Drugs

A PRIMER FOR COURTS

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The judicial primers project is a unique collaboration between members of the judiciary, the Royal Society and the Royal Society of Edinburgh. The primers have been created under the direction of a Steering Group initially chaired by Lord Hughes of Ombersley, who was succeeded by Dame Rafferty DBE, and are designed to assist the judiciary when handling scientific evidence in the courtroom. They have been written by leading scientists and members of the judiciary, peer reviewed by practitioners, and approved by the Councils of the Royal Society and the Royal Society of Edinburgh.

Each primer presents an easily understood, accurate position on the scientific topic in question, and considers the limitations of the science and the challenges associated with its application. The way scientific evidence is used can vary between jurisdictions, but the underpinning science and methodologies remain consistent. For this reason, we trust these primers will prove helpful in many jurisdictions throughout the world and assist the judiciary in their understanding of scientific topics. The primers are not intended to replace expert scientific evidence; they are intended to help understand it and assess it, by providing a basic and (so far as possible) uncontroversial statement of the underlying science.

The production of this primer on drugs, drug testing and toxicology has been led by Professor Kim Wolff MBE. We are most grateful to her, to the Executive Director of the Royal Society, Dame Julie Maxton CBE, the Chief Executive of the Royal Society of Edinburgh, Professor Sarah Skerratt, and the members of the Primers Steering Group, the Editorial Board and the Writing Group. For the full list of acknowledgements, see page 107.

Sir Adrian Smith
President of the Royal Society

Sir John Ball
President of the Royal Society of Edinburgh

Introduction and scope

This primer is concerned with drugs likely to be encountered in courts, especially in the criminal justice systems (CJSs) of the UK, with drug testing and with toxicology. It is largely a reference tool. This introduction outlines the topic in broad terms and helps the reader to navigate the sections that follow.

In a clinical context, a drug is a chemical used in the diagnosis, treatment or prevention of disease. The World Health Organization (WHO) defines a drug as "any chemical entity or mixture of entities not required for the maintenance of health that alters biological structure or function when administered"[1], thus referring to non-clinical use. Drugs produce quantitative changes in cell behaviour, increasing or decreasing the magnitude or duration of normal cell activities. However, not all drug effects can be easily quantified.

Many drugs have legitimate medical applications but are also used for non-prescription or recreational purposes. Over the past decade new and often more dangerous synthetic drugs have come to market. Their producers might attempt to circumvent the law by continuously modifying chemical composition to avoid prosecution and to obfuscate the processes required to identify them.

This primer is intended for courts throughout the UK. Differences in the collection and reporting of data across nations mean that direct comparisons are not always possible within this text. Evidence of drug use trends is monitored through the Crime Survey for England and Wales (CSEW) and the Scottish Crime and Justice Survey. In England and Wales there was no change in the overall level of any drug use in 2022 compared to 2020. In adults (16 – 59 years old), almost half of all illegal drugs were obtained through a friend, neighbour or colleague (48.4%) rather than a dealer (22.8%)[2]. Most adult drug misusers in treatment in the UK still report opiates (primarily heroin) as their main problem.

In Scotland, during 2018 – 2020, 13.5% of adults self-reported using one or more drugs during the 12 months prior to the survey, which was up from 9.5% in 2017 – 2018. The most reported drug used was cannabis, followed by non-prescribed use of prescription drugs (5.1%), cocaine (3.0%), ecstasy (1.6%) and poppers (isobutyl nitrite or amyl nitrate) (1.2%)[3].

1 World Health Organization. (n.d.). *Drugs (psychoactive).* https://www.who.int/health-topics/drugs-psychoactive (accessed 12 February 2024)

2 Office for National Statistics. (2022). *Drug misuse in England and Wales: year ending June 2022.* https://www.ons.gov.uk/peoplepopulationandcommunity/crimeandjustice/articles/drugmisuseinenglandandwales/yearendingjune2022 (accessed 12 February 2024)

3 Scottish Government. (2021). *Scottish Crime and Justice Survey 2019/20: main findings.* https://www.gov.scot/publications/scottish-crime-justice-survey-2019-20-main-findings (accessed 12 February 2024)

In the UK the misuse of Class A drugs is less common among young people who often use a variety of substances recreationally without treatment for addiction disorders. At present, therefore, cases handled within the CJSs might involve more than one substance.

Regarding deaths from drug use in England and Wales (registered in 2021), about half involved an opiate (45.7%; 2,219 deaths). Of these, 840 involved cocaine, which was 8.1% more than in 2020 and >7 times higher than a decade ago (112 deaths in 2011). The Northeast of England continued to have the highest rate of deaths relating to drug poisoning and drug misuse; London had the lowest rate of drug poisonings and the East of England was lowest for drug misuse[4]. The number of people dying from drug misuse in Scotland had fallen for the first time in 5 years but remains higher than elsewhere in Europe. Figures released by the National Records of Scotland (NRS) show that in 2022, even with the decrease, Scotland's drug deaths were still 3.7 times higher than in 2000. Most of the 1,051 deaths recorded were due to accidental drug overdoses[5,6].

Drug testing reports provided to the police or CJS vary across the country. The reasons for this are that there are several forensic science providers that work under contracts issued by police forces or collaborations of such forces. The requirements in these contracts differ, which can lead to different information being produced for the CJS. Additionally, the regional structures of the Crown Prosecution Service can have an impact. In Scotland prosecutions are led by the Crown Office Procurator Fiscal Service rather than the Crown Prosecution Service.

The Forensic Science Regulator (Section 6) sets out detailed requirements specific to the CJS in the Codes of Practice and Conduct (the Codes). The Codes are supported by guidance documents issued by the Regulator. The Regulator requires that providers demonstrate their achievement and maintenance of the standards by means of independent assessment and accreditation. In the areas of drugs, the Regulator requires accreditation to both ISO 17025 and the Codes. In Scotland and Northern Ireland, the forensic science laboratories follow the guidance of the Regulator but are not bound by this in a statutory way.

4 Office for National Statistics. (2023). *Deaths related to drug poisoning in England and Wales: 2022 registrations.* https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2022registrations (accessed 12 February 2024)

5 Christie, B (2023). *Drug deaths fall in Scotland but major problems persist. BMJ, 382,* 1947. https://doi.org/10.1136/bmj.p1947 (accessed 12 February 2024)

6 National Records of Scotland. (2023). *Drug-related deaths in Scotland in 2022.* https://www.nrscotland.gov.uk/files//statistics/drug-related-deaths/22/drug-related-deaths-22-report.pdf (accessed 12 February 2024)

Forensic chemistry is the discipline that underpins the analysis of material in its broadest sense. Forensic toxicology is the application of toxicology and disciplines such as analytical chemistry, clinical chemistry and pharmacology to determine the presence of a drug of interest as evidence in a forensic case. Items recovered by the police are commonly submitted for forensic analysis to determine whether an illegal substance is present.

Drugs can be grouped into the following broad categories:

- **natural origin**
  pharmacologically active substances extracted and purified from plants, such as delta^{9}-tetrahydrocannabinol (THC), the principal pharmacologically active constituent of cannabis from the sativa plant;
- **semi-synthetic origin**
  where naturally occurring substances are chemically altered to create new pharmacologically active materials such as diacetylmorphine (heroin);
- **fully synthetic origin**
  such as 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) or fentanyl.

Most questions involving drug use and testing focus upon the following two concepts:

- what the body does to the drug (pharmacokinetics);
- what the drug does to the body (pharmacodynamics).

Both are relevant to the potential of a drug to injure the user. Pharmacokinetics is also particularly relevant to:

- which methods of administration are available;
- knowing where to look for either the drug or its derivatives if testing for use, and for how long it might have been present.

Properties of pharmacokinetics can be summarised by the acronym LADME (Table 1).

TABLE 1

Key pharmacokinetic principles as demonstrated by the acronym LADME.

LADME	Definition
Liberation	Release of a drug from its pharmaceutical formulation to achieve active impact on the body.
Absorption	Movement into the body following different means of administration, such as oral swallowing and inhalation.
Distribution	A drug's movement around the body, the extent of distribution and where it may be found.
Metabolism	The way in which the body converts (metabolises) some drugs into other substances (metabolites). Metabolites can often be identified and measured. Some, but not all, are specific to a particular drug.
Elimination	Where a drug is removed from the body, especially through excretion. Excreted products can consist of metabolised or unmetabolised substances and the timescales for excretion can vary.

Courtesy K Wolff.

The second concept (pharmacodynamics) is particularly relevant to the potential to injure. Scientists need to know the mechanisms of the drug's action, the parts of the body that are likely to be affected and how. In conjunction with pharmacokinetics, pharmacodynamics also indicates how long the drug or its derivatives might be present and where. This is directly relevant to testing.

It is also important to know which cell receptors a given drug can act upon and how it binds to them. Key concepts are agonists, which bind to and activate a receptor, and antagonists, which bind to a receptor without activating it, blocking or reducing activation by agonists (Section 3.2.1).

Many drugs are considered psychoactive. This medical term denotes substances that influence the brain and the central nervous system (CNS), and that alter behaviour, cognition and perceptions of reality. Psychoactive drugs can be freely available, illicit or controlled. Under the Psychoactive Substances Act 2016 it is illegal to produce, supply or import any substance that can produce a psychoactive effect following human consumption, including for personal use. The Act excludes food, alcohol, tobacco, nicotine, caffeine and medical products, as well as controlled drugs, which are regulated by the Misuse of Drugs Act 1971. The 2016 Act also exempts healthcare activities and approved scientific research.

Some substances exist in prodrug form. This term denotes a pharmacologically inactive compound that must undergo chemical conversion (metabolism) in the body to become an active pharmacological agent. Examples include psilocybin (the compound found in 'magic mushrooms'), which becomes pharmacologically active when metabolised into psilocin, and oxycodone, a semi-synthetic opioid used to treat moderate to severe pain.

Many drugs are available in a formulation. This is a mixture, made to a specific recipe, of the active medicinal drug and one or more inactive substances (excipients). The formulation often influences the onset and pace of pharmacological activity within the body.

A drug, metabolite or other substance undergoing analysis is commonly referred to as an analyte. Testing is undertaken in prison medical facilities, secure units, drug-driving cases, inquests, in other medico-legal situations and during statutory supervision. It might also be required during employment screening for roles with significant health and safety considerations and that require abstinence from psychoactive substances such as driving, handling machinery or responsibility for the safety of others.

Every substance, or compound, has a unique chemical signature (set of characteristics). This is typically used to identify a given compound by deploying scientific methods replicable by other analysts and presentable as fact in court. Sample identification involves separating out and investigating the chemical signature of each compound and comparing this against standard reference materials.

The primer is structured as follows:

Section 1
A summary of key terminology.

Section 2
Different methods of drug administration. This section explores key pharmacokinetic processes in the body and offers a brief overview of pharmacodynamics.

Section 3
Drug classes likely to be encountered within the CJS. This section also outlines the actions of various drugs and associated implications for testing.

Section 4
Methods of use and abuse such as addiction, dependence, overdose and withdrawal.

Section 5
Sample collection and processing, including:

- the Forensic Science Regulator and the accreditation of laboratories by the UK Accreditation Service (UKAS);
- sources of testable samples such as hair, urine, oral fluid and blood;
- the chain of custody for sample handling.

Section 6
Principal testing methods and considerations, from laboratory procedures such as spectrometry and chromatography to on-site immunoassay screening tests.

References are in footnotes to highlight areas for further reading. A glossary is in Appendix A, and a summary of relevant legislation in Appendix B. Appendix C sets out a table of principal drugs, with their colloquial name(s), likely to be encountered within the CJSs. Appendix D provides some technical detail on high, medium and low selectivity analytical techniques.

1. Key terminology

This section considers some core terminology used in the CJSs of the UK.

1.1 Anabolic steroid drugs

Also known as anabolic-androgenic steroids (AAS), they are a class of drugs that are structurally related to testosterone, the main male sex hormone, and produce effects by binding to the androgen receptor. Anabolic steroids can be divided into two groups:

- synthetic hormones: eg oxandrolone, oxymetholone;
- steroid ester derivatives: eg testosterone cypionate, nandrolone decanoate.

AAS are Class C drugs and are taken to promote an enhanced body image by body builders and gym attendees or to improve performance to gain an unfair advantage in professional sports events.

1.2 Chemsex drugs

'Chemsex' is used to describe intentional sex under the influence of psychoactive drugs. Chemsex drugs are used during sexual activity. Stimulant drugs, which increase arousal and confidence, include mephedrone and crystallised methamphetamine. Sedative drugs, which might reduce inhibition, include gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL) and amyl nitrate.

1.3 Controlled drugs

In the UK this means drugs specified in the Misuse of Drugs Act 1971, which regulates import, export, possession, supply and licensing.

1.4 Crude drugs

These are drugs that have a plant, animal or microbiological origin, are found in a raw form, and are used for the diagnosis, treatment or prevention of disease in humans or other animals. Examples include digitalis, nutmeg, honey and ginger.

1.5 Date rape drugs

These are drugs that facilitate sexual assault. Administration of date rape drugs is typically used to render a victim physically incapacitated or helpless and thus incapable of giving consent. Examples include alcohol, GHB, flunitrazepam (Rohypnol) and ketamine (Ketalar).

1.6 Designer drugs

These are synthetic drugs designed to mimic the pharmacological effects of controlled drugs to avoid detection of illegal substances during routine drug screening. They can be structural or functional analogues of the controlled drug. Designer drugs largely comprise: (a) psychoactive substances designated by the EU as new psychoactive substances (Section 3.12); and (b) analogues of performance-enhancing drugs such as designer steroids. Certain designer drugs are now covered by the Psychoactive Substances Act 2016.

1.7 Empathogenic drugs

These drugs increase an individual's feelings of empathy, benevolence and emotional openness. The archetypical drug is MDMA.

1.8 Generic drugs

This is a term used within the pharmaceutical industry. Generic drugs (such as sildenafil, used to treat erectile disfunction) can be manufactured once the branded drug (in this case Viagra) comes off patent. The active ingredients must be identical in composition and their chemical and physical properties must meet pharmaceutical quality requirements.

1.9 Illicit drugs

Illicit drugs do not generally serve a medical purpose. However, this definition is not clear cut, since some drugs technically considered illicit are tested in clinical trials for illnesses, such as lysergic acid diethylamide (LSD) for anxiety and depression. New drugs recently emerging might be illicit in nature but not yet controlled by the Misuse of Drugs Act 1971.

1.10 Image- and performance-enhancing drugs

This wide-ranging heterogenic group of drugs includes androgenic anabolic steroids (Section 1.1), growth hormones and related products, peptide hormones, and other drugs used to increase muscularity and modify appearance. Use of these has increased significantly over the past decade. A class of substances named erythropoiesis-stimulating agents enhance performance and endurance by raising the number of circulating red blood cells. Beta blockers disrupt the effects of stress hormones and are used legally in various sporting activities such as snooker and darts.

1.11 Medicinal drugs

The Medicines Act 1968 and Council Directive 2001/83/EC control the sale and supply of medicines. Establishing the legal status of a medicinal product is part of its marketing authorisation, and products might be available as:

- Prescription-only medicines (POMs). These are controlled drugs specified in and regulated by the Prescription Only Medicines (Human Use) Order 1997 (SI 1997/1830), as amended. Some, such as preparations containing codeine or morphine, might be controlled drugs specified in the Misuse of Drugs Act as exempted for medicinal use. POMs may be supplied to the public only on a practitioner's prescription. Prescriptions may be issued by doctors, dentists, nurse independent prescribers, pharmacist independent prescribers and supplementary prescribers.
- Over the counter (OTC) medicines. These drugs do not require a prescription. Certain OTC medicines might contain small quantities of controlled drugs. Whilst some OTC medicines can be sold only by a pharmacist, others (such as paracetamol or ibuprofen) can be purchased off-the-shelf in retail outlets.
- General sales licence drugs. These drugs can be sold in retail outlets without pharmacist supervision. These medicines must not contain controlled drugs.

1.12 Mimetic drugs

Mimetic drugs imitate the pharmacological effects of another compound. For instance, synthetic cannabinoids were originally designed to mimic the effects of the active ingredient in cannabis, THC. Synthetic opioids are intended to mimic the effects of opiates like heroin.

1.13 Psychostimulant drugs

This is a large class of drugs characterised as either direct or indirect sympathomimetic stimulants (Table 2). Psychostimulant activity is linked to the release of dopamine and heightened arousal, alertness and motor activity. Psychostimulant drugs mimic the effects of the sympathetic nervous system, increasing heart rate and blood pressure. Directly acting sympathomimetic stimulants act on α or β receptors, whereas those acting indirectly increase norepinephrine to activate α or β receptors.

TABLE 2

Common drugs classified as psychostimulants, including direct and indirect sympathomimetics[7].

Direct sympathomimetics	Indirect sympathomimetics
Epinephrine/adrenaline	Amphetamine
Norepinephrine	Methamphetamine
Phenylephrine	Cocaine
Phenylpropanolamine	Methylphenidate

Courtesy K Wolff.

1.14 Recreational drugs

This loose term denotes a variety of legal and illegal drugs used without medical supervision, often in the belief that occasional use is not habit forming or addictive. Recreational drugs are typically taken during group activities to relax, improve mood and enhance confidence. They can be broadly categorised as follows:

- **Depressant drugs** slow heart rate, respiratory rate and blood pressure. They include alcohol, cannabis, GHB and the gabapentinoids.
- **Stimulant drugs** activate the CNS to increase heart rate, respiratory rate and blood pressure. They include cocaine, methamphetamine and MDMA.
- **Hallucinogenic drugs** distort perception and generate subjective changes in thought, emotion, and consciousness, though to a lesser extent than psychoactive drugs.

7 Koob, G F, Arends, M A and Le Moal, M. (2014). *Drugs, addiction and the brain* (1st ed.). Academic Press. https://www.sciencedirect.com/book/9780123869371/drugs-addiction-and-the-brain (accessed 12 February 2024)

1.15 Small and large molecule drugs

Small molecule drugs (SMDs) are chemically synthesised compounds with low molecular weight and simple, known structures. Most drugs can be considered SMDs.

Large molecule drugs, also known as biologics, can consist of peptides, proteins or nucleic acids. They might be isolated from natural sources or generated using complex biological or chemical production methods. Their chemical composition and structure are more difficult to analyse than those of SMDs and they are less stable during storage and within the body. Examples of biologics include performance-enhancing drugs such as erythropoietin (an erythropoiesis-stimulating hormone, Section 1.10) and human growth hormone and drugs used for weight loss such as Wegovy, Ozempic and Mounjaro. Synthetic versions of biologics can be very difficult to distinguish from their endogenous forms.

Whereas many SMDs can be administered orally and can pass through cell membranes to reach the site of action, biologics generally require injection or other non-oral administration. Biologics have a high commercial value, which can be further increased by changing the labels or by refilling used vials for re-sale.

