessed 04.03.2018[14]

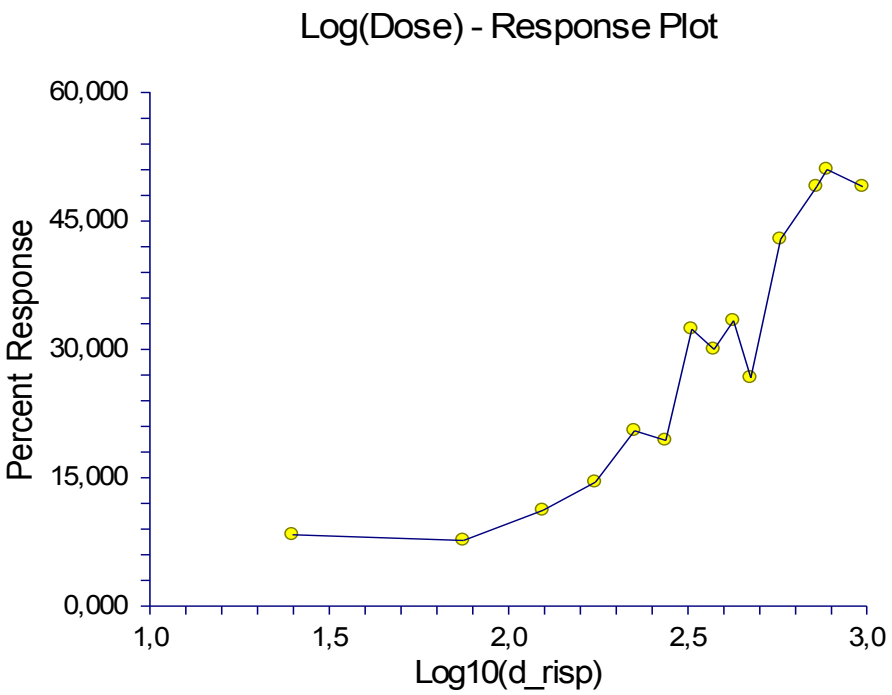


Figure 5: Example of Dose-Response-Curve (Probit-Analysis) from own clinical data. The curve shows the increasing risk of getting dyskinesia which required administration of biperidene following administration of risperidone (given chlorpromazine equivalent units). The ED50 [exactly TD50) amounts to 3.25 (SEM 0.15) CPUs (Note: the dose is given in a log10 scale (NCSS 2007; Version 07.1.21).

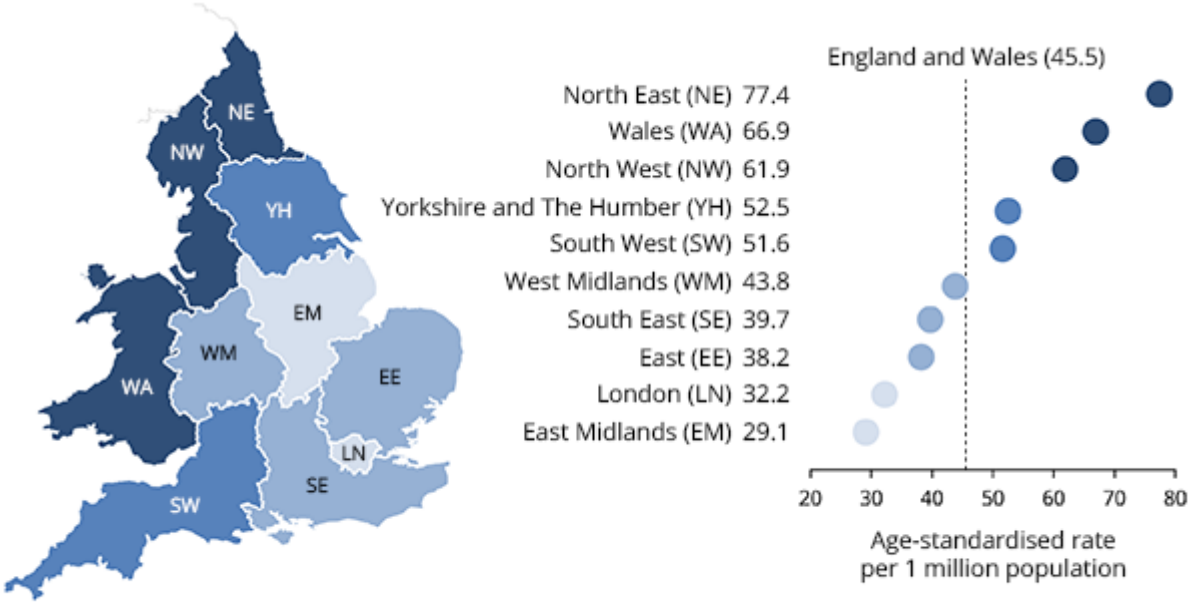


Figure 6: Distribution of drug related deaths in England and Wales.Comparing the statistics with the figure below rural regions have quite astonishing high rates of drug related deaths. Source: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations. Accessed 03.03.18[2]