1.16 Smart drugs (nootropics)

Nootropic, or cognitive enhancer, drugs affect nerve cell metabolism to improve executive functions such as memory, concentration or stress tolerance. The term also refers to drugs that improve the intellectual capacity of individuals suffering neurological diseases and psychological disorders. Nootropics include natural and synthetic substances. Examples include Panax ginseng (Asian ginseng), ginkgo biloba (herbal supplement), modafinil (non-amphetamine CNS stimulant) and methylphenidate (Ritalin, used to treat attention deficit hyperactivity disorder).

1.17 Sympathomimetic drugs

These drugs have stimulant properties that increase heart rate and blood pressure. Examples include dopamine and epinephrine/adrenaline.

1.18 Veterinary drugs

Drugs typically administered to animals are sometimes prescribed for human consumption, particularly for pain relief. Examples include tramadol and ketamine. Boldenone is a veterinary steroid not approved for human use but remains popular with professional weightlifters and/or bodybuilders[8].

8 Linhares, B L, Miranda, E P, Cintra, A R *et al.* (2022). Use, misuse and abuse of testosterone and other androgens. *Sexual Medicine Reviews, 10(4),* 583-595. https://doi.org/10.1016/j.sxmr.2021.10.002 (accessed 12 February 2024)

2. Pharmacokinetics and pharmacodynamics

2.1 Pharmacokinetics

This section outlines basic pharmacokinetics (PK); that is, what happens to a drug in the body following consumption. This branch of pharmacology explores the relationship between administered doses of a substance and observed blood (plasma or serum) or tissue concentrations in the body. The following paragraphs explain the key concepts of liberation, absorption, distribution, metabolism and elimination/excretion (Table 1).

2.1.1 Liberation

There are various types of drug release from a formulation, most commonly including:

- immediate (typical administration);
- delayed (release some time after administration);
- extended (slow release over a prolonged period with reduced dosing).

For drugs taken orally, liberation processes include disintegration of tablets or dissolution of soluble capsule coatings. The formulation of the drug can therefore influence the onset of pharmacological activity and, importantly, prolong it in slow-release formulations.

2.1.2 Absorption

Absorption is the movement of a drug across cell membranes to reach the site of action (for drugs, the receptor site) via the circulatory system. It is an important consideration for users who seek fast absorption for a rapid onset of effects and for scientists who seek to interpret drug concentrations following oral administration. The extent and rate of absorption depends upon a substance's chemical properties, the formulation and the administration route. Time to peak plasma concentration (Tmax) is the most widely used index of absorption rate. The slower the absorption, the longer the time taken.

There are four principal methods of drug administration:

- **Transmucosal routes:** Mucous membranes form the moist surfaces that line the mouth, nose, eye sockets, throat, rectum and vagina. They have a superior blood supply and are more permeable than the epidermis. This leads to rapid absorption across mucous membranes into the bloodstream, particularly for lipophilic (fat-soluble) drugs.

  Certain illicit drugs are administered rectally, sometimes using tampons. Absorption across the rectal mucosa may rapidly deliver significant quantities of drug into the bloodstream via anorectal venous circulation (the flow of blood through veins and sinuses)[9]. Nicotine in the form of chewing tobacco and cocaine powder placed sublingually on the gums is absorbed through mucous membranes in the mouth.

- **Insufflation:** Illicit substances such as cocaine, ketamine and tobacco snuff are often insufflated (sniffed or snorted), which leads to absorption across mucous membranes in the nose and sinus cavities into the cerebral circulation (the flow of blood through arteries and veins that supply the brain), producing the sought-after euphoric state or 'high'. After nasal administration, the concentration of some drugs in the CNS may be higher than in plasma[10].

- **Inhalation:** For many drugs, inhalation is the quickest route to the desired effects. Inhaled drugs are absorbed into the bloodstream across alveolar membranes in the lungs. This might in healthy individuals occur in gaseous form (such as vapours from solvents), in fine liquid drops (such as heroin or cocaine) or in fine particles of matter suspended in a gas (such as aerosols, or tobacco smoke vaped using e-cigarettes).

9 Gupta, M, Bailey, S and Lovato, L M. (2009). Bottoms up: methamphetamine toxicity from an unusual route. *The Western Journal of Emergency Medicine, 10(1)*, 58-60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2672287/ (accessed 12 February 2024)

10 Calvey, T N and Williams, N E. (2008). Drug absorption, distribution and elimination. In Calvey, T N, and Williams, N E. (Ed.). Principles and practice of pharmacology for anaesthetists (5th ed, pp 1-22) https://doi.org/10.1002/9781405194853.ch1 (accessed 12 February 2024)

Glue 'sniffing' is a technically incorrect expression, as glue vapours are inhaled and absorbed across the linings of the lung. Smoking as a joint or in a water pipe is a common mode of cannabis administration, which requires heating through smoking to convert the non-psychoactive precursor tetrahydrocannabinolic acid (THCA, 2-COOH-THC) into THC. Most synthetic cannabinoids are already present in stable psychoactive forms and vaporise without decomposition when smoked, leading to rapid absorption[11].

- **Parenteral (injection):** Some drugs are administered directly into the body, usually via one of four routes:
  - **Subcutaneous injection ('skin popping'):** injecting a drug under the skin. Absorption from the injection site is slower than the intravenous route but faster than oral administration.
  - **Intramuscular injection:** deeper penetration of a drug into muscle tissue. The drug is injected in solution or suspension directly into the muscle mass, where it is slowly absorbed into the bloodstream by perfusion (the circulation of blood through tissues). Resting muscle has a lower blood supply than subcutaneous tissue.
  - **Intravenous use ('mainlining'):** direct administration of a drug into the bloodstream. It allows relatively large quantities to be administered rapidly and at one time but poses the highest risk of toxicity and overdose[12]. Needle spiking is when a person is injected with a substance without their consent. This would be difficult to achieve unless the individual was incapacitated or very intoxicated. In practice it is thought very unlikely to be a legitimate means to 'drug' someone because of the time it would take to empty a syringe containing a drug solution into the body without this being noticed.

11 Auwärter, V, Dresen, S, Weinmann, W *et al.* (2009). 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? *Journal of Mass Spectrometry, 44,* 832-837. https://doi.org/10.1002/jms.1558 (accessed 12 February 2024)

12 Wolff, K. (2002). Characterization of methadone overdose: clinical considerations and the scientific evidence. *Therapeutic Drug Monitoring, 24(4),* 457-470. https://doi.org/10.1097/00007691-200208000-00001 (accessed 12 February 2024)

- **Oral administration:** swallowing drugs that are absorbed primarily in the small intestine. This absorption route is often slow and can be delayed by food in the digestive tract, which can also contribute to variability in drug response. The benzodiazepine diazepam, for example, is rapidly absorbed, with the time to peak plasma concentration in the blood within an hour for adults and more quickly for children (15 – 30 minutes). Water-soluble, lipophobic drugs such as cocaine hydrochloride are rarely fully absorbed within the typical 2 – 4-hour transit period through the small intestine, thus for these drugs insufflation is a preferred administration route.

Certain drugs might be rendered ineffective by stomach acidity when taken orally. Heroin users, for example, avoid the oral route when seeking an immediate 'rush'. Lipophobic compounds such as alcohol readily cross cell membranes by passive diffusion and are rapidly absorbed from the gut, particularly on an empty stomach. Drugs absorbed after oral ingestion traverse the gut wall and pass into the portal vein, which flows directly to the liver. Many are metabolised (the 'first-pass' effect) before reaching the bloodstream and therefore do not enter the general circulation or appear in low concentrations.

Complications associated with intestinal absorption of illicit drugs have been reported for body packers and stuffers. Body packers or 'mules' deliberately swallow packets (such as condoms) containing large quantities of drugs with the intention of subsequently defecating the packets intact. Body stuffers swallow drugs in haste in an attempt to avoid prosecution. These individuals may experience toxicity when packets fail, inadvertently releasing drugs into the gastrointestinal tract or when absorption occurs following rapid consumption of haphazardly packaged drugs. Once an individual is in custody, elimination of drug packages usually occurs without severe complications[13].

Bioavailability indicates the proportion of active drug that reaches the general blood circulation and which is available at the site of action. In practice, this parameter is difficult to establish for drugs acting through the CNS, which need to cross the blood-brain barrier. Bioavailability is expressed as the letter 'F' (fraction of the dose). Drugs administered intravenously are assumed to have an absolute bioavailability of 100% (F = 1), while drugs administered by other routes usually have an absolute bioavailability of less than one[14].

13 Heymann-Maier, L, Trueb, L, Schmidt, S *et al.* (2017). Emergency department management of body packers and body stuffers. *Swiss Medical Weekly, 147(3738).* https://doi.org/10.4414/smw.2017.14499 (accessed 12 February 2024)

14 Wolff, K. (2016). Basic pharmacokinetics of substance misuse Chapter 2, In Wolff, K, White, J and Karch, S. (Eds.), *The SAGE Handbook of Drug and Alcohol Studies* (pp 37-57). London: SAGE publications Ltd. https://doi.org/10.4135/9781473922143 (accessed 12 February 2024)

2.1.3 Distribution

Distribution is the reversible transfer of drug from one location to another via bodily fluids and tissues after it enters the bloodstream. Some drugs, such as fentanyl and alcohol, are widely distributed whilst others, such as methadone, may become concentrated in certain tissues. Hydrophilic (water-soluble) drugs tend to remain within the blood and in the fluid that surrounds cells.

Most drugs, however, do not spread evenly throughout the body. High degrees of plasma protein binding, where drugs attach to blood proteins such as albumin, inhibit drugs from crossing cell membranes to achieve a pharmacological effect, although binding is reversible. The extent of binding will affect the concentration of unbound (free) drug in the blood and thus the amount available to reach the drug target (receptor site). Binding is also influenced by a drug's physicochemical properties, an individual's disease state and/or the physiological condition of the body. It is often expressed as the bound-to-total drug concentration ratio, presented as a fraction of 1.0 or as a percentage.

As unbound drug is distributed to tissues, the concentration in the circulatory system decreases. Blood proteins gradually release the drug that is bound to them. Some drugs, such as diazepam or lorazepam, are sequestered in adipose (fat) tissue, whilst others, such as methadone, display affinity for bone tissue. Lipophilic drugs accumulate in tissues, which can act as a reservoir, slowly releasing the drug into the bloodstream, preventing rapid decreases in drug blood concentration and maintaining its effect. Some drugs, such as diazepam, leave tissues so slowly that they circulate in the bloodstream for days after cessation of use.

To enter the brain drugs must be highly lipophilic, such as THC and heroin. Such drugs can also cross the placenta to affect the fetus; these drugs can also be found in the milk of lactating women. Other drugs concentrate mainly in one small area of the body. For example, tissues in the thyroid gland have a special affinity for iodine[15].

15 Le, J. (2022). *Drug distribution*. School of Pharmacy and Pharmaceutical Sciences, University of California San Diego. Retrieved from https://www.msdmanuals.com/en-gb/professional/clinical-pharmacology/pharmacokinetics/drug-distribution-to-tissues (accessed 12 February 2024)

Most analytical procedures measure the total amount of bound and unbound drug in the blood since it is not always possible to distinguish the two. Analysts are typically aware, however, that blood concentrations of highly bound drugs (such as cannabis) are usually low compared to those of drugs (such as amphetamine) that exist in blood largely unbound. Analysis of the former requires sophisticated techniques.

These considerations are important when assessing drug concentrations in the body. Uneven distribution hampers accurate interpretation and complicates efforts to correlate blood drug concentrations with behaviour. High blood drug concentrations are usually related to greater behavioural effects, most of which increase linearly with dose. Some drugs, however (such as cannabis and the barbiturates), pass peak plasma concentration (Cmax) before the most pronounced behavioural effects emerge. In individuals with low alcohol tolerance, blood alcohol concentrations are highly correlated with behavioural effects but for dependent individuals this relationship does not apply.

The measure of the extent of distribution is V (or Vd). V is a purely hypothetical term and does not represent an actual physical volume inside the body. It is defined as the volume of drug that would be needed, uniformly distributed, to produce the observed blood concentration, assuming that concentration across tissues and plasma is the same.

It is generally assumed that if a drug is found (‘held’) in the bloodstream it will have a small V, and vice versa. Both the parent drug and its metabolites can be detected in blood. Many basic drugs, such as amphetamine, are extensively absorbed by tissues and thus may have an apparent V larger than the volume of the entire body. If V lies between 7.4 and 15.7 L, the drug is understood to be distributed throughout the blood (plasma and red blood cells). If V is larger than 42 L, the drug is thought to be distributed to all tissues, especially the adipose tissue. The V for alcohol is estimated to be about 37 L, for GHB 52.7 ± 15.0 L and for ketamine 7.35 ± 0.74 L.

2.1.4 Metabolism

Metabolism is the irreversible and universal biotransformation of drugs, which changes lipophilic into hydrophilic compounds. Variability in metabolism can be observed between individuals. Some drugs have specific metabolites (eg cocaine and benzoylecgonine) whilst others, such as opiates and benzodiazepines, have common metabolites shared by other drugs in the same class. Many metabolites are derived from the same parent drug. There are, for example, at least 25 known metabolites for THC. Some drug metabolites are pharmacologically active, producing the same or stronger effects than the parent drug.

Some drug metabolites may be found in the blood and identified there, whilst others are produced during elimination and are detected in urine. Once in metabolite form the drug is compatible for excretion and the psychoactive effect is typically diminished. Drugs that are rapidly metabolised (eg cocaine) may be particularly difficult to detect in urine. In such cases the metabolites themselves can offer an indirect indication of use.

Drugs are metabolised by enzymes, acting as catalysts. This occurs mostly in the liver, although enzymes in the kidneys, gut, lungs and blood may also contribute to the metabolic process. The liver contains microsomal (insoluble) drug-metabolising enzymes and cytoplasmic (soluble) drug-metabolising enzymes; the latter metabolise alcohol and similar drugs. Because the liver is the primary site of drug metabolism, the pharmacokinetic profiles of drugs may be altered in patients with liver disease (cirrhosis). This may be an important consideration in unexplained or unexpected death. Drugs with a low extraction ratio, such as lorazepam, rely heavily on the metabolic capacity of the liver for clearance, meaning that their pharmacokinetic profiles are more likely to be impacted significantly than those with a high extraction ratio (such as morphine and ketamine).

The effects of some metabolites are markedly different from those of the parent drug and might be more harmful. For example, methanol is metabolised to generate two very toxic metabolites: formaldehyde and formic acid. During methanol poisoning these metabolites disrupt the body's acid-base balance and can damage the optic nerve.
In certain circumstances drugs can increase liver enzymes. This is known as auto-induction. The result is a higher metabolic rate, and usually a more rapid conversion of the ingested drug into its metabolites. This increased metabolic rate can result in increased intensity and speed of onset of drug effects if the original drug was inactive and the metabolites active. The reverse may be true if the original drug was active and the metabolites inactive.

The activities of enzymes in the body may also be influenced by genetics, and the metabolism of a given drug may be affected by an individual's genotype. This is known as genetic polymorphism. For example, the speed (fast, extensive (normal), intermediate or poor) at which codeine metabolises to morphine is influenced by the user's genotype. Poor metabolisers may therefore experience diminished pain relief whereas fast metabolisers may suffer severe opioid side effects. Metabolism of MDMA and nicotine are also affected by the genetic polymorphism of two specific enzymes. This may be important when considering abnormal or unexpected responses to drugs.

In post-mortem analysis the lifetime of certain metabolites can be used to estimate the time elapsed between injection and death.

2.1.5 Elimination

Elimination results from a combination of metabolism and excretion. The primary excretion route for most drugs is via the kidneys. Net excretion by this route may be greatly reduced by subsequent reabsorption into the bloodstream via the bile, which is known as enterohepatic cycling. Here, drugs are conjugated to glucuronic acid in the liver and then excreted into the bile, where they are metabolised back into the free drug by intestinal bacteria. The drug is then reabsorbed into plasma, prolonging its activity and delaying elimination from the body. Although not directly relevant to interpreting drug testing results, authorised scientists will be expected to know about the process and to determine whether it has affected a test result.

In pharmacokinetic terms, the plasma elimination half-life of a drug is an important parameter. This is the time taken for the concentration of a drug in the plasma to fall by 50%, usually denoted by the abbreviation t1/2. Knowledge of t1/2 helps to estimate the time at which dosing might have occurred (if the dose itself is known) and/or the time that it would take for all the substance to be fully eliminated from the body (Table 3).

TABLE 3

The elimination of a drug from the blood expressed as a function of its half-life.

Number of half-lives elapsed	Fraction of drug remaining	Percentage of drug remaining
0	1/1	100
1	1/2	50
2	1/4	25
3	1/8	12.5
4	1/16	6.25
5	1/32	3.125
6	1/64	1.563
7	1/128	0.781
8	1/256	0.39

As noted above (Section 2.1.3), parameter V relates blood concentration to the total amount of drug in the body. It may be increased by kidney failure (due to fluid retention) and liver failure (due to altered body fluid and plasma protein binding). Conversely, V may fall during severe dehydration or starvation.

The parameter CL (clearance) relates drug concentration to the rate of elimination. The CL of a drug is the volume of plasma from which the drug is completely removed per unit of time.

The elimination half-life is directly related to V and inversely related to CL. The formula for half-life is ($t_{½} = 0.693 \times V/CL$). This is because a decrease in the efficiency of elimination (and therefore in clearance) will increase the time needed to reduce the plasma concentration by 50%. Drugs with a large V are concentrated in tissues rather than plasma. However, it is the drug in plasma that is exposed to the elimination mechanisms, so an increase in V also raises the plasma elimination half-life (Table 4).

TABLE 4

Plasma elimination half-life for a selection of different substances of relevance to the criminal justice system.

Substance	Half-life	Notes
Alcohol	No half-life	The percentage of alcohol (ethanol) in the blood falls by 0.019/hour (15 mg/100 mL/hour) at a constant rate. The rate of disappearance is independent of blood alcohol concentration and is not affected by weight, gender or race.
Diamorphine (heroin)	1 – 2 minutes	Heroin acts as a prodrug and travels swiftly across the blood-brain barrier. Its half-life is so short that heroin is never detected in urine.
Cocaine	1.5 – 2 hours	Cocaine is a very fast-acting drug and metabolises into benzoylecgonine (BZE), which is non-active.
Ketamine	2 – 3 hours	The active metabolite is norketamine (with a half-life of about 1 hour), which can be detected in urine alongside minor metabolites hydroxynorketamine and dehydronorketamine.
Etizolam	3.4 – 6.9 hours	Etizolam has an active main metabolite, α-hydroxyetizolam, with an elimination half-life of approximately 8.2 hours.
Mescaline	6 hours	Usually taken orally lasting between 12 and 18 hours.
Amphetamine	10 – 12 hours	Amphetamine is water soluble and is almost entirely eliminated in urine in its parent state.
Diazepam	20 – 50 hours	Diazepam is absorbed rapidly and onset of action occurs quickly. Peak plasma concentration is achieved 0.5 – 2 hours after oral dosing. The active metabolite desmethyldiazepam has a half-life of 30 – 200 hours.
Methadone	24 – 36 hours	Methadone is a long-acting drug. Dosing usually occurs once daily.
Fluoxetine	1 – 6 days	The active metabolite, norfluoxetine, is lipophilic and has a half-life of 4 – 16 days.

Courtesy K Wolff.

Influences upon CL include drug-drug interactions, genetics, and liver and kidney function. Forensic toxicologists should be aware of these relationships when interpreting sudden unexplained drug deaths and consider or eliminate them as possible confounding factors.

When interpreting drug test results, it is usual to assume that it takes five times the elimination half-life of a drug to reach a steady state after regular dosing commences. This calculation should be done a second time where dosing was stopped and started or if dosing changes. The same rule applies to elimination and can be used to calculate the detection of drugs in urine, although with modern analytical techniques a drug may still be detectable after five half-lives, and it may be more accurate to use seven or eight half-lives (see Table 3).

It is not necessarily the case that the rate of elimination of a drug is dependent on the dose administered. For instance, if the substance follows a zero-order process, the amount eliminated will be dependent on time and not the amount ingested. Alternatively, if the substance follows first-order kinetics, the amount eliminated will be dependent on the maximum blood/plasma concentration and not time.

Elimination of zero-order (non-linear) kinetics drugs

- A constant amount of drug is eliminated per unit time.
- Occurs when drug exceeds capacity for enzymes (saturation). For example, 10 mg of a drug may be eliminated per hour; this rate of elimination is constant and is independent of the total drug concentration in the plasma.
- Intrinsic capacity of the enzymes determines the amount of drug metabolised.

Elimination of first-order (linear) kinetics drugs

- A constant proportion of the drug is eliminated per unit time.
- Rate of elimination is proportional to the amount of drug in the body.
- The higher the concentration of drug in the blood, the greater the amount of drug eliminated per unit time.

Excretion is loss of the drug from the body, mainly through the kidneys or via a pulmonary route (for inhaled drugs). The kidney acts as a pressure filter through which blood passes. Most of the water and some dissolved substances in the blood are reabsorbed during its passage through the kidney.

Minor excretion sites include sweat, oral fluid (saliva), tears, breast milk and exhaled air. They can be important in forensic analysis. For instance, detection of illicit drugs in a baby might be due to breastfeeding, or to accidental or intentional poisoning. Sweat patches can be utilised to monitor prisoners and sweat deposits can be collected as a latent fingerprint for drug-testing purposes.

Urine

The time lapse between urine formation and urination makes it difficult to produce accurate estimates of blood drug concentration from urine concentrations of drugs and metabolites. Urinary drug concentrations determined using analytical testing do not offer a reliable indication of the time of drug administration and therefore should not generally be used to estimate the degree of intoxication or level of impairment. Although the drink-driving limit is expressed in Section 11 of the Road Traffic Act 1988 in alternative concentrations for blood (80 mg/mL) and urine (107 mg/mL), the occasion for a urine test to be required of a driver by a police officer under Section 7 of the Road Traffic Act 1988 will nowadays be rare. There are practical reasons for this: a test must be performed on a second specimen of urine, given within an hour, whilst the first specimen is disregarded.

Oral fluid

Drug concentrations in oral fluid (saliva) have a stronger correlation than urine with blood drug concentrations, although large variations in oral fluid/blood ratios have been reported for different drugs within and between individuals. As there are currently no satisfactory conversion factors that can be routinely and widely used to accurately estimate blood drug concentrations based on oral fluid, this should not be relied upon in driving under the influence of drugs cases. Oral fluid is, however, used to screen for drug use in populations where abstinence is required, such as certain workplaces.

Breath

Volatile drugs such as solvents are commonly excreted in the breath. Although breath is a minor route of elimination for alcohol, the quantity of alcohol vapour excreted in this way can be reliably related to the breath alcohol concentration (BrAC). BrAC is measured using a breathalyser and serves to estimate the degree of intoxication.

The ratio of breath alcohol to blood alcohol is roughly 2,100:1. This means that 2,100 mL of breath will contain approximately the same amount of alcohol as 1 mL of blood. This value is used to calculate blood alcohol level from a breathalyser test. It is not currently believed to be influenced by gender or race[16].

2.2 Pharmacodynamics

Pharmacodynamics is the study of the biochemical and physiological effects of drugs and their mechanism(s) of action on the body. Pharmacodynamics modelling can covey the magnitude and variation of the drug response and help explain the plasma concentration and effect relationship.

Drug molecules exert their effects by interacting with target sites or 'drug targets', within or on the surface of cells. These include drug receptors, ion channels, enzymes and membrane transporters. For these interactions to occur, a drug must be transported to the site of action, which for psychoactive drugs is predominantly in the brain and which will require drugs to cross the blood-brain barrier.

2.2.1 Receptors

When drugs are considered to bind to receptors they are referred to as ligands. Psychoactive drugs act by binding to receptors (protein molecules) largely in the brain. This triggers a cascade of biological responses that the user will experience as the drug effect. It is important to note that the relationship between concentration and effect is usually non-linear, ie double the concentration does not result in a two-fold increase in effect but will increase the duration of effect by one half-life[17].

16 Jones, A W and Cowan, J M. (2020). Reflections on variability in the blood-breath ratio of ethanol and its importance when evidential breath-alcohol instruments are used in law enforcement. *Forensic Sciences Research, 5(4),* 300-308. https://doi.org/10.1080/20961790.2020.1780720 (accessed 12 February 2024)

17 Salahudeen, M S and Nishtala, P S. (2017). An overview of pharmacodynamic modelling, ligand-binding approach and its application in clinical practice. *Saudi Pharmaceutical Journal, 25(2),*165-175. https://doi.org/10.1016/j.jsps.2016.07.002 (accessed 12 February 2024)

The neurochemical mechanism common to the majority of, if not all, drugs causing abuse in humans is the increase of the neurotransmitter dopamine. It is released from the ventral tegmental area to a region in the mesocorticolimbic part of the brain when a psychoactive drug binds with a receptor. Physiological reward and reinforcement mechanisms that are important in the development of addiction are enhanced[18].

Although drug effects are largely initiated in the brain, drug receptors are widely distributed throughout the body. For example, adenosine receptors are present in the brain and are involved in eliciting the effects of psychostimulant drugs but are also present in many major organs and are responsible for the regulation of a broad spectrum of other physiological and pathological actions[19].

Drug molecules can interact only with specific receptors. This selectivity is referred to as drug specificity. To produce a pharmacological effect the drug molecule must have the right shape to 'fit into' the binding site of a receptor and the correct properties (molecular components) to 'activate' it.

The chemical structure (moiety) of both drugs and receptors is important: a small change can result in a limited or null response. A ligand can bind either reversibly or irreversibly to a receptor to either activate or antagonise the receptor. A drug-receptor interaction can open or close an ion channel across the cell membrane.

18 Volkow, N D, Wang, G J, Fowler, J S *et al*. (2012). Addiction circuitry in the human brain. *Annual Review of Pharmacology and Toxicology, 52,* 321-336. https://doi.org/10.1146/annurev-pharmtox-010611-134625 (accessed 12 February 2024)

19 Ballesteros-Yáñez, I, Castillo, C A, Merighi, S *et al*. (2018). The role of adenosine receptors in psychostimulant addiction. *Frontiers in Pharmacology, 8*. https://doi.org/10.3389/fphar.2017.00985 (accessed 12 February 2024)

2.2.2 Drug response (effect)

There are several possible outcomes when a drug ligand binds with a receptor (Table 5).

TABLE 5

The drug responses elicited by different types of interactions between drugs and receptors[18].

Type	Drug response	Example
Agonists	Drug that binds to and activates a receptor, causing a physiological effect that mimics the endogenous receptor ligand to bring about a biological response. Full agonist produces largest response on a given receptor.	Morphine and fentanyl are full agonists at the Mμ opioid receptor.
Partial agonists	Drug that binds and activates a receptor but does not elicit a full response; can block the effect of a full agonist.	Buprenorphine blocks effect of heroin against opioid receptors.
Inverse agonist	Drug binds to the same receptor site as an agonist but exerts the opposite pharmacological response and may block activity of receptor.	Clozapine is an inverse agonist of the H1 and H2 histamine receptors.
Biased agonist	Drug is designed to select (bias) which signalling pathway will become activated upon binding with receptor; a phenomenon of synthetic ligands.	Steroid hormone receptors.
Antagonists	Drug binds to, but does not activate, a receptor or causes a direct physiological or psychoactive effect. High concentrations of antagonist may completely block actions of agonist.	Naltrexone blocks the activity of opioid drugs. Flumazenil inhibits benzodiazepine receptors on GABA/benzodiazepine receptor complex.
Competitive antagonists	Drug can compete with the agonist for the same receptor binding site. Binding is reversible and there is no reduction in maximal response.	Naloxone is a competitive antagonist at all opioid receptors.
Non-competitive antagonists	Drug binds irreversibly to receptor, reducing ability of agonist to bind and produce a response.	Ketamine is a non-competitive antagonist at the N-methyl-D-aspartate receptor.

Courtesy K Wolff.

The drug response of an agonist drug may be altered by the presence of other drugs that exhibit inhibitory effects at the receptor site. A good example is the agonist diacetylmorphine (heroin), which is a dependence-forming drug. Heroin enters the brain and is rapidly converted to morphine via the intermediate metabolite 6-monoacetylmorphine, which saturates endogenous opioid ligands to produce an opioid effect (Section 3.13). This can be diminished by the administration of buprenorphine, a partial opioid agonist. Indeed, if any morphine is present in the body when buprenorphine is administered, the individual will develop withdrawal symptoms. Complete inhibition of the activity of morphine is achieved by the administration of naltrexone (antagonist) or naloxone (competitive antagonist), which are used to reverse the effects of opioid overdose.

3. Drug classes and types

In this section drugs in their freebase (pure) and salt form are discussed to highlight different administration routes and associated pharmacological effects. Many drugs are produced as salts since these are usually more water soluble, offering greater pharmaceutical stability. However, freebasing is a more efficient mechanism to self-administer illicit drugs, particularly by smoking.

3.1 Alcohol

Alcohol is the most consumed psychoactive drug in the UK. Ethanol molecules cross the blood-brain barrier easily and interact with various neurotransmitter systems, thus depressing the CNS and leading to disinhibition followed by sedation and impairment of performance and behaviour.

The disposition and fate of ethanol in the body has been studied extensively. Absorption is from both the stomach and intestines. Peak concentration in peripheral (circulating) blood is usually reached within 60 minutes, depending on factors that influence gastric emptying such as food in the stomach before drinking. Ethanol has a low molecular weight, is completely miscible with water and distributes into the total body water compartment without binding to plasma proteins. This is important because the distribution of alcohol around the body is not restricted. It is important to note that ethanol is a nutrient with a calorific value of about 7 kcal/g, whereas carbohydrates and protein have an approximate calorific value of 4 kcal/g. However, while carbohydrates are stored as glycogen in the liver and muscle, alcohol is not stored and remains in body water until eliminated. Because there is little hormonal regulation to pace the rate of alcohol elimination, there is a major burden on the liver to oxidise alcohol for its removal from the body[20]. Hence, excessive use of alcohol can damage the liver and in severe cases lead to cirrhosis.

Concentrations of ethanol in alcoholic drinks are expressed as percentage by volume (% v/v), often abbreviated to ABV. In the UK alcohol consumption is often measured in terms of units. One UK unit equals 10 mL or 8 g of 100% ethanol. When interpreting blood alcohol concentrations (BAC) during forensic casework, the number of grams of pure ethanol consumed must be established.

20 Cederbaum, A I. (2012). Alcohol metabolism. *Clinics in Liver Disease, 16(4),* 667-685. https://doi.org/10.1016/j.cld.2012.08.002 (accessed 12 February 2024)

One unit of alcohol is broadly equivalent to one-third of a pint of ordinary strength beer (5 – 6% ABV), more for draught (3.5 – 4.5% ABV), half a standard (175 mL) glass of wine (ABV 12%) or a 25 mL single measure of whisky/spirits. An expert group, convened by the Chief Medical Officer for England and Wales, recommended that it was "safest not to drink regularly more than 14 units per week"[21] and that this should be spread out evenly over 3 days or more. Most people drink within recommended limits.

3.2 Amphetamine-type substances

Amphetamine-type drugs are CNS stimulants that increase alertness and physical activity, elevate heart rate and blood pressure, and activate or enhance brain activity.

3.2.1 Amphetamine

Amphetamine is an illicit substance that can be obtained from legitimate medical sources, but which is usually manufactured illegally. In the UK it can be used to treat attention deficit hyperactivity disorder (ADHD).

As a powerful stimulant the main effects include increased alertness, prolonged wakefulness, weight loss, increased heart rate and blood pressure. Catecholaminergic effects include changes to the force and speed of muscle contraction, to heart rate and rhythm, and to blood pressure. A peculiar feature of chronic (meth)amphetamine use includes delusions of parasitosis (fixed belief of having been infested by a parasite) and chronic skin-picking.

Taken orally amphetamine is well absorbed and has no major pharmacologically active metabolites. Highly acidic urine speeds up elimination, whilst highly alkaline urine will prolong effects and delay excretion. The half-life is approximately 12 hours. After large doses, amphetamine may be detected in urine for several days. After normal therapeutic dosing (5 – 30 mg/day), the plasma concentration of amphetamine is usually less than 100 µg/L. The window of opportunity to detect amphetamine in blood after a single dose is around 60 hours.

21 Department of Health. (2016). *UK Chief Medical Officers' alcohol guidelines review.* https://assets.publishing.service.Gov.uk/media/5a7f51b4e5274a2e87db5206/summary.pdf (accessed 12 February 2024)

3.2.2 Methamphetamine

Methamphetamine is an analogue of amphetamine. Its use is not widespread in the UK, although it can be used as a chemsex drug[22] (Section 1.2). Methamphetamine is predominantly self-administered by smoking. At around 11.7 hours, the half-life is like that of amphetamine. The range of concentration observed in plasma usually lies between 10 and 50 µg/L. In its crystalline form (Figure 1), methamphetamine is highly addictive and has been linked to increased risk-taking, in particular of a sexual nature.

Methamphetamine has a rapid onset of action. Effects, like those of amphetamine, are felt within 15 – 30 seconds when used intravenously and within 15 – 20 minutes when snorted. Frequent high dose use results in a psychological condition called 'ice psychosis', characterised by paranoid delusions and bizarre aggressive behaviour. These symptoms readily disappear after cessation of use.

The window of opportunity for the detection of methamphetamine in blood after a single dose is, like amphetamine, around 60 hours.

FIGURE 1

Methamphetamine in its crystalline form appearing as clear crystals commonly called 'ice'[23].

22 Whitlock, G G, Protopapas, K, Bernardino, J I *et al.* (2021). Chems4EU: chemsex use and its impacts across four European countries in HIV-positive men who have sex with men attending HIV services. *HIV Medicine, 22(10),* 944-957. http://doi.org/10.1111/hiv.13160 (accessed 12 February 2024)

23 Source: Alcohol and Drug Foundation. (2024). *Amphetamines.* https://cdn.adf.org.au/media/images/amphetamines-social.width-1524.jpg (accessed 12 February 2024)

3.2.3 3,4-Methylendioxymethamphetamine

MDMA, also known as ecstasy, is the archetypal recreational drug. MDMA displays non-linear kinetics. This means that whilst higher doses lead to higher concentration of MDMA in tissues, the increase is not proportionate. Stimulatory effects are accompanied by enhanced empathy and sociability. MDMA toxicity is associated with disturbed water homeostasis and an extremely high temperature (hyperpyrexia). The half-life of MDMA is reported to be approximately 7.6 hours. The window of opportunity for the detection of MDMA after a single dose is up to 38 hours and maybe longer for multiple doses taken in one session.

3.2.4 Methylphenidate

Methylphenidate is a CNS stimulant that can be used to treat ADHD. Its pharmacology is like amphetamine and cocaine but through a different mechanism of action[24]. Following oral administration peak plasma concentrations occur after 1 – 2 hours. The half-life of methylphenidate is about 2 hours (range 2 – 7 hours), or 3 – 9 hours after sustained-release methylphenidate. Methylphenidate is metabolised to ritalinic acid. Since <1% of methylphenidate is excreted unchanged in the urine and >80% of an oral dose is excreted as ritalinic acid, the metabolite is often used as a marker of methylphenidate ingestion.

Abuse may occur by the oral route to improve cognition or for sports performance; parenteral application is the more common route to induce euphoria[25].

24 Morton, W A and Stockton, G G. (2000). Methylphenidate abuse and psychiatric side effects. *Primary Care Companion to The Journal of Clinical Psychology, 2(5)*, 159-164. https://doi.org/10.4088/pcc.v02n0502 (accessed 12 February 2024)

25 Gahr, M and Plener, P L. (2016). Methylphenidate abuse: an overview. In Preedy, V R. (Ed.), *Neuropathology of drug addictions and substance misuse* (pp 651-659). Cambridge: Academic Press.

3.3 Anabolic steroids

Most performance-enhancing steroids are synthetic AAS designed to mimic the male sex hormone testosterone (Table 6). Testosterone-derived steroids are relatively inexpensive to buy, and because testosterone is produced endogenously, they are generally harder to identify in a drug test.

Recreational AAS users generally develop complicated multidrug regimens using oral and intramuscular preparations at progressively higher doses (40 – 100 times normal levels), known as stacking. Multiple forms of AAS (five different drugs on average) from different steroid classes are commonly used to take advantage of the different pharmacokinetic properties of these drugs to gain maximum performance enhancement[26].

There has been significant research about AAS abuse linked to criminal or anti-social behaviour. Some key findings of relevance to the CJS include:

- It has long been debated whether use of testosterone causes aggressive behaviour. Research in the 1990s suggests supraphysiological doses of testosterone, when administered to normal men in a controlled setting, do not increase aggressive behaviour[27]. However, very high doses of multiple steroids might provoke angry behaviour in men with pre-existing psychopathology.
- AAS-induced criminal behaviour has been described (homicides and violent assaults)[31].
- AAS abusers are at a higher risk of dying violently because of impulsive/aggressive behaviour and/or depression.
- AAS abuse has been used to explain road rage.
- Domestic violence may be linked with AAS use[28].

26 Hall, R C, Hall, R C W and Chapman, M J. (2005). Psychiatric complications of anabolic steroid abuse. *Psychosomatics, 46(4)*, 285-290. https://doi.org/10.1176/appi.psy.46.4.285 (accessed 12 February 2024)

27 Tricker, R, Casaburi, R, Storer, T W *et al.* (1996). The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men – a clinical research center study. *The Journal of Clinical Endocrinology and Metabolism, 81(10),* 3754-3758. https://doi.org/10.1210/jcem.81.10.8855834 (accessed 12 February 2024)

28 Choi, P Y and Pope, H G. (1994). Violence toward women and illicit androgenic-anabolic steroid use. *Annals of Clinical Psychiatry, 6(1),* 21-25. https://doi.org/10.3109/10401239409148835 (accessed 12 February 2024)

TABLE 6

Commonly used anabolic androgenic steroids[29,30].