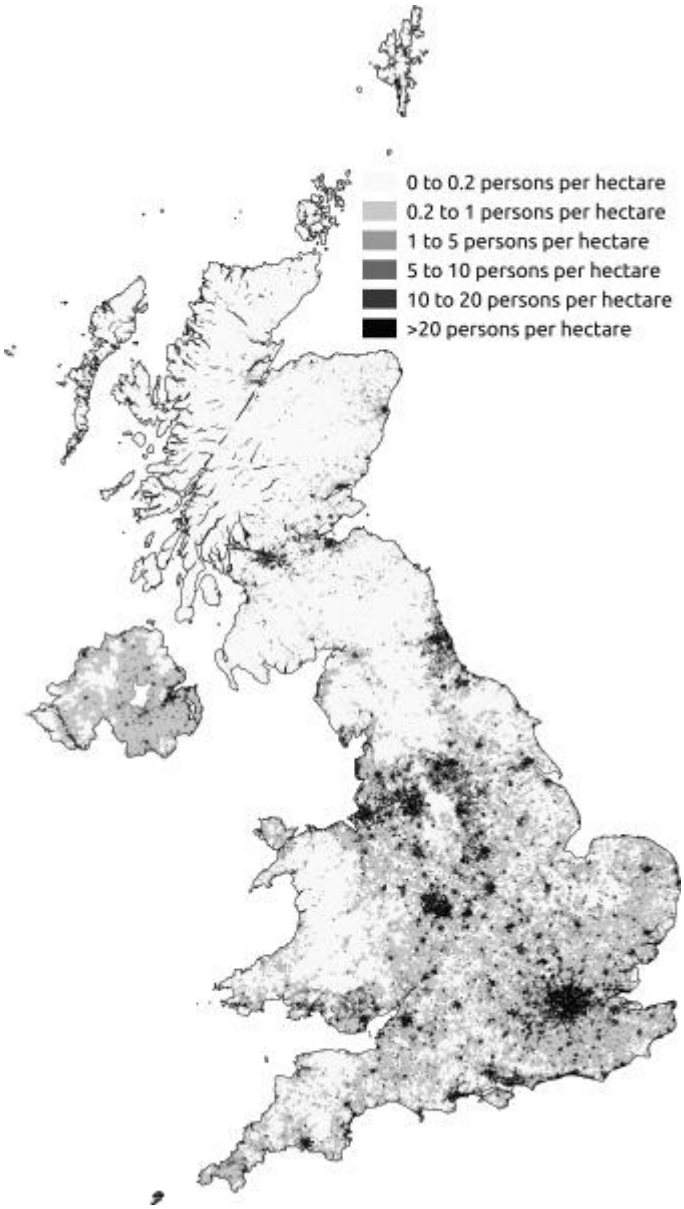


Figure 7: In order to understand the distribution of drug related deaths in the UK , one must have an idea about distribution of the population: Source: https://de.wikipedia.org/wiki/Vereinigtes_K%C3%B6nigreich. Accessed 03.03.18[94]

Abbreviations

AchEI	Acetyl-Choline-Esterase-Inhibitor
ATC	Acute toxic class. A probit based model to estimated toxicity with reduced number of animals.
ADH	alcohol dehydrogenase
AMP	α-Aminotryptamine
α-PVP	α-Pyrrolidino-pentio-phenone (NPS)
BBC	British Broadcasting Cooperation
BP	Blood Pressure (normally given as mmHg)
BW	Body Weigth
CPS	Crown Prosecution Service
CPU	Chlopromazine Equivalent Units (e. g. haloperidol or risperidone have a CPU of 50)
DMT	Dimethyl-Tryptamine
ED50	Effective Dose 50 (50 % of the individuals show a specific – in general wished - effect). Analogously EC50 can be defined.
F	female
Fig	Figure
H	Hour
HAART	High Active Anti-Retroviral Therapy

HR	Heart Rate (generally bpm - beats per minute)
LADME	Liberation – Absorption – Distribution – Metabolism - Elimination
LD50	Lethal Dose 50; the dose at which half of the species die, normally given as mg/kg BW. Analogously LC50 can be defined.
LSD	Lyserg-Acid-Diethylamide
OECD	Organisation for Economic Co-operation and Development
ONS	Office for National Statistics
OTC	Over the Counter
M	male
MAOH	Mono-Amino-Oxidase-Inhibitor
MDA	Misuse of Drugs Act (1971)
MDMA	3,4 Methylene-dioxy-methamphetamine (ecstasy)
MDPV	Methylene-dioxy-Pyrovalerone
MLD	Mean Lethal Dose
MOE	Margin of Exposure (Ratio of NOEL to the estimated in take in humans; therefore it is an indicator of the potential risk)
NOEL	No observed adverse effect level
NOEC	No observed adverse effect concentration (corresponds to the highest dose or concentration without toxic effects)
Nac	Nucleus accumbens
NPS	New Psychoactive Substances (also NPD New Psychoactive Drugs)

PACE	Police and Criminal Evidence Act of 1984
PF	Procurator Fiscal (in some way similar to the coroner)
PFC	Prefrontal Cortex
pka	Acid dissociation constant (note: pka + pkb=14)
sl	sublingual
SSRI	selective serotonin re-uptake inhibitor (antidepressant)
TD50	Toxicity Dose 50 (dose causing an adverse effect in 50 % a population). Analogously TC50 can be defined.
THC	Tetrahydrocannabinol
TI	Therapeutic Index (defines as ED50/LD50 or ED50/TD50 with regard to the preclinical or clinical model)
VTA	Ventral Tegmental Area
VX	Highly toxic war poisons (Acetylchloline-esterase-inhibitors) (“Venomous”).
YLL	Years of Life lost