Anabolic-androgenic steroid	Route of administration	Half-life	Comment
Testosterone	Oral gel, long acting injectables	1.5 hours Depot 12 days	Requires specialist analysis to identify misuse
Trenbolone	Intramuscular	1 – 2 days Trenbolone enanthate 11 days	Veterinary drug
Methandrostenolone	Transdermal patches, gel or intramuscular	3 – 6 hours	Detected in urine for about 19 hours
Nandrolone	Deep intramuscular injection	Decanoate 14 days	The main metabolite 19-norandrossterone (19-NA) is screened for in sports testing
Stanozolol	Oral or intramuscular	9 hours	Derived from dihydro-testosterone (DHT)
Boldenone	Long-acting injectable	14 days	Boldenone and epiboldenone tested for in urine
Oxandrolone	Oral or sublingual, transdermal	10.4 hours[31]	Drug or metabolites detected in urine for 10 – 14 days

Courtesy K Wolff.

29 Ruiz, P and Strain, E C. (2011). *Lowinson and Ruiz's substance abuse: a comprehensive textbook* (5th ed.). New York, NY: Lippincott Williams and Wilkins.

30 Llewellyn, W. (2011). *Anabolics*. Molecular Nutrition, LLC.

31 Karim, A, Ranney, R E, Zagarella, J *et al.* (1973). Oxandrolone disposition and metabolism in man. *Clinical Pharmacology and Therapeutics*, 14, 862-869. https://doi.org/10.1002/cpt1973145862 (accessed 12 February 2024)

3.3.1 Designer steroids

Designer steroids are manufactured in laboratories and can be purchased online. They increase lean body mass, strength and aggressiveness, and lead to a shorter recovery time between training sessions. Designer steroids (eg Methylstenbolone) are often sold as nutritional supplements (eg Ultradrol, Methyl-Sten or M-Sten).

The current approach for testing for AAS involves urine drug testing. To detect exogenous testosterone, the ratio of testosterone and epitestosterone, both endogenous compounds, are compared to determine if athletes have been doping. Most individuals have an approximate ratio of 1:1. For Olympic (elite) athletes, the World Anti-Doping Agency has set the permissible testosterone-to-epitestosterone ratio at 4:1 to allow for individual variation.

3.4 Anaesthetics

Anaesthesia is induced with either a volatile drug given by inhalation or with an intravenously administered drug. Some anaesthetics also offer analgesic effects such as the short-acting opioids heroin, morphine, fentanyl and oxycodone.

3.4.1 Gamma-hydroxybutyrate, Gamma-butyrolactone and 1,4-Butanediol (1,4-BD)

GHB, GBL and 1,4-BD are closely related with similar sedative and anaesthetic effects. GHB is a naturally occurring fatty acid originally investigated for its anaesthetic properties. GHB has been employed for a variety of purposes including the treatment of sleep disorders, anxiety and depression, and for symptomatic treatment of alcohol and opiate withdrawal. Whilst GBL and 1,4-BD are not active forms, they can be consumed and serve as prodrugs, being rapidly converted into GHB in the body.

GHB can be produced clandestinely from ingredients available in kit form over the internet. The salt form (sodium oxybate) is licensed in the UK as a therapeutic agent (Xyrem®) for the treatment of cataplexy (loss of voluntary muscle tone) in adult narcolepsy. GBL and 1,4-BD are both commercially available as industrial solvents and are sold as natural dietary supplements.

After ingestion GBL is rapidly converted into GHB, with a half-life of less than 1 minute. GHB exhibits a very steep dose-response curve such that a slight increase in dose can render an individual unconscious (comatose). The maximum plasma concentration occurs after 20 – 40 minutes. GHB is also eliminated quickly and has an average half-life of 27 minutes within a range of 20 – 60 minutes[32]. Approximately 1 – 5% of a GHB dose is recoverable in urine and the detection window is relatively short (3 – 10 hours). Sampling must therefore be expedited when evidence of drug use is required. Urine sampling lengthens the detection window by 3 – 4hours compared with blood. GHB is also produced endogenously (within cells), which can make it challenging to interpret blood GHB concentrations.

GHB effects include euphoria, relaxation, increased sensuality, disinhibition and possibly the loss of consciousness. At higher blood concentrations GHB use effects can also include cognitive impairment, ataxia and a lack of awareness of surroundings.

GHB is sold on the black market as a white crystalline powder or in liquid form (Figure 2). Recreational doses range from 500 to 3,000 mg usually dissolved in water or alcohol, and significantly exceed therapeutic doses. A concentration in plasma of approximately 100 mg/L produces euphoria and disinhibition, whereas 500 mg/L might cause death from cardiorespiratory depression[33].

32 Årnes, M, Bachrs, L, Al Sammarai, M *et al.* (2020). Rate of elimination of γ-hydroxybutyrate from blood determined by analysis of two consecutive samples from apprehended drivers in Norway. *Forensic Science International, 314,*110374. https://doi.org/10.1016/j.forsciint.2020.110374 (accessed 12 February 2024)

33 Advisory Council on the Misuse of Drugs. (2020). *Assessment of the harms of gamma hydroxybutyric acid, gamma butyrolactone and closely related compounds.* https://www.gov.uk/government/publications/assessment-of-the-harms-of-gamma-hydroxybutyric-acid-gamma-butyrolactone-and-closely-related-compounds (accessed 13 February 2024)

FIGURE 2

GHB is sold illegally as a clear or blue liquid that comes in a small vial such as fish-shaped sushi soy sauce containers[34].

GHB has been implicated in many types of forensic cases. Whilst it has gained attention in 'drink spiking' it is associated mainly with recreational drug and chemsex scenes, with overdose deaths and with murder[35]. Impaired performance is reported when driving. In 13 driving under the influence of drugs cases where GHB was detected, most symptoms resembled those of CNS depressants (confusion, disorientation, incoherent speech, dilated pupils and unsteady gait).

34 Source: Alcohol and Drug Foundation. (2024). *GHB.* https://cdn.adf.org.au/media/images/ghb-para-930x620.width-1524.jpg (accessed 1 October 2024)

35 Busardò, F P and Jones, A W. (2019). Interpreting γ-hydroxybutyrate concentrations for clinical and forensic purposes. *Clinical Toxicology, 57(3),* 149-163. https://doi.org/10.1080/15563650.2018.1519194 (accessed 13 February 2024)

3.4.2 Ketamine

Ketamine is an anaesthetic derivative of phencyclidine (PCP)[36] and is most frequently taken recreationally for its psychedelic properties. It has many effects associated with other substances including intoxication, stimulation and calming. Clinically ketamine has been used as a sedative, an analgesic and to treat major depression. It is a veterinary anaesthetic and can be used safely in humans in an emergency.

In powdered form, ketamine's appearance resembles cocaine (Figure 3). It can be insufflated, injected, placed in beverages, or smoked in a joint or pipe usually mixed with cannabis and tobacco. Ketamine bladder ('K cramps') is a painful condition caused by long-term misuse. The bladder shrinks and becomes fibrotic, resulting in permanent ulceration, inflammation and frequent urination. In serious cases partial or full bladder removal is required.

FIGURE 3

Ketamine in its crystalline form[37].

36 Li, L and Vlisides, P E. (2016). Ketamine: 50 years of modulating the mind. *Frontiers in Human Neuroscience, 10*, 612. https://doi.org/10.3389/fnhum.2016.00612 (accessed 13 February 2024)

37 Landmark Recovery. (n.d.). *Ketamine drug facts*. https://landmarkrecovery.com/sober-facts/ketamine/ (accessed 13 February 2024)

Ketamine is well absorbed and has excellent bioavailability. The intranasal route favoured by recreational users is associated with a rapid onset of action and an estimated half-life of 2 – 3 hours. Elimination is variable, depending upon the administration route. Effects may be prolonged due to the presence of the active metabolite, norketamine. Ketamine is eliminated mainly as water-soluble metabolites, with less than 4% appearing in urine. Both ketamine and norketamine are detectable in urine for approximately 14 – 21 hours[38].

3.4.3 Nitrous oxide (NOS)

NOS is a colourless, odourless gas and a CNS depressant. Inhalation improves mood and relaxes the user. Individuals often become giggly, hence the name 'laughing gas'. Sold under the brand name Entonox it is used as a pain medication and, together with other medications, for anaesthesia during childbirth, dentistry and end-of-life care. In March 2023, the government announced plans as part of its Anti-Social Behaviour Plan to ban NOS by making it a Class C drug under the Misuse of Drugs Act 1971 and the ban came into effect on 8 November 2023. The maximum sentences possible are therefore higher (14 years, an unlimited fine or both) for production and supply offences, and for the first time it is an offence to possess the substance for 'wrongful inhalation'. It is also an offence for producers and suppliers to be reckless as to whether the substances will be wrongfully inhaled[39].

NOS use has become increasingly common, usually inhaled from a balloon filled from pressurised metal canisters or directly from a 'bulb' (Figure 4). Frequent users inhale approximately 8 balloons/day on average and non-frequent users 5 balloons/day[40]. In a French study daily and/or high-dose use (≥20 bulbs or cylinders equivalent per occasion/day) was reported alongside substance use disorder-associated criteria[41].

38 Wolff, K and Winstock, A R. (2006). Ketamine: from medicine to misuse. *CNS Drugs, 20(3)*,199-218. https://doi.org/10.2165/00023210-200620030-00003 (accessed 13 February 2024)

39 UK Government. (2023). *Nitrous oxide ban: guidance.* www.gov.uk/government/publications/nitrous-oxide-ban (accessed 13 February 2024)

40 Nabben, T, van der Pol, P and Korf, D J. (2017). *Roes met een luchtje. Gebruik, gebruikers en markt van lachgas (Inebriating air. Nitrous oxide use, users and market).* Amsterdam: Rozenberg Publishers. https://www.trimbos.nl/docs/e3f9a3a4-d25c-4fa7-a981-ccba3d937997.pdf (accessed 14 February 2024).

41 Guerlais, M, Aquizerate, A, Lionnet, A *et al.* (2023). Nitrous oxide: a unique official French addictovigilance national survey. *Frontiers in Public Health, 11,* 1167746. https://doi.org/10.3389/fpubh.2023.1167746 (accessed 13 February 2024)

FIGURE 4

An example of metal cannisters containing nitrous oxide. These are typically 3 – 4 cm in length[42].

NOS affects normal respiratory function by reducing tidal volume and increasing respiratory rate. When inhaled NOS displaces oxygen from the lungs, limiting its availability for gaseous exchange. This can cause blood oxygen and carbon dioxide concentrations to decrease (diffusion hypoxia). Reports of weakness in the legs, loss of balance and dizziness during inhalation of NOS are likely a consequence of decreased oxygen saturation levels.

Breathing high concentrations can quickly reduce blood oxygen concentrations resulting in reduced blood pressure, fainting, B12 deficiency anaemia and nerve damage (peripheral neuropathy). The Global Drugs Survey found that about 4% of users experienced numbness, tingling and shooting pains in the limbs[43]. The onset of action is approximately 30 seconds and the duration of effect about 1 minute[44].

42 Source: Alcohol and Drug Foundation. (2024). *Nitrous oxide*. https://cdn.adf.org.au/media/images/nangs-card.width-1524.jpg (accessed 1 October 2024)

43 Global Drugs Survey. (2015). *What did we learn from GDS2015? An overview of our key findings*. http://www.globaldrugsurvey.com/the-global-drug-survey-2015-findings/ (accessed 13 November 2024)

44 Brugnone, F, Perbellini, L, Cerpelloni, M *et al.* (1995). Nitrous oxide in blood and urine of operating theatre personnel and the general population. *International Archives of Occupational and Environmental Health, 68(1),* 22-26. https://doi.org/10.1007/BF01831629 (accessed 13 February 2024)

The rapid on- and offset of NOS action (30 seconds to 15 minutes) is attributable to a low blood-gas partition coefficient[45].

The detection and quantification of NOS in biological fluids including post-mortem samples is mainly undertaken using head-space gas chromatography (HS-GC). Matrices such as exhaled breath and oral fluid may be possible alternatives to blood for the detection of NOS but our understanding of the time course of NOS in these biological fluids is poor.

3.5 Benzodiazepines and Z-drugs

3.5.1 Benzodiazepines (BZDs)

BZDs are a large class of controlled medicines with psychoactive effects that depress CNS function. In most Western countries they are available as POMs to treat conditions including anxiety, insomnia, epilepsy and assisted alcohol withdrawal. 'Hypnotic' (sedative) BZDs have a short half-life and 'anxiolytic' (anxiety-reducing) BZDs a long half-life. BZDs are commonly misused in combination with illicit substances and less frequently as a drug of first choice. BZDs are predominantly consumed orally and tend to be readily absorbed. Acute intake leads to concentration-dependent deterioration of performance.

Following oral administration BZDs are usually well absorbed by the gastrointestinal tract. After intravenous administration they quickly reach the brain and CNS. Intramuscular injection leads to slow absorption of diazepam and chlordiazepoxide, but rapid and complete absorption of lorazepam and midazolam.

Some BZDs exert additional action by producing active metabolites, an important consideration when considering extent of intoxication. Midazolam (a short-acting BZD) produces no active metabolites, whereas diazepam (being long-acting) produces the active metabolites oxazepam, desmethyl-diazepam and temazepam, which further increase the duration of effects. BZDs can be grouped according to their duration of action (Table 7).

45 Van Aerts, L, De Morais, J, Evans-Brown, M *et al.* (2022). *Recreational use of nitrous oxide: a growing concern for Europe* (pp 1-86). Luxembourg: Publications Office of the European Union.

TABLE 7

Duration of action of common benzodiazepines.

Examples	Approximate half-life (t½)
Short-acting (half-life approximately 2 hours)	
Midazolam	1.5 – 2.5 hours
Triazolam	1.5 – 5.5 hours
Flurazepam	2 – 3 hours
Intermediate-acting (half-life 6 – 24 hours)	
Oxazepam	6 – 9 hours
Chloradiazepoxide	6 – 30 hours
Alprazolam	8 – 16 hours
Temazepam	8 – 20 hours
Lorazepam	10 – 20 hours
Flunitrazepam	18 – 26 hours
Long-acting (half-life more than 24 hours)	
Nitrazepam	15 – 38 hours
Diazepam	20 – 100 hours
Clonazepam	30 – 40 hours
Clobazam	36 – 42 hours

Courtesy K Wolff.

Misuse of BZDs falls into two categories: iatrogenic and polydrug[46]. Iatrogenic use occurs when BZDs are prescribed for anxiety or insomnia and continue to be used over a long-term period. Polydrug misuse involves consuming three or more drugs at a time and/or one after the other.

46 Bond, A and Lader, M. (2016). Benzodiazepines: a discussion of pharmacokinetic and pharmacodynamic effects. In Wolff, K, Karch, S and White, J. (Eds.). *The SAGE handbook of drug and alcohol studies: biological approaches.* Sage Publications Ltd.

Non-medical use is more common in polydrug users and in individuals with alcohol and opioid problems. Such individuals may seek prescriptions from medical practitioners, obtain BZDs from family and friends or buy them from illicit sources such as dealers. When used in conjunction with alcohol and other CNS depressants BZDs have an additive effect, increasing the risk of harm.

Most BZDs available on the illicit market appear to be diverted from legitimate sources[47]. 'New' BZDs have also been found in fake products made to resemble prescribed BZDs such as diazepam and alprazolam. New BZDs are monitored by the European Early Warning System[48].

3.5.2 Z-drugs

Z-drugs (zopiclone, zolpidem and zaleplon) are CNS depressants, licensed for the short-term (up to 2 weeks) management of insomnia. Use is restricted because of the risks associated with hypnotic drugs such as falls, cognitive impairment and withdrawal symptoms[49]. The Medicines and Healthcare products Regulatory Agency advises that individuals taking zolpidem should not drive, operate machinery or work at heights until at least 8 hours after the latest dose.

Z-drugs act on the same receptor sites as BZDs and have similar addiction potential but are not related at a molecular level. Death from Z-drugs is rare. They are fast acting with an elimination half-life of 1 hour for zaleplon, 2 – 3 hours for zolpidem and 5 hours for zopiclone[50]. The drugs can be detected in biological fluids using chromatographic techniques, and the detection window is 24 – 48 hours[51] in plasma and 6 – 20 hours in urine.

47 European Monitoring Centre for Drugs and Drug Addiction. (2020). *European drug report 2020*. https://www.emcdda.europa.eu/edr2020_en (accessed 14 February 2024)

48 European Monitoring Centre for Drugs and Drug Addiction. (n.d.). *The EU early warning system on NPS*. https://www.emcdda.europa.eu/publications/topic-overviews/eu-early-warning-system_en (accessed 14 February 2024)

49 National Institute for Health and Care Excellence (NICE). (2024). *What issues should I be aware of when prescribing Z-drugs?* https://cks.nice.org.uk/topics/insomnia/prescribing-information/z-drugs/ (accessed 14 February 2024)

50 Schifano, F, Chiappini, S, Corkery, J M *et al.* (2019). An insight into Z-drug abuse and dependence: an examination of reports to the European Medicines Agency database of suspected adverse drug reactions. *International Journal of Neuropsychopharmacology, 22(4),* 270-277. https://doi.org/10.1093/ijnp/pyz007 (accessed 13 February 2024)

51 Gunja, N. (2013). The clinical and forensic toxicology of Z-drugs. *Journal of Medical Toxicology, 9(2),* 155-162. https://doi.org/10.1007/s13181-013-0292-0 (accessed 13 February 2024)

3.6 Cannabinoids

Cannabinoids encompass all substances derived from the plant Cannabis sativa (Figure 5).

3.6.1 Cannabis

After alcohol, cannabis (weed, pot, hash) is the most frequently detected psychoactive substance among driving populations. Cannabis is a potent drug and produces significant effects, and when mixed with alcohol may dramatically increase the risk of a road traffic collision (RTC)[52]. The primary metabolite responsible for the psychoactive effects of the drug is THC.

Currently the form of cannabis that is most frequently encountered in the UK is home-grown 'skunk', cultivated for seedless plants (sinsemilla). This form is significantly stronger than more traditionally sourced hash/herbal/resin. It has a higher concentration of THC but also a lower level of cannabidiol (CBD), which tends to moderate the effects of THC[53,54].

The effects of acute cannabis use are euphoria and relaxation, sociability, perceptual and time distortions, and the intensification of sensory experiences, followed by introspection and dreaminess. Short-term memory and attention are impaired. The risk of acute toxicity is very low and there is no overdose risk. Adverse mood effects can occur after large doses, particularly in inexperienced users. These include anxiety, paranoia, depersonalisation, panic, depression and hallucinations, which normally disappear a few hours after cessation of use. Large doses, or smaller doses in vulnerable individuals, can produce acute psychosis marked by confusion, amnesia, hallucinations and hypomanic symptoms. These effects abate within a few days of cessation of use. Continued use in adolescents and young adults is a major risk factor for schizophrenia and psychosis in later life[55].

52 National Highway Traffic Safety Administration. (2014). *Drugs and human performance fact sheets*. https://www.nhtsa.gov/sites/nhtsa.gov/files/809725-drugshumanperformfs.pdf (accessed 13 February 2024)

53 Potter, D J, Hammond, K, Tuffnell, S *et al.* (2018). Potency of Δ9–tetrahydrocannabinol and other cannabinoids in cannabis in England in 2016: implications for public health and pharmacology. *Drug Testing and Analysis, 10(4),* 628-635. https://doi.org/10.1002/dta.2368 (accessed 14 February 2024)

54 Di Forti, M, Marconi, A, Carra, E *et al.* (2015). Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case-control study. *Lancet Psychiatry, 2(3),* 233-238. https://doi.org/10.1016/S2215-0366(14)00117-5 (accessed 14 February 2024)

55 Marconi, A, Di Forte, M, Lewis, C M *et al.* (2016). Meta-analysis of the association between the level of cannabis use and risk of psychosis. *Schizophrenia Bulletin, 42(5),* 1262-1269. https://doi.org/10.1093/schbul/sbw003 (accessed 13 February 2024)

FIGURE 5

Dried Cannabis sativa leaves, stems and buds[56].

Since cannabis must be heated to release THC, recreational use often involves smoking. After inhalation THC is absorbed quickly, leading to blood concentrations of up to 27% within minutes. Absorption is slow and unpredictable, with maximal blood concentrations of up to 6% occurring 1 – 5 hours later. THC is lipophilic and circulates widely in the body upon consumption with a half-life of approximately 24 hours, but which can be longer in chronic users[57].

THC is stored in tissues and organs throughout the body. In regular or frequent users this leads to continual release of THC into the bloodstream, maintaining consistent detectable concentrations in the general circulation. It is, however, not advisable to predict effects based on blood THC concentrations alone. It is possible for an individual to be affected by cannabis use with concentrations of THC in their blood below the limit of detection of relevant analytical methods. In urine the THC-COOH metabolite is usually detected as evidence of previous use, but these indicate prior THC exposure only. Detection time is often well past the window of intoxication and impairment.

56 Source: Drug Enforcement Administration. (n.d.). *Marijuana.* https://www.dea.gov/sites/default/files/styles/slide/public/2018-07/marijuana1.jpg?h=07adfb57&itok=Zh9ntBiK (accessed 1 October 2024)

57 Huestis, M A. (2007). Human cannabinoid pharmacokinetics. *Chemistry and Biodiversity, 4(8),* 1770-1804. https://doi.org/10.1002/cbdv.200790152 (accessed 13 February 2024)

Monitoring acute cannabis use with a commercial cannabinoid immunoassay that has a 50 ng/mL cut-off concentration provides only a narrow window of detection of 1 – 2 days. However, mean detection times were up to 6 days using a lower cut-off of 20 ng/mL. Gas-chromatography mass-spectrometry (GC-MS) analysis doubled the detection window when compared to the 50 ng/mL immunoassay test[58].

3.6.2 Synthetic cannabinoid receptor agonists (SCRAs)

SCRAs are manufactured in laboratories. They are collectively referred to as 'spice' or synthetic cannabinoids and encapsulate diverse substances. SCRAs are designed to mimic the psychoactive effects of THC but have no chemical relationship to natural cannabinoids, despite acting on the two principal cannabinoid receptors. This means that they can be difficult to identify using mainstream analytical methods and levels of detection can vary between laboratories.

More than 200 different SCRAs were detected on the illicit drug market between 2008 and 2020 with substances appearing, evolving and disappearing in response to market demand and national and international legislative controls. SCRAs are often sold in herbal form (herbal incense or smoking blends) in unmarked bags. SCRAs rapidly enter the bloodstream via the lungs and this leads to rapid onset of intense psychoactive effects. Many SCRAs are significantly more potent and harmful than THC, with shorter half-lives, and display stimulant-like effects. Common effects include confusion, dilated pupils, reddened conjunctivae, nausea and vomiting, slurred speech, shortness of breath, increased blood pressure and heart rate, and unconsciousness[59,60].

58 Huestis, M A, Mitchell, J M and Cone, E J. (1995). Detection times of marijuana metabolites in urine by immunoassay and GC-MS. *Journal of Analytical Toxicology, 19(6),* 443-449. https://doi.org/10.1093/jat/19.6.443 (accessed 13 February 2024)

59 Castaneto, M S, Gorelick, D A, Desrosiers, N A *et al.* (2014). Synthetic cannabinoids: epidemiology, pharmacodynamics, and clinical implications. *Drug and Alcohol Dependence, 144,* 12-41. https://doi.org/10.1016/j.drugalcdep.2014.08.005 (accessed 13 February 2024)

60 Jackson, M A, Brown, A L, Johnston, J *et al.* (2021). The use and effects of synthetic cannabinoid receptor agonists by New South Wales cannabis treatment clients. *Journal of Cannabis Research, 3(1),* 33. https://doi.org/10.1186/s42238-021-00091-z (accessed 13 February 2024)

A semi-formal naming system has been widely adopted, based on four chemical structural components[61]. These controls are updated as new compounds appear, giving rise to the terms first, second and third generation SCRAs. Some SCRAs are not (yet) controlled under the Misuse of Drugs Act 1971 and are simply prosecuted under the Psychoactive Substances Act 2016.

SCRAs are detected increasingly in infused papers that are smoked or vaped using e-cigarettes or dissolved in e-liquids. Less commonly, SCRAs may be taken sublingually. Although the prevalence of SCRAs in the general population is relatively low compared to cannabis, they are more widely used in vulnerable populations such as rough sleepers and prisoners. SCRAs can be difficult to detect in prisons since their high potency makes them easy to conceal, they are easily disguised in e-cigarettes and because they evolve continually[62].

3.7 Cathinones

Cathinones are stimulant drugs of natural origin found in the leaves and fresh shoots of khat, a shrub cultivated in East Africa (Figure 6). Khat is a weak CNS stimulant often used to maintain wakefulness or chewed as a recreational drug to elevate mood. It is similar to amphetamine in structure and pharmacological activity.

The principal active components in khat are cathinone and cathine (norpseudoephedrine). Both increase concentrations of dopamine, serotonin and noradrenalin neurotransmitters, collectively associated with pleasure and reward. The elimination half-life of cathinone is approximately 1.5 hours and 5 hours for cathine. Chewing khat releases these substances into oral fluid. Both compounds are rapidly absorbed and metabolised in the liver. Only 2% of cathinone is excreted unchanged in the urine.

61 Potts, A J, Cano, C, Thomas, S H L *et al.* (2020). Synthetic cannabinoid receptor agonists: classification and nomenclature. *Clinical Toxicology, 58(2),* 82-98. https://doi.org/10.1080/15563650.2019.1661425 (accessed 13 February 2024)

62 Advisory Council on the Misuse of Drugs. (2022). *Synthetic cannabinoid receptor agonists* https://www.gov.uk/government/publications/synthetic-cannabinoid-receptor-agonists (accessed 14 February 2024)

FIGURE 6

Khat leaves (shown as a bundle) need to be chewed whilst fresh to achieve pharmacological effects[63].

Synthetic cathinones (bath salts, plant food, M-cat) are illicitly manufactured derivatives. Common types include mephedrone (4-methylmethcathinone), butylone and 3,4-methylenedioxyypyrovalerone (MDPV). Synthetic cathinones have been described as 'legal highs' and are often sold as 'bath salts' or 'plant food' to circumvent legislation (Figure 7).

63 Source: Drug Enforcement Administration. (n.d.). *Khat.* https://www.dea.gov/sites/default/files/styles/slide/public/2018-07/khatfive_highres.jpg?h=7a30731c&itok=looUelyn (accessed 1 October 2024)

FIGURE 7

Image of synthetic crystalline cathinones often sold as bath salts[64].

3.7.1 Mephedrone

Mephedrone became available online in 2007 and by the end of July 2010 had been identified in at least 38 drug-related fatalities. It is a powerful CNS stimulant whose effects resemble those of amphetamine. It is a short-acting drug with a half-life of approximately 2 hours. Effects may include heart palpitations, insomnia, loss of short-term memory, teeth grinding and sweating. Recreational use can produce blood concentrations up to 0.74 mg/L, although the most common concentration ranges between 0.2 and 0.3 mg/L[65]. The half-life of mephedrone has been reported to be about 2.5 hours[66]. Mephedrone can be detected in head hair[67]. The window of detection for mephedrone in urine is about 15 hours.

64 Source: Drug Enforcement Administration. (n.d.). *Bath salts*. https://www.dea.gov/factsheets/bath-salts (accessed 13 February 2024)

65 Cosbey, S H, Peters, K L, Quinn, A *et al.* (2013). Mephedrone (methylmethcathinone) in toxicology casework: a Northern Ireland perspective. *Journal of Analytical Toxicology, 37(2),* 74-82. https://doi.org/10.1093/jat/bks094 (accessed 13 February 2024)

66 Papaseit, E, Pérez-Mañá, C, Mateus, J A *et al.* (2016). Human pharmacology of mephedrone in comparison with MDMA. *Neuropsychopharmacology, 41(11)*, 2704-2713. https://doi.org/10.1038/npp.2016.75 (accessed 13 February 2024)

67 Kintz, P. (2017). Evidence of 2 populations of mephedrone abusers by hair testing: application to 4 forensic expertises. *Current Neuropharmacology, 15(5),* 658-662. https://doi.org/10.2174/1570159X14666161026152107 (accessed 13 February 2024)

3.8 Cocaine

Cocaine is a powerful CNS psychostimulant found in the leaves of the coca plant native to South America. It is refined into paste, powder and freebase (crack) for the black market (Figure 8). The salt form (cocaine hydrochloride) is a white, crystalline, water-soluble powder, readily absorbed intravenously or by snorting (Figure 9). Cocaine hydrochloride cannot be smoked as it decomposes at high temperatures.

Kits to convert cocaine hydrochloride to the freebase (crack) are available commercially online. Crack is crystalline in nature and is formed when cocaine is heated in an alkaline solution. It is more volatile so can be smoked or inhaled. Since it is more rapidly absorbed than the salt, it has greater addictive potential. Euphoria occurs within seconds and lasts for 30 – 90 minutes, depending on the mode of administration. This short duration leads to binge use over several hours, putting the individual at risk of toxicity and overdose.

FIGURE 8

Crystalline cocaine commonly known as ‘crack’[68].

68 Source: Drug Enforcement Administration. (n.d.). *Cocaine*. https://www.dea.gov/sites/default/files/styles/slide/public/2018-07/crack_cocaine3.jpg?itok=5NHrRs__ (accessed 1 October 2024)

Acute effects include alertness and increased confidence. Cocaine significantly increases heart rate and blood pressure and can lead to aggressive and/or enhanced sexual behaviour. Chronic high-dose use may lead to cardiovascular abnormalities such as irregular heartbeats (arrhythmia). Cocaine is sometimes injected concurrently with heroin (speed balling). Since cocaine requires more oxygen whilst heroin depresses the respiratory rate, speed balling increases the risk of death through stroke, aneurysm (bulge in blood vessel) or heart attack.

The half-life of cocaine is very short and dose dependent, ranging from 0.7 to 1.5 hours. The cardiotoxic nature of cocaine is exacerbated by concurrent use of alcohol, producing a psychoactive substance known as cocaethylene. Cocaethylene has a half-life of approximately 2.5 hours, a stronger effect on heart rate and blood pressure, and brings greater risk of seizures and liver damage to the user.

Detection of cocaine use is impacted by the short-acting nature of the drug. The presence of the main metabolite benzoylecgonine in urine is routinely used to confirm cocaine use in workplace and drug treatment drug screening programmes.

FIGURE 9

Cocaine in powder form[69].

69 Source: Drug Enforcement Administration. (n.d.). *Cocaine*. https://www.dea.gov/sites/default/files/styles/slide/public/2018-06/cocaine.jpg?itok=lofRJblZ (accessed 1 October 2024)

Care must be taken following the collection of urine for the detection of cocaine use. For instance, it is well known that cocaine is labile in biological fluids and may convert to benzoylecgonine when the pH is alkaline[60]. A study of the in vitro stability of cocaine compounds (cocaine, benzoylecgonine, ecgonine methyl ester and benzoylecgonine ethyl ester) found that storage of biological samples at -20°C is optimal for maintaining the stability of these compounds[70]. Maintaining a pH of 4 in urine samples and using a preservative in blood samples is also beneficial. Confirmation of the chain of custody and information about the storage of samples collected to detect cocaine abuse should be sought when validating results.

3.9 Gabapentinoids

The gabapentinoid drugs are antiepileptic drugs that are used as first-line treatments for the management of neuropathic pain. These depressant drugs are used in the UK off-label in primary care to manage a wide range of conditions such as bipolar disorder, sleep disorders, headaches, alcohol withdrawal syndrome, chronic back pain and fibromyalgia. Both gabapentin and pregabalin were discovered during research into gamma-aminobutyric acid (GABA), the neurotransmitter whose inhibition can cause seizures.

The gabapentinoids stimulate feelings of sociability, euphoria and relaxation, and can enhance psychoactive effects of other drugs [71]. The abuse potential of pregabalin is higher than gabapentin due to its pharmacokinetic properties. The incidence of abuse is significantly higher in secure settings and in those with current or past substance use disorders[72].

70 Huertas, T, Jurado, C, Salguero, M *et al.* (2020). Stability of cocaine compounds in biological fluids during post-analytical sample storage. *Journal of Analytical Toxicology, 44(8),* 864-870. https://doi.org/10.1093/jat/bkaa044 (accessed 13 February 2024)

71 Smith, B H, Higgins, C, Baldacchino, A *et al.* (2012). Substance misuse of gabapentin. *British Journal of General Practice, 62,* 406-407. https://doi.org/10.3399/bjgp12X653516 (accessed 13 February 2024)

72 Bonnet, U and Scherbaum, N. (2017). How addictive are gabapentin and pregabalin? A systematic review. *European Neuropsychopharmacology, 27(12),* 1185-1215. https://doi.org/10.1016/j.euroneuro.2017.08.430 (accessed 13 February 2024)

3.9.1 Gabapentin

Gabapentin and pregabalin are structurally similar drugs acting via the alpha-2-delta subunit of voltage-gated calcium channels. The mechanism by which the drugs may induce dependence is not well worked out. Pregabalin and gabapentin are predominantly excreted unchanged in the urine; they undergo respectively negligible or no metabolism in humans. They do not inhibit drug metabolism in vitro and are not bound to plasma proteins, so they are unlikely to produce, or be subject to, pharmacokinetic interactions. However, respiratory depression is exacerbated if consumed with other respiratory depressants such as alcohol[73]. The half-life of gabapentin is 5 – 7 hours and it can be detected in blood if sample collection is ideally within 24 hours. Gabapentin is not detectable in oral fluids tests. Routine urine screening does not usually cover gabapentin but immunoassay-based test strips are available.

3.9.2 Pregabalin

Pregabalin is the more sought-after drug. It has greater addiction potential being rapidly and completely absorbed: oral bioavailability for pregabalin is >90% as compared to 30 – 60% for gabapentin. Pregabalin is 2.4 – 2.8 times more potent than gabapentin. Peak plasma concentrations are seen within 60 minutes compared to 3hours with gabapentin. The half-life for pregabalin is 5.5 – 6.7 hours and the drug is excreted in urine predominantly unchanged. In subjects with normal renal function, a urine specimen would not remain positive for pregabalin for >5 – 6 days after intake[74].

3.10 Hallucinogens

Hallucinogens are a broad class of psychoactive drug that can temporarily alter a user's state of consciousness and can lead to hallucinations. Whilst the term is sometimes used interchangeably with psychedelic drugs, the latter are particularly powerful serotonergic hallucinogens that affect mood and numerous cognitive processes. Psychedelics are generally considered physiologically safe and do not lead to dependence or addiction. Examples include mescaline, LSD and psilocybin.

73 Public Health England and NHS England. (2014). *Advice for prescribers on the risk of the misuse of pregabalin and gabapentin.* https://www.gov.uk/government/publications/pregabalin-and-gabapentin-advice-for-prescribers-on-the-risk-of-misuse (accessed 13 February 2024)

74 Spigset, O and Westin, A A. (2013). Detection times of pregabalin in urine after illicit use: when should a positive specimen be considered a new intake? *Therapeutic Drug Monitoring, 35(1),* 137-140. https://doi.org/10.1097/FTD.0b013e31827789dd (accessed 13 February 2024)

3.10.1 Dissociative drugs

Dissociative drugs are a type of hallucinogen that cause users to feel detached from their surroundings, sensory experiences and sense of self. They can produce visual and auditory distortions and a sense of floating. Users may experience a distorted sense of time, colour, sound and motion. Examples include phencyclidine, ketamine, NOS and the cough suppressant dextromethorphan.

3.10.2 Lysergic acid diethylamide

LSD is a psychedelic drug derived from the ergot fungus that grows on wheat and rye. It is available in liquid, powder, gel, tablet and capsule form, but most commonly a solution containing LSD is applied to absorbent paper and sold in small squares called blotters. A dose of LSD is colloquially called a 'tab' and is taken by placing on or under the tongue (Figure 10) whereupon the drugs enter the bloodstream and are transported to the brain.

FIGURE 10

LSD blotter sheet[75].

75 Source: Drug Enforcement Administration. (n.d.). *LSD*. https://www.dea.gov/galleries/drug-images/lsd (accessed 1 October 2024)

Typically, illicit LSD doses start at 15 – 20 µg (micro-dose), but an average dose can range from 80 to 200 µg. A dose above 250 µg would be considered high. Doses as low as 25 – 50 µg produce significant psychedelic effects. LSD impairs auditory, visual and choice reaction time and visual acuity for up to 4 hours and can lead to grossly distorted perception.

LSD has a half-life of approximately 2.5 – 4 hours. The onset of effects occurs within 10 minutes of intravenous administration. After oral ingestion initial effects are experienced in 20 – 30 minutes, peaking after 2 – 4 hours, and gradually diminishing over 6 – 8 hours. Effects are unpredictable and will depend on the dose, the user's personality and mood, expectations and on the surroundings. Micro-dosing is a newer approach and is reportedly used to induce physical and mental stimulation and encourage creative thinking without producing full hallucinations, although some studies suggest that micro-doses are too low to produce a pharmacological effect[76].

3.10.3. Psilocybin and psilocin

Psilocybin is a hallucinogenic alkaloid and an active ingredient that occurs naturally in a variety of mushrooms commonly referred to as 'magic mushrooms'. Psilocin is also found in these mushrooms in smaller quantities. Both substances are chemically related to LSD but are approximately 200 times less potent.

Like other hallucinogens psilocybin works by activating serotonin receptors and has a half-life of 2.72 ± 1.1 hours when taken orally or 1.2 ± 0.32 hours when used intravenously[77].

Effects are typically experienced after elimination has taken place[78].

76 Szigeti, B, Kartner, L, Blemings, A *et al.* (2021). Self-blinding citizen science to explore psychedelic microdosing. *Elife, 10,* e62878. https://doi.org/10.7554/eLife.62878 (accessed 13 February 2024)

77 Hasler, F, Bourquin, D, Brenneisen, R *et al.* (1997). Determination of psilocin and 4-hydroxyindole-3-yl-acetic-acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharmaceutica Acta Helvetiae, 72,* 175-184. https://doi.org/10.1016/S0031-6865(97)00014-9 (accessed 13 February 2024)

78 Barrett, F S, Doss, M K, Sepeda, N D *et al.* (2020). Emotions and brain function are altered up to one month after a single high dose of psilocybin. *Scientific Reports, 10,* 2214. https://doi.org/10.1038/s41598-020-59282-yppp (accessed 13 February 2024)

3.10.4 New psychoactive hallucinogens

Novel hallucinogens are often classified as 'classical hallucinogens', because they mimic the effects of LSD, or 'dissociative and anaesthetic hallucinogens', which mimic the effects of ketamine. All distort consciousness and perception, accompanied by various degrees of auditory or visual hallucinations. Most psychoactive hallucinogens are found in plants, fungi and animals. Examples include tryptamines such as 5-methoxy-N,N-diisopropyltryptamine and methoxetamine.

3.11 Inhalants

Inhalants are volatile substances. They generate chemical vapours that can be inhaled to induce a pharmacological effect or 'high'. Inhalants can cause confusion, slurred speech, mood swings, aggressive behaviour, hallucinations, vomiting, blackouts and breathing difficulties. In certain situations, they can cause cardiovascular arrythmias that, if severe, can lead to a heart attack. Since inhalants are not identified in routine urine drug screenings, detection relies on accurate clinical diagnosis.

Although other abused substances can be inhaled, the term 'inhalants' is used to describe substances that are rarely, if ever, taken by any other route. Inhalants are often found in household, industrial and medical products and fall largely into four categories:

- **Aerosols:** sprays containing propellants and solvents. Examples include spray paints, deodorants and hair sprays, cooking oil sprays and fabric protector sprays.
- **Gases:** these include medical anaesthetics such as ether, chloroform, halothane and nitrous oxide, and gases found in household or commercial products such as butane lighters, propane tanks and refrigerants.
- **Nitrites:** unlike most other inhalants, nitrites act primarily to dilate blood vessels and relax the anal muscles for sexual enhancement. Examples include cyclohexyl nitrite, isoamyl (amyl) nitrite and isobutyl (butyl) nitrite.
- **Volatile solvents:** liquids that vaporise at room temperature and include paint thinners and removers, dry-cleaning fluids, gasoline, glues and felt-tip pens. They are CNS depressants and their effects share some similarities with those of alcohol, although volatile solvents have a much shorter half-life.

3.12 New psychoactive substances

The United Nations Office for Drugs and Crime (UNODC) has adopted the term new psychoactive substances (NPS) to describe "substances of abuse, either in a pure form or a preparation, that is not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat"[79]. The term does not always refer to 'newly produced compounds' because many NPS were first synthesised and evaluated for clinical and research purposes decades ago. NPS instead denotes substances that have recently become available on the illicit drug market.

NPS are often designed to replicate the effects of illegal substances like cannabis, cocaine and MDMA whilst remaining legal under national or international legislation, hence their previous name 'designer drugs' or 'legal highs'. They may be substances previously included in scientific studies, abandoned pharmaceutical drug candidates that did not proceed to clinical trial, but which are reported in scientific literature or patents, analogues/derivatives thereof or completely novel substances. NPS began to appear in the UK around 2008 and can also be referred to as 'bath salts' and 'research chemicals'. In 2023 more than 1,000 NPS have been identified worldwide and fall into five main categories:

- **Psychostimulants**, which activate or enhance brain activity and increase arousal. They mimic substances such as amphetamine, cocaine and MDMA, and include drug classes such as the cathinones and their derivatives (Section 3.7). They are frequently associated with a risk of abuse.
- **Synthetic cannabinoid or synthetic cannabinoid receptor agonists**, which mimic the effects of the psychoactive constituents of cannabis (primarily THC). The colloquial term 'spice' denotes substances that contain one or more synthetic cannabinoids (Section 3.6.2).
- **Anxiety-relieving (downer/anxiolytic/tranquiliser-type) drugs**, which mimic anti-anxiety drugs. Many have evolved from the benzodiazepine drug family and include etizolam, pyrazolam and flubromazepam (Section 3.5).

79 United Nations Office for Drugs and Crime. (n.d.). *UNODC early warning advisory on new psychoactive substances.* https://www.unodc.org/LSS/Page/NPS (accessed 13 February 2024)

- **Hallucinogenic drugs**, which mimic naturally occurring hallucinogens such as psylocibin, tryptamine etc. They may be semi-synthetic like LSD, or synthetic such as ketamine and phencyclidine, PCP or angel dust (Section 3.10).
- **Opioid drugs**, which mimic the effect of naturally occurring opiates such as morphine or man-made opioids such as fentanyl. They are often derivatives of existing drugs. Some are referred to as novel synthetic opioids (NSOs) (Section 3.13).

NPS are now subject to the Psychoactive Substances Act 2016, which makes it an offence to produce or supply, but not to possess, a substance that can produce a psychoactive effect. There are specific exemptions provided for in Schedule 1: medicinal products, alcohol, nicotine, caffeine and food not containing prohibited ingredients.

3.13 Opioids

Opiates are naturally occurring chemicals found in the opium poppy including codeine, morphine and thebaine. The term can also include semi-synthetic derivatives of these drugs such as diacetylmorphine (heroin). The overarching term opioids also includes the synthetic opioids, a diverse group of substances such as tramadol, buprenorphine, methadone and fentanyl.

Opioids interact with 5 different opioid receptors in the human body, particularly the Mμ receptor, as follows[80]:

- **Mμ receptors** have several subtypes. Mμ-1 receptor is responsible for analgesia and dependence; Mμ-2 receptor is vital for euphoria, dependence, respiratory depression, miosis and decreased digestive tract motility/constipation; Mμ-3 receptor causes vasodilation.
- **Kappa receptors** provide analgesia, diuresis and dysphoria.
- **Delta receptors** play a role in analgesia and reduction in gastric motility.
- **Nociceptin receptors** cause analgesia and hyperalgesia.
- **Zeta receptors** regulate cell and tissue development.

These receptors are involved in triggering neurological reward systems and can relieve pain by decreasing pain signal transmission. They are found largely in the brain, the spinal cord and in the nerves controlling intestinal function.

80 Dhaliwal, A and Gupta, M. (2023). Physiology, opioid receptor. In *StatPearls*. Treasure Island, FL: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK546642/ (accessed 13 February 2024)

3.13.1 Natural opiates

Opium is one of the oldest medications known to man. The main active ingredient is morphine, widely used as an effective analgesic for the relief of severe and chronic pain. Morphine also acts on the CNS and produces respiratory depressant effects, somnolence and mood changes. Codeine is a less potent opiate but also causes drowsiness, slower breathing and constipation. Codeine is frequently used in combination with paracetamol or aspirin.

Morphine is well absorbed following subcutaneous, intravenous or intramuscular administration. Following oral administration, however, bioavailability is low (20 – 30%). The half-life is short at 2 – 3 hours such that the window of opportunity for detecting morphine in urine would be 10 – 15 hours after ingestion of a single dose. Care is therefore needed when undertaking urine tests.

Codeine is a prodrug and is metabolised to the active drug (morphine) in the liver. This process is rather slow and limiting, and the 'high' from codeine is less intense than for heroin or morphine. Codeine is well-absorbed after oral administration with peak plasma concentrations occurring after about an hour. As it is a metabolite of morphine care is needed when interpreting urine drug tests.

3.13.2 Semi-synthetic opioids

Heroin is a lipophilic prodrug with a very short half-life of between 2 and 5 minutes. It reaches the CNS soon after administration and penetrates the blood-brain barrier to achieve the euphoric 'rush'. Heroin shows little activity at receptor sites and is rapidly metabolised to 6-monoacetylmorphine (6-MAM), a pharmacologically active metabolite, and then to morphine. 6-MAM has a half-life of 6 – 25 minutes and is often used as conclusive evidence of heroin consumption. Heroin is detectable in blood for between 10 and 25 minutes after dosing, although it is the presence of 6-MAM in urine that usually confirms heroin use. Trace amounts of 6-MAM are excreted for 6 – 8 hours following use, suggesting that urine specimens must be collected soon after the latest use. Heroin is not detected in urine samples.

Oxycodone is synthesised from thebaine, a derivative of opium. Oral oxycodone medications are generally prescribed to relieve moderate to severe pain. Oxycontin® is the most common modified-release preparation and demonstrates nearly double the pharmacological activity of morphine. The half-life of oxycodone is 2 – 3 hours and that of hydrocodone, a less potent metabolite of codeine, is about 4 hours.

Dihydrocodeine (DHC) bears a chemical resemblance to codeine and is at least as potent. The pharmacologically active metabolites are nor-dihydrocodeine, dihydromorphine and dihydromorphine-6-glucuronide. The plasma elimination half-life of DHC is about 4 hours and DHC may be detected in urine for up to 28 hours.

Buprenorphine is a partial opioid agonist and is increasingly popular within clinical practice in several developed countries, including the UK, to treat heroin dependence with lower overdose risk. Buprenorphine is administered sublingually in acute oromucosal form (Subutex) to avoid the first-pass effect. Sublingual buprenorphine is also available in combination with naloxone (Suboxone) to prevent diversion for intravenous administration. When taken sublingually naloxone is not absorbed but if injected it acts in the brain to prevent the action of buprenorphine[81]. A depot preparation (Buvidal) is also available and lasts for 1 month. Although diversion of depot forms of the drug has not been reported, Subutex tablets are available on the black market and are used for non-medical purposes.

Dextromethorphan (DXM) is an isomer of levorphanol, an opioid related to codeine. Its antitussive (cough-suppressing) activity is based on its action on certain opioid receptors. Abuse of DXM is characterised by consuming very high doses of OTC medicines, either alone or combinations with other drugs such as paracetamol or decongestants such as pseudoephedrine. Dissociative effects include dysphoria, hallucinations, agitation and sedation. It is a relatively short-acting drug with a half-life of 2 – 4 hours[82] and is detectable in urine 14 – 28 hours after cessation of dosing.

81 Kumar, R, Viswanath, O and Saadabadi, A. (2023). Buprenorphine. In *StatPearls.* Treasure Island, FL: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK459126/ (accessed 13 February 2024)

82 Ganetsky, M, Babu, K M and Boyer, E W. (2007). Serotonin syndrome in dextromethorphan ingestion responsive to propofol therapy. *Pediatric Emergency Care, 23(11),* 829-831. https://doi.org/10.1097/PEC.0b013e31815a0667 (accessed 14 February 2024)

3.13.3 Synthetic opioids

Synthetic opioids are a class of drug made in laboratories and are designed to have a chemical structure and pharmacological effect similar to natural opiates.

Methadone is used largely to prevent withdrawal symptoms when reducing dependence on illicit opioids such as heroin but can also be taken as an analgesic and as an antitussive. Adverse effects include sedation and respiratory depression. It is well absorbed when taken orally in liquid form, reaching peak plasma concentrations after approximately 4 hours. It is metabolised largely to 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), a non-pharmacologically active compound that is commonly identified in urine as evidence of consumption. The half-life is estimated at 33 – 46 hours. Upon cessation of use, blood drug concentrations fall but methadone can remain in the body for between 9 and 13 days.

Tramadol is of moderate strength and is five to ten times less potent than morphine. It is rapidly absorbed after oral or parenteral administration, reaching peak plasma concentrations after approximately 2 hours. The therapeutic tramadol blood concentration is 100 – 800 µg/L. The half-life is approximately 6 hours and the half-life for the main active metabolite is approximately 9 hours. Tramadol may be used in emergency situations such as accidents or acute organ injury.

Fentanyl is a powerful agonist estimated to have 75 – 100 times more analgesic potency than morphine. Fentanyl is used in medical settings as an anaesthetic agent, including for postoperative pain, but has also been abused under the pseudonym ‘China White’. Fentanyl is highly lipophilic and binds strongly to plasma proteins. It is metabolised predominantly in the liver resulting in the inactive metabolite norfentanyl. It is a short-acting drug with a half-life of 3 – 7 hours that can be detected in urine for approximately 21 – 49 hours.

Brorphine is known as ‘purple heroin’ and displays similar pharmacological effects to fentanyl. It has been detected in fake pain medication tablets such as oxycodone[83].

Pharmaceutical fentanyls include three fentanyl analogues licensed as medicines for human use in the UK: alfentanil (half-life about 1.5 hours), remifentanil (half-life 3 – 10 minutes) and sufentanil (half-life about 2.5 hours). These are all potent drugs used to relieve pain, but they also have euphoric effects and most have potential for misuse[84].

Other fentanyl analogues include:

- **Ocfentanyl**, an analgesic opioid with fewer cardiovascular and respiratory effects. It is similar in action to fentanyl but more potent.
- **Carfentanyl**, which has around 10,000 times the analgesic potency of morphine and 100 times that of fentanyl. It is not licensed for human use. It is used in veterinary medicine for the immobilisation of large animals. However, many cases of human carfentanyl poisoning have been reported[85].
- **Cyclopropylfentanyl**, another very potent and selective receptor agonist.
- **Lofentanyl**, a carfentanyl analogue that is the most potent of all fentanyls and that is used for research.

83 Verougstraete, N, Vandeputte, M M, Lyphout, C *et al.* (2021). First report on brorphine: the next opioid on the deadly new psychoactive substance horizon? *Journal of Analytical Toxicology, 44(9),* 937-946. https://doi.org/10.1093/jat/bkaa094 (accessed 14 February 2024)

84 Advisory Council on the Misuse of Drugs. (2020). *Misuse of fentanyl and fentanyl analogues.* https://www.gov.uk/government/publications/misuse-of-fentanyl-and-fentanyl-analogues (accessed 14 February 2024)

85 Fomin, D, Baranauskaite, V, Usaviciene, E *et al.* (2018). Human deaths from drug overdoses with carfentanyl involvement-new rising problem in forensic medicine: a STROBE-compliant retrospective study. *Medicine (Baltimore), 97(48),* e13449. https://doi.org/10.1097/MD.0000000000013449 (accessed 14 February 2024)

3.13.4 Novel synthetic opioids

NSOs are a class of opioid agonists that are not structurally related to fentanyl and that have arisen to circumvent drug control laws. NSOs are more potent and have greater opioid receptor affinity than natural or synthetic opiates. They are consequently associated with intoxication and fatalities.

NSOs can be used as heroin adulterants or as constituents of counterfeit pain pills. They can be purchased directly from online vendors on the internet or on the crypto market or dark web. NSOs depress the CNS and produce standard effects such as respiratory depression, analgesia, hypothermia, sedation, euphoria, anxiety, sweating, disorientation and nausea. They belong to four separate structural families:

- **Benzamides**, some of which can induce respiratory depression and can even be used to target certain solid tumours.
- **Acetamides**, which are not well-reported in the scientific literature, but that demonstrate some analgesic properties in animals.
- **Piperazines**, which have analgesic and sedative effects, are nearly as potent as morphine and are highly addictive.
- **Nitazenes**, which are also highly potent. Pharmacokinetic data for some nitazenes are not yet available.

4. Drug use behaviour

This section considers commonly observed behaviours and experiences with reference to the CJS.

4.1 Abuse

This term, also known as drug misuse, denotes the use of a substance for non-therapeutic purposes to obtain psychotropic (eg euphoric, sedative or anxiolytic) effects, and may include use that contradicts medical advice. It usually entails harm to the user or to others and may present specific risks related to overdose, polydrug and alcohol misuse, mental health, unsafe injecting practices, and unsafe sex.

4.2 Addiction

Addiction is primarily defined as compulsive substance use involving neurobiological dysfunction that occurs despite personal harm or other negative consequences. A medical diagnosis usually frames addiction as a chronic condition associated with craving and impaired control and that requires pharmacotherapy, such as substitution therapy.

4.3 Alcohol use

The following terms are internationally agreed definitions of drinking behaviours:

- **At-risk drinking** denotes consumption in excess of recommended guidelines, placing individuals at risk of physical, psychological and/or social harm.
- **Drinking at increasing risk** (hazardous use) denotes weekly alcohol consumption of 22 – 49 units for men and 15 – 34 units for women.
- **Higher risk drinking** (harmful use) denotes alcohol consumption of over 50 units per week for men and of over 35 units per week for women, associated with alcohol-related harm such as high blood pressure, liver problems, prosecution for drink driving, or psychological problems such as depression and sleeping difficulties.
- **Binge drinking** denotes drinking more than eight units on a single occasion for men and more than six units for women.
- **Alcoholic ketoacidosis** (AKA) denotes symptoms and a metabolic state typically observed after a binge without food resulting in nausea, severe vomiting and abdominal pain. It can cause ketones (acids) to accumulate in the blood leading to agitation, high respiratory rate, tachycardia (fast heart rate) and hypotension (low blood pressure). Severe AKA can result in sudden death. Laboratory testing can often diagnose or exclude AKA by indicating concentrations of blood glucose, alcohol and acetone.

- **Dependent drinking** denotes a sustained pattern that places an individual at risk of alcohol dependence and where the brain has adapted to the presence of alcohol. This usually involves a compulsion to drink and loss of control during drinking. Sudden interruptions lead to physiological withdrawal symptoms. In early dependence this might emerge as mild anxiety or finger tremor. As alcohol dependence develops the individual needs to drink around the clock to prevent symptoms. While it can take up to 10 years for alcohol dependence to evolve in men progression is more rapid in women, who can become dependent after 2 – 5 years. Concurrent use of drugs such as cannabis can accelerate the path to dependence[86]. Diagnosis can be made using the International Classification of Diseases 11th Revision (ICD-11)[87].

Increasing BAC has a detrimental effect on a wide range of bodily functions and human behaviour. BAC can be established as follows:

- **BAC 20 – 30 mg/100 mL blood:** most individuals become more talkative and less inhibited. There may be a decline in visual functions (rapid tracking of a moving target) and in the ability to perform two tasks at the same time (divided attention).
- **BAC 50 mg/100 mL blood:** reaction times are slower and performance worsens in divided attention tasks. Risk taking is more likely. This is the legal limit for driving in Scotland.
- **BAC 80 mg/100 mL blood:** concentration, information capability and short-term memory are impaired. The risk (odds) of a road traffic collision is increased by 2.69[88]. This is the legal limit for alcohol for driving in England and Wales.
  - **Odds ratio (OR):** is the ratio of odds (risk) of a collision in one group (eg drink driver/ exposed group) versus the odds of the collision in the other group (eg non-drinker/ unexposed group). An OR of 1.0 indicates no difference in odds between the groups. An OR of more than 1.0 indicates an increased odds in the exposed group.

86 UK Government. (2021). *Delivering better oral health: an evidence-based toolkit for prevention.* Chapter 12: *Alcohol.* https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention/chapter-12-alcohol (accessed 14 February 2024)

87 World Health Organization. (n.d.) *International classification of diseases 11th revision.* https://icd.who.int/browse10/2019/en (accessed 14 February 2024)

88 Voas, R B, Torres, P, Romano, E *et al.* (2012). Alcohol-related risk of driver fatalities: an update using 2007 data. *Journal of Studies on Alcohol and Drugs, 73(3),* 341-350. https://doi.org/10.15288/jsad.2012.73.341 (accessed 14 February 2024)

- **BAC >100 mg/100 mL blood:** impairment is reflected in balance disturbances and, in some individuals, an inability to walk straight or stand upright without support.
- **BAC 150 mg/100 mL blood:** there is substantial impairment and loss of coordination. The individual has limited vehicle control, attention to driving, and poor visual and auditory information processing. The odds of a collision are increased by 22[89].
- **BAC >150 mg/100 mL:** most individuals become drowsy or fall asleep, displaying 'troublesome' behaviour and communication difficulties.
- **BAC >350 – 400 mg/100 mL:** the individual cannot walk unaided, is at risk of collapse, and is unable to coordinate basic actions or communicate effectively.
- **Fatal BAC** is understood to be more than 500 mg/100 mL blood, although the amount necessary to reach these concentrations can be tolerated only by dependent individuals, who risk becoming comatose and dying from respiratory failure and/or cardiopulmonary arrest.

4.4 Craving

Craving is defined by the WHO as the very strong desire for a psychoactive substance or for the intoxicating effects of that substance. Craving is a psychological phenomenon and is particularly associated with efforts to stop using cocaine, nicotine, alcohol, BZDs, and opiates or opioids.

4.5 Dependence

A state of dependence develops after chronic administration of certain drugs and is characterised by the need to maintain consumption to avoid withdrawal symptoms, which may have serious medical consequences. Substance use or certain behaviours continue despite psychological and/or physical harm. The dependence-forming potential of a drug depends upon:

- Potency of effect.
- Speed at which the drug crosses the blood-brain barrier. Users of lipophilic drugs are particularly vulnerable to dependence. Drugs that enter the bloodstream through intravenous use, smoking or intranasal use are typically more habit-forming than those consumed orally (eg heroin, cocaine etc).

89 European Road Safety Observatory. (2006). *Alcohol*. https://road-safety.transport.ec.europa.eu/system/files/2021-07/02-alcohol_en.pdf (accessed 14 February 2024)

- Speed of binding to receptors. The more quickly the drug binds the greater the psychological and/or physical effect.
- Elimination rate. A short half-life and rapid elimination from the body increases the addiction potential of a drug (eg nicotine).
- Predictability of effect. A predictable effect is powerfully reinforcing (eg BZDs such as diazepam or opiates such as morphine).

Dependence is usually diagnosed by a specialist consultant psychiatrist or clinical psychologist.

4.6 Detoxification

Detoxification involves cessation of use of dependence-forming drugs. As CNS function begins to return to normal withdrawal symptoms may render users physiologically and psychologically vulnerable. Detoxification can require drugs to be prescribed to attenuate withdrawal symptoms, and behavioural or cognitive therapy to address stressors such as anxiety and insomnia. Mental health is an important consideration because detoxification can lead to confusion and/or mood changes with irritation, disorientation and suicidal ideation. Unfortunately, many users attempt detoxification in a poorly controlled manner when their drug of choice is no longer available.

Ideally, detoxification should involve a thorough medical examination with routine blood tests to assess the risk of underlying medical problems related to specific drug-related harm (such as endocarditis in intravenous users) or to lifestyle (such as malnutrition). Detoxification from recreational drugs may cause psychological distress such as mood changes or cravings but does not usually require clinical intervention.

4.7 Overdose

A true 'overdose' is a biological response to the consumption of a drug or drugs in quantities greater than an individual's prevailing tolerance. It usually involves respiratory failure. Examples include:

- **Alcohol:** the human body can generally process around one unit of pure alcohol per hour. Consuming very high concentrations in a short period of time can lead critical areas of the brain that control breathing, heart rate and body temperature to fail. In extreme cases this may result in alcohol poisoning, unconsciousness and death. Symptoms of alcohol toxicity include confusion, severe lack of coordination, vomiting, irregular or slow breathing, pale or blue-tinged skin, unresponsive consciousness, unconsciousness, and loss of bladder or bowel control[90].
- **Stimulants:** these increase heart rate, blood pressure, body temperature and respiratory rate. Excessive use over a single session may eventually cause cardiovascular failure and respiratory arrest. Acute cocaine toxicity, for instance, may require urgent treatment to prevent acute coronary syndrome, stroke and death[91]. Clinical signs of amphetamine overdose include hyperactivity, hyperthermia, tachycardia, tachypnea, mydriasis, tremors and seizures[92] .
- **Opioids:** when the body becomes overwhelmed by opioids respiration is depressed and receptors blocked. Sedation, bradycardia and emesis may occur and often result in death.

90 Drinkaware. (n.d.). Alcohol poisoning. https://www.drinkaware.co.uk/facts/health-effects-of-alcohol/effects-on-the-body/alcohol-poisoning (accessed 14 February 2024)

91 Richards, J R and Le, J K. (2023). In: *StatPearls [Internet].* Treasure Island, FL: StatPearls Publishing; 2024 Jan-. Available from https://www.ncbi.nlm.nih.gov/books/NBK430976/ (accessed 14 February 2024)

92 Fitzgerald, K T and Bronstein, A C. (2013). Adderall® (amphetamine-dextroamphetamine) toxicity. *Topics in Companion Animal Medicine, 28(1),* 2-7. https://doi.org/10.1053/j.tcam.2013.03.002 (accessed 14 February 2024)

4.8 Passive exposure

This occurs when drugs enter blood, urine or oral fluid following accidental exposure by an individual other than the intended drug user. The involuntary inhalation of smoke from cigarettes or tobacco products is a classic example and may include second- and third-hand smoke.

A review of passive exposure to cannabis found that positive tests for THC and THC-COOH, a common metabolite, were observed following only extremely high passive exposure[93]. Modern analytical methods suggest that due to the rapid distribution of THC in the body, which occurs after passive exposure to low doses, THC concentration in blood serum is typically less than 1 µg/L, whilst similar and very low serum concentrations of THC-carboxylic acid are observed (<2 µg/L). Studies have demonstrated that individuals exposed to cocaine smoke under naturalistic or artificial conditions absorbed small amounts of cocaine that were insufficient to produce positive urine specimens at standard cut-offs. Thus, unless drug exposure occurs over a protracted period and at a high dose passive exposure should not be seen as an explanation for a positive drug test. THC or THC-COOH in hair argues for regular consumption of cannabis, and in sweat or oral fluid for recent consumption. A positive test for cocaine suggests consumption of amounts in excess of 1 mg.

Accidental exposure to cocaine has been used as a defence in sports testing cases. In 2016, the Sport Dispute Resolution Centre of Canada (SDRCC) found a pole vaulter had inadvertently absorbed cocaine while kissing a woman the night before a national competition, after undergoing a urine test, which detected the drug.

This defence has been largely dismissed by the scientific community as improbable. Dr Juurlink, head of clinical pharmacology and toxicology at Sunnybrook Health Sciences Centre in Toronto, noted that it was “very difficult to imagine a scenario in which the exchange of saliva through kissing transfers from one person to another a sufficient amount of cocaine to result in a positive test”. Whilst it is possible that small amounts of the drug would be transferred from the lips and presumably swallowed into the stomach the bioavailability of cocaine following consumption ranges from 20 to 60% and is much less than by the intranasal route[94] and very unlikely to be in quantities that would be detected in a urine drug test.

93 Berthet, A, De Cesare, M, Favrat, B *et al.* (2016). A systematic review of passive exposure to cannabis. *Forensic Science International, 269,* 97-112. https://doi.org/10.1016/j.forsciint.2016.11.017 (accessed 14 February 2024)

94 Coe, M A, Jufer Phipps, R A, Cone, E J *et al.* (2018). Bioavailability and pharmacokinetics of oral cocaine in humans. *Journal of Analytical Toxicology, 42(5),* 285-292. https://doi.org/10.1093/jat/bky007 (accessed 14 February 2024)

4.9 Tolerance

Tolerance is reached when a user experiences markedly diminished effects during consumption of consistent quantities of a given substance. Users typically require increased amounts to achieve intoxication or the desired effect. Tolerance typically develops over days to weeks and can result from multiple mechanisms, including changes in drug metabolism and alteration to the number or responsiveness of receptors. This type of neural adaptation commonly occurs with alcohol and the opiates/opioids.

Tolerance can be divided into three functional categories[95]:

- **Acute:** The onset of tolerance may occur within minutes, during a single exposure for instance to alcohol.
- **Rapid:** Similar to chronic tolerance but develops faster, typically within 8 – 24 hours (eg nicotine).
- **Chronic:** Following prolonged exposure to a drug such as heroin.

4.10 Withdrawal

Withdrawal is the constellation of physiological and behavioural changes directly related to sudden cessation or significant reduction in use of a psychoactive drug to which the body has become adapted. It manifests through:

- characteristic withdrawal syndrome (such as heroin users going 'cold turkey'); or
- taking the same or closely related substance to relieve or avoid withdrawal symptoms (such as using codeine to alleviate heroin withdrawal).

Although withdrawal is underpinned by biological changes in cells and receptors, psychological symptoms are usually significant and may be manifest differently by individuals in different settings.

Withdrawal symptoms may resemble conditioned responses that develop more quickly if associated with a cue (such as the need for a cigarette with a pint) and can be evoked by environmental stimuli (such as seeing a used needle) when the drug has not been used for some time. This helps to explain why symptoms vary considerably over time and space.

95 Pietrzykowski, A Z and Treistman, S N. (2008). The molecular basis of tolerance. *Alcohol Research and Health, 31(4),* 298-309. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3860466/ (accessed 14 February 2024)

Opiate/opioid withdrawal

Symptoms of opiate withdrawal syndrome can resemble influenza and are very rarely life-threatening. They are, however, unpleasant and must be overcome by users as the first step towards abstinence. Several pharmacological options are available to manage opiate withdrawal, most of which can be tailored to a given user.

The time taken to develop withdrawal effects will depend on the pharmacokinetics of the drug. Withdrawal from methadone, which has a long half-life, will not commence for several days (96 – 144 hours) whereas withdrawal from heroin, with a shorter half-life, will occur within 8 – 12 hours of the last dose[96].

Stimulant withdrawal

Withdrawal from stimulant drugs can lead to moderate or severe symptoms. These typically include neurochemical changes that result in dysphoric mood and further effects such as fatigue, vivid dreams, insomnia or hypersomnia, and increased appetite. Psychomotor retardation (slow thinking or body movements) or agitation are common. Drug craving and anhedonia may also be present. Cocaine withdrawal has been reported to reach its peak in 2 – 4 days, with symptoms such as lowering of mood, fatigue and general malaise lasting for several weeks but without threat to life.

Amphetamine withdrawal is reported to peak within 2 – 4 days following cessation of dosing. The most characteristic symptom is low mood.

Alcohol withdrawal

Alcohol withdrawal syndrome is a clinical diagnosis and requires specialist nursing care in a hospital setting. It may vary in severity, and complicated withdrawal may be accompanied by hallucinations, seizures or delirium tremens.

96 Kleber, H D. (2007). Pharmacologic treatments for opioid dependence: detoxification and maintenance options. *Dialogues in Clinical Neuroscience, 9(4),* 455-470. https://doi.org/10.31887/DCNS.2007.9.2/hkleber (accessed 14 February 2024)

Benzodiazepine withdrawal

The benzodiazepine physiological withdrawal syndrome is well known and is characterised by sleep disturbance, irritability, increased tension and anxiety, panic attacks, sweating, difficulty in concentration, dry-retching and nausea, palpitations, headache, muscular pain and stiffness. In chronic users seizures and psychotic reactions may occur and hospitalisation is required. Rebound anxiety and insomnia occurs 1 – 4 days after dosing cessation, depending on the half-life of the particular BZE. A return of anxiety symptoms may also occur[97].

Cannabinoid withdrawal

Cannabis withdrawal is a well-characterised phenomenon that occurs in approximately half of dependent users after abrupt cessation of use and symptoms typically occur within 24 – 48 hours. The early phase of withdrawal is usually characterised by insomnia, irritability, decreased appetite, shakiness and, less often, sweating and chills. These early symptoms are most likely to peak after 2 – 6 days with some symptoms in heavy cannabis users lasting up to 3 weeks or more[98].

97 Pétursson, H. (1994). The benzodiazepine withdrawal syndrome. *Addiction, 89(11),* 1455-1459. https://doi.org/10.1111/j.1360-0443.1994.tb03743.x (accessed 14 February 2024)

98 Connor, J P, Stjepanović, D, Budney, A J *et al.* (2022). Clinical management of cannabis withdrawal. *Addiction,117(7),* 2075-2095. https://doi.org/10.1111/add.15743 (accessed 14 February 2024)

5. Accreditation and quality standards for testing

This section sets out principles of accreditation for forensic science and toxicology laboratories in the UK, explores relevant quality standards and considers methods for sample collection.

5.1 Laboratory accreditation and quality assurance

The Forensic Science Regulator Act 2021[99] gave statutory powers to the Forensic Science Regulator for England and Wales (the Regulator). Under the Act the Regulator, appointed by the Home Secretary, has issued a Code of Practice, which came into force on 2 October 2023, with which forensic science practitioners must comply. The Code requires that the testing of human material for drugs must be carried out by laboratories accredited by bodies that have been approved by the Regulator. Accreditation within the UK is administered by the UKAS. In most analytical areas of forensic science and toxicology the Regulator has based the quality requirements on the International Organization for Standardization's IEC/ISO 17025[100] or ISO 15189 standard, which apply to calibration and testing laboratories generally. Quality requirements serve to ensure that:

- the laboratory environment is fit-for-purpose, with equipment calibrated and maintained to a high standard;
- methods are appropriately validated (demonstrated to be fit-for-purpose and limitations understood) for all drugs for which the laboratory routinely tests, although this may not be possible for some SCRAs and NPS; and
- individuals employed in the laboratory are competent in the areas in which they work, and that their competence is regularly reviewed.

99 UK Government. (2021). *Forensic Science Regulator Act 2021.* https://www.legislation.gov.uk/ukpga/2021/14/contents/enacted (accessed 14 February 2024)

100 International Organization for Standardization. (2017). *Quality requirements for ISO.* https://www.iso.org/files/live/sites/isoorg/files/store/en/PUB100424.pdf (accessed 14 February 2024)

The International Laboratory Accreditation Cooperation (section-G19)[101], LAB 51 (second edition, January 2023) is intended to provide guidance for those involved in forensic process examination and testing by providing application to the ISO/IEC standards 17025 and 17020[102].

In Scotland and Northern Ireland, forensic science practitioners and laboratories are not under statutory regulation but should nonetheless follow the Regulator's guidance. For each laboratory UKAS issues a Schedule of Accreditation. Amongst other items it lists the drugs for which the laboratory has demonstrated accredited methods and may indicate whether the relevant method covers identification and/or quantification of substances.

Method validation entails a series of experiments to establish the assay performance characteristics against predetermined criteria. Detailed validation requirements can be found in LAB 51, which is considered the reference standard. In forensic toxicology the most commonly used validation guide is ANS/ASB Standard 036 – Standard Practices for Method Validation in Forensic Toxicology[103].

It should be noted that laboratories occasionally send samples to EU laboratories (particularly in hair-testing cases) and that these laboratories are not required to be accredited by UKAS, but their accreditation must be approved by the Regulator.

5.1.1 Measurement uncertainty

The measurement uncertainty is defined as the degree of confidence or the margin of doubt for a measurement. Quantification is commonly reported in a form such as '20 ± 0.5 mg/L at a 95% confidence interval', which indicates that the laboratory is 95% certain that the result lies between 19.5 and 20.5 mg/L. This is useful in forensic casework for ensuring that the cut-off or threshold for an offence has been met. There are acceptable limits for each drug or metabolite that are standardised and universally applied, despite the (im)precision of any particular method.

101 International Laboratory Accreditation Cooperation. (2022). *ILAC G19:06/2022 modules in a forensic science process*. https://ilac.org/publications-and-resources/ilac-guidance-series/ (accessed 14 February 2024)

102 United Kingdom Accreditation Service. (2023). *UKAS accreditation of laboratories performing analysis of toxicology samples.* https://www.ukas.com/wp-content/uploads/2021/06/LAB-51-UKAS-Accreditation-of-Laboratories-Performing-Analysis-of-Toxicology-Samples.pdf (accessed 14 February 2024)

103 AAFS Standards Board. (2019). *Standard practices for method validation in forensic toxicology.* https://www.aafs.org/sites/default/files/media/documents/036_Std_e1.pdf (accessed 14 February 2024)

5.1.2 Matrix effects

Matrix effects denote bias incurred during sample analysis. The sample matrix (such as urine, blood or hair) or the remaining matrix components following a sample extraction process (to separate the drug of interest from the matrix) can influence the efficiency of, particularly, a mass spectrometer, which may affect the quantification of a particular analyte. The presence of matrix effects does not always mean that assays are unreliable; using an internal standard can often compensate for any effects, although this must be demonstrated during method validation.

5.1.3 Stability

Knowledge of stability is a critical consideration in the interpretation of analytical results. Adequate storage conditions in forensic laboratories are of paramount importance when testing may have legal implications. Stability experiments therefore usually form part of the validation process. This involves using quality control samples stored in, or exposed to, different environmental conditions (such as varying temperature and light) that might influence the measured concentration of a given analyte. This is especially important for labile (easily broken down) drugs or metabolites such as THC. As an example, in whole blood samples (required for confirmation of drug-driving cases) stored at 5°C approximately 60% of the initial concentrations of THC and CBD were recovered after 19 weeks of storage[104].

5.1.4 Cut-off concentration (threshold)

This is the concentration above which results are reported as positive and below which results are reported as negative. It is important to note that a result below the cut-off concentration does not mean that the substance in question has not been identified in a sample. Cut-off concentrations are often specified according to the particular circumstance or legislation in place, for example:

- Employment screening cut-offs in urine, oral fluid or hair are based on those outlined in the European Workplace Drug Testing Society (EWDTS) guidelines[105].

104 Sorensen, L K and Hasselstrom, J B. (2017). Sensitive determination of cannabinoids in whole blood by LC-MS-MS after rapid removal of phospholipids by filtration. Journal of Analytical Toxicology, 41(5), 382-391. https://doi.org/10.1093/jat/bkx030 (accessed 14 February 2024)

105 European Workplace Drug Testing Society. (2022). *European guidelines for workplace drug testing in urine*. https://www.ewdts.org/ewdts-guidelines.html (accessed 14 February 2024)

- Test thresholds in oral fluid or urine for employment drug screening are usually set very low or at zero tolerance. An exception is some opiates that have high thresholds to account for possible medicinal use.
- In the UK the standard cut-off concentration for THC-COOH (the urinary metabolite of cannabis) used by drug test manufacturers is 50 ng/mL, but in blood tests this is usually much lower, at 2 ng/mL.

5.1.5 Chain of custody

The chain of custody (CoC) is an essential process of evidence documentation used to ensure that evidence is authentic. The CoC form records all changes in the seizure, custody, control, transfer, analysis and disposition of physical and biological evidence. This process should be followed whenever it is known in advance that analysis may have legal implications. Apart from criminal cases, examples include family law cases where the custody of a child is in question or workplace drug testing where an individual may be subject to sanctions or dismissal.

The CoC process tracks the movement of samples/materials by documenting everyone who handles the evidence, the date and time of collection and transportation to the laboratory, and the identity and the sample integrity. Required checks include:

- visual examination, including of blood (colour and composition);
- photography;
- examination for signs of contamination or tampering (such as a broken bottle seal, irregular paperwork, unusual appearance); and
- leaking of biological fluids within sealed evidence bags.

The laboratory monitors the CoC process and records any anomalies in the documentation process. The process also encompasses recording, interpretation and reporting of results, storage, any retesting and subsequent disposal, ensuring that at all stages the location of and access to samples can be evidenced. This helps to identify potential post-analytical errors and delays.

5.1.6 Streamlined forensic report

The streamlined forensic report (SFR) process focuses on the issues in dispute and seeks to avoid any unnecessary analysis or report-writing. The first report (SFR1) outlines the outcome of the scientific examination that is served on the other party with the aim of achieving agreement. An SFR1 is not admissible as evidence other than as agreed fact. If the other party is not willing to agree to the evidence, they must explain why. This leads to an SFR2 that addresses the concerns, and which is designed to serve as admissible evidence. The SFR is not applicable in Scotland or Northern Ireland, although in Scotland there is a separate statutory duty on parties to seek agreement of evidence; either party may serve a statement of uncontroversial evidence that, if unchallenged, will lead to the facts in the notice being deemed to have been conclusively proved.

5.2 Sample collection

5.2.1 Collection of biological samples

A controlled collection process is an integral element of a robust CoC. Sample collection must follow formal processes to consider how opportunities for contamination, substitution, adulteration, dilution or tampering will be mitigated. The donor of a sample should be positively identified prior to collection and must provide informed consent.

The volume and type of samples are influenced by the breadth of testing required, the pharmacokinetics of the drug(s) of interest, and the collection facilities and laboratory expertise available.

For most accredited laboratories acceptable sample characteristics are defined for fluid matrices. Urine, oral fluid and hair samples are commonplace in workplace drug testing, and breath testing is often used for alcohol detection. Urine or oral fluid samples may also offer an overview of an individual's drug use.

Oral fluid

Oral fluid is relatively straightforward to collect. It is difficult to switch or adulterate samples, although drugs are present in lower concentrations and samples are usually much smaller than those taken from urine. For most drugs the detection window for oral fluid is only 24 – 48 hours. The World Anti-Doping Agency, which polices drug use in sport, has set lower limits for drugs in oral fluid: for example, 15 ng/mL nandrolone for male athletes.

Hair

Adult hair grows at approximately 1 cm per month. Drugs or metabolites can be detected in the hair shaft or follicle. Collection of hair samples is a non-invasive process where a small section is cut with scissors as close to the scalp as possible. The orientation of hair is noted to ensure that the laboratory can identify the proximal (scalp end) and distal end (farthest from the scalp), enabling results to be related to the appropriate time frame. Hair samples can be stored easily and have a long-term detection window. They are often used to assess retrospective consumption, abstinence from drugs of abuse or alcohol, to undertake workplace drug testing and in childhood custody cases.

Hair samples cannot, however, differentiate occasional from regular drug use, and are poor at detecting recent use. Hair treatments, particularly peroxide, can reduce the concentration of drug traces in hair, and are a popular means of manipulation to minimise the risk of a positive test.

Urine

Urine remains the most versatile biological fluid for drug testing and can indicate use over several previous days (ie longer than blood or oral fluid). Drugs are present in relatively high concentrations and large samples can usually be obtained quickly and safely. Any toilet tissue used by donors should be frozen and exhibited separately. Urine samples may, however, be manipulated by dilution, contamination or substitution. In some circumstances, such as in prison settings and sports testing, the collection process will be observed to reduce this risk.

Blood

Blood samples are required to estimate the concentration of a drug or metabolite in the body at a given time and must be obtained by trained personnel. Legal requirements can determine the sample type required (whole blood, serum or plasma). In driving under the influence of drugs cases, whole blood samples are required for evidential testing. In competitive sport, biomarkers of growth hormone are measured in blood serum. Where testing is performed for clinical purposes, whole blood, serum or plasma samples can be used to establish compliance with, or efficacy of, prescribed medication and whether consumption falls within the therapeutic range.

Blood is the preferred sample when testing to support investigations of sudden and unexpected deaths, or during police casework to determine the possible effects of drug(s) on a suspect or victim. Urine, vitreous humour, stomach contents and tissue samples may also be used.

When a sample is collected under CoC it may be divided into two parts, commonly referred to as the 'A' and 'B' sample. This process is witnessed by the donor and tamper-evident seals are used for both samples. To maintain CoC, checks are performed when samples arrive at the laboratory, including to confirm that seals remain intact. The A sample is analysed and the B sample is stored at the laboratory for future use, if needed. This may not apply in post-mortem cases where the quantity of sample that can be collected is often limited.

5.2.2 Collection of tablets, powders and herbal materials

Only very small samples are required, which means that subsamples of seized material must be representative of the items of interest. If the item is a single bag of powder or a tablet the sample is homogenised, and a subsample is taken for analysis. Homogenisation involves breaking a sample into identical parts that accurately reflect the composition of the substance and thus ensuring uniform and repeatable results. Various methods are used, including mortar and pestle, shearing, beating and blending, depending on the type of sample and methodological requirements.

If the item of interest is large (a seizure of tablets or material in bulk), then a sampling strategy has to be applied. This may involve sorting material into types, which can include presumptive testing (Section 6.2.1), followed by statistical sampling to ensure that the subsamples analysed are representative of the whole. Where items share common external characteristics, they are placed into a 'black box' and samples are chosen at random. This aims to minimise selection bias.

Knowledge of the metabolism of a given drug is essential to determine whether a particular testing method will identify the drug of interest or whether some form of sample pre-treatment is required to detect it in drug conjugates (where a drug compound is chemically linked to another compound such as an antibody).

6. Key analytical techniques and test parameters

This section explains the scientific basis for a range of analytical techniques to support investigation of death, poisoning and drug use. Toxicology reports indicate the types of substances present in an individual and whether the quantity of those substances is consistent with therapeutic dosage or whether it exceeds a harmful level. The Scientific Working Group for the Analysis of Seized Drugs (SWGDRUG) provides the minimum requirements for the development of an analytical scheme for proper identification of a drug or chemical.

In recent years herbal medicines have emerged that are adulterated with undeclared synthetic drugs or their structurally modified analogues. This may occur because natural substances are in short supply, too expensive or to provide illegal drugs under a banner of authenticity[106].

6.1 Quantitative vs qualitative tests

Qualitative tests confirm whether a particular analyte is present in a sample. Quantitative tests indicate the amount, with semi-quantitative analysis providing an estimate.

6.2 Two-tier testing

Two-tier testing usually involves an initial screen on one portion of the sample followed by a confirmatory test on a second portion, each with specified cut-off concentrations for the drug in question. Confirmatory tests are often required where significant decisions rest on the result. The screening test is designed to separate negative specimens from those that require further consideration. Two-tier testing is not commonly employed in drug and alcohol treatment settings due to the high cost.

6.2.1 Screening / presumptive / indicator tests

Screening tests are conducted largely on urine and oral fluid samples. They are often (but not always) immunoassay based, where specific antibodies detect and bind to a drug or metabolite of interest. These tests are quick, cheap, straightforward and are useful in the workplace and clinical practice, especially since they are readily available at the point of care.

106 Haneef, J, Shaharyar, M, Husain, A *et al.* (2013). Analytical methods for the detection of undeclared synthetic drugs in traditional herbal medicines as adulterants. *Drug Testing and Analysis, 5(8),* 607-613. https://doi.org/10.1002/dta.1482 (accessed 14 February 2024)

In recent years there has been substantial growth in the development of near-patient test kits, also known as bedside testing. These are immunoassay tests that are used mostly to collect urine samples and that offer rapid results. Accuracy varies across different tests and devices. There is concern that without sufficient staff training the number of false negative results using these test kits could be unacceptably high. Confirmatory tests are always recommended.

In most cases, immunoassays produce qualitative or semi-quantitative results against a pre-defined 'cut-off' concentration. However, they lack specificity, especially for small and structurally similar molecules, and there is a comparatively high risk of false positive or false negative results.

True and false positives and negatives

In qualitative screening tests, each sample is reported either positive or negative for a particular drug or group of drugs. There are four possible interpretations: true and false positives, and true and false negatives. However, a true positive will not indicate the dose, time or route of administration, nor will it distinguish chronic from single dosing.

False positives typically arise when an antibody cross-reacts with another compound in the sample matrix, especially when this compound has structural similarities with the drug of interest. For example, codeine and morphine cross-react in most immunoassays for opiates. Cross-reactions can also arise from more unexpected sources, such as food or dietary supplements, or in some cases, drugs or metabolites from structurally unrelated compound classes. False positives may also be reported if medication taken legitimately, and which shares chemical properties with the drug of interest, is not acknowledged. For example, immunoassays from certain patients receiving antiretroviral therapy can indicate a false positive for cannabis, and pseudoephedrine in cough medicine may suggest a false positive for amphetamine. False positives can also arise due to misinterpretation of test reports.

True negatives must be underpinned by knowledge of the time taken for the drug of interest to be eliminated from the body. It is possible that a negative test could result from sampling that is conducted too late after drug consumption.

False negative results arise when compounds that may be of relevance do not cross-react with the chosen immunoassay. The emergence of novel psychoactive substances is of particular concern. For most immunoassays it is not known whether these new compounds (and/or their metabolites) will or will not cross-react. In addition, commercially available products to 'flush' illicit substances from the body have been designed to achieve false negative test results. This may occur because the sensitivity threshold of the analytical procedure is set above the detection limit for the drug (a consideration often not recognised by clinicians or therapists). It may also be explained by sample adulteration.

6.2.2 Confirmatory / evidential tests

Confirmatory tests detect drugs and/or their metabolites with greater accuracy. They are normally undertaken only on samples that have generated a positive result during a screening test that sits at or above the relevant cut-off concentration. Cut-offs are designed to give sample donors every benefit of the doubt and to rule out passive exposure or use of OTCs. Although confirmatory tests are usually slower and more expensive than screening tests, they are essential in cases where findings may have significant consequences for individuals or their families (such as child protection cases) and in other circumstances such as drug-driving.

Confirmatory tests are almost always conducted in laboratories and use definitive methods that identify and quantify with precision the drug or metabolite in the sample.

6.3 Analytical techniques

Analytical techniques are usually grouped according to the degree of selectivity, which reflects the extent to which a method can identify a drug or metabolite without interference from other compounds. Common high, medium and low selectivity techniques are listed in Appendix D

Appendix A
Glossary of terms and abbreviations

Alveolar	Relating to the lungs.
Analogue	Drug similar in chemical structure to another compound.
Anhedonia	Reduced ability to feel emotion.
Antitussive	A medicine that suppresses cough (cough suppressant).
Anxiolytic	A medicine that reduces anxiety.
Arrhythmia	An abnormal heart rhythm.
Ataxia	A term for a group of disorders that affect coordination, balance and speech.
Bioavailability	A measurement of the amount of active drug (fraction of the dose) that reaches the general circulation.
Biopharmaceutics	The study of the physical and chemical properties of drug as related to the onset, duration and intensity of drug action.
Biotransformation	Process by which substances are changed from hydrophobic to hydrophilic molecules to facilitate elimination from the body.
Bradycardia	Lower than normal heart rate.
Cardiopulmonary arrest	When the heart stops pumping blood around the body and normal breathing stops.
Cardiotoxic	The occurrence of heart dysfunction as electric or muscle damage, resulting in heart toxicity caused by drugs used in cancer treatments.
Cataplexy	The sudden loss of muscular tone triggered by strong emotions such as laughter, anger and surprise.
Catecholaminergic	Related to the catecholamine neurotransmitters (made by nerve cells and which operate as signal transmitters) dopamine, adrenaline (epinephrine) and noradrenaline (norepinephrine).
CBD	Cannabidiol, a compound found in cannabis.
Circulatory system	A system of organs that includes the heart, blood vessels and blood, which is circulated throughout the body.
CNS	Central nervous system.

Cross-reactivity	In an analytical method whether other similar substances react in the same way as the drug of interest or causes results other than those expected.
Depot preparation	A prescription medicine that is delivered intravenously to deliver a drug over a prolonged period, providing sustained drug delivery.
Disintegration	Breakdown of a substance into small particles or into its constituent elements.
Dopamine	Important neurotransmitter in the brain that is associated with pleasurable reward and motivation.
Drug conjugate	A drug compound produced as a result of metabolism to render it more soluble and easily excreted by the kidneys.
DUID	Driving under the influence of drugs.
Elimination half-life	The time it takes the concentration of a drug in blood to fall by half (50%).
Emesis	Vomiting.
Endocarditis	An infection of the inner lining of the heart (the endocardium).
Endogenous	Originating from within the body.
Enzyme	Protein that acts as a biological catalyst to accelerate chemical reactions.
Epidermis	Outermost layer of skin on the body.
Excipient	An inactive substance formulated alongside the active ingredient of a medication.
Fluorescence	A form of luminescence that occurs when a substance that has absorbed light or other electromagnetic radiation emits light.
Freebase form	A drug in its free ‘base’ often used to describe the solid form of an illicit drug rather than its water-soluble salt form.
Half-life	The time it takes for the concentration of a drug in plasma to fall by half.

Homogenisation	The process by which a sample is broken into identical parts so that removing one portion does not disrupt and still accurately reflects the molecular composition of the remaining sample.
Hydrochloride salt	A salt made up of a hydrogen and chloride ion that can be linked to a drug making it water soluble.
Hydrophilic	Water soluble.
Hyperactivity	Constantly active above what might be considered normal.
Hypersomnia	A condition where an individual falls asleep repeatedly during the day.
Hyperthermia	An abnormally high temperature.
Hypnotic	A drug that brings about sleep or is sedating.
Iatrogenic	An unintended consequence of prescribing a drug.
Immunoassay test	A bioanalytical method in which quantitation of drug or metabolite depends on its reaction with a specific antibody.
Ingestion	Taking a substance into the body by swallowing or absorption.
Insufflation	To snort a drug into the nasal cavity.
Ion channels	Transmembrane proteins that help bring about the passive movement of drug ions across biological membranes such as the plasma membrane.
Isomer	Two or more different substances with the same molecular formula. An example is R(-)-MDMA, which tends to have hallucinogen-like effects, whereas S(+)-MDMA tends to have stimulant-like effects. Recreationally MDMA is a mixture of both isomers.
Ligand	A drug molecule that can bind to a receptor.
Lipophilic	Fat soluble.
Mass to charge (m/z)	A physical quantity relating the mass (quantity of matter) and the electric charge of a given particle, expressed as a ratio.
Matrix	The material that contains the drug of interest.

Membrane transporters	Proteins responsible for carrying a particular drug or drug class across the membrane.
Mydriasis	Dilated pupils.
Narcotic	An American term often used to describe any psychoactive compound with 'numbing' properties. It has recently become associated with opiates and opioids.
Package	A container for a single unit, several units or for a number of other sub-packages.
Parenteral	Drug introduced into the body other than by way of the intestines.
Phenotype	A set of observable characteristics or traits.
Polydrug	The use of more than one type of drug at one time or one after the other.
Psychoactive	Alters perception, mood, cognition and behaviour.
Receptor	A region of tissue, or a molecule in a cell membrane, that responds specifically to a particular neurotransmitter, hormone, antigen or drug/metabolite.
Seizure	An entire quantity of items seized. A seizure may consist of one or more items.
Sensitivity	The ability of an analytical method to detect a specific substance.
Sensitivity threshold	The minimum detectable amount of a drug that can be measured.
Serotonergic	A nerve ending that is stimulated by and releases the neurotransmitter serotonin, which promotes feelings of happiness.
Serum	The fluid component of blood that does not play a role in clotting.
Smoking blends	Dried herbal smoking mixes.
Somnolence	A state of drowsiness or 'nodding off'.

Steady state	The equilibrium reached when a drug concentration in the bloodstream becomes stable after a period of regular dosing and stays within defined therapeutic levels.
Sublingual	Administered under the tongue.
Supraphysiological	A larger than recommended dose or concentration of drug found at normal therapeutic levels.
Systemic circulation	The network of vessels supplying oxygenated blood to and returning deoxygenated blood from bodily tissues.
Tachycardia	A faster than normal heart rate.
Tachypnea	An abnormal 'rapidly beating' heart rate.
THC	Delta^{9}-tetrahydrocannabinol is the main psychoactive constituent of the cannabis plant.
Transmucosal	The route of entry of a drug through or across a mucous membrane.
Unit	An individual element of a seizure (such as a single tablet or a single package containing powder).
Vitreous humour	The transparent, colourless gel in the eye.
Xenobiotic	Foreign to the body (typically described a synthetic chemical).

Appendix B
Legislation

1961 Single Convention on Narcotic Drugs

This United Nations treaty established an international framework to restrict the production, possession, use and distribution of narcotic substances. The Convention also established the International Narcotics Control Board, an independent treaty body responsible for monitoring the availability and use of controlled substances.

Medicines Act 1968

This Act of Parliament of the United Kingdom governs the manufacture and supply of all medicines for human and veterinary use. The Act established three categories of medicine: prescription only medicines, pharmacy medicines and general sales list medicines.

1971 Convention on Psychotropic Substances

This United Nations treaty established a framework for the international control of hallucinogenic substances not covered by the 1961 Single Convention on Narcotic Drugs (see above). It entered into force in 1976. Substances are categorised under four Schedules that balance potential for abuse with therapeutic value. Use of Schedule I substances is prohibited except for limited medical or scientific research purposes, while Schedule IV substances are less strictly controlled and are available for medical purposes.

Misuse of Drugs Act 1971 (amended)

This Act of Parliament of the United Kingdom aligns with treaty commitments made under the 1961 Single Convention on Narcotic Drugs and 1971 Convention on Psychotropic Substances (see above). Substances are categorised within three classes (A, B and C) with differing penalties associated with possession, use and supply. A framework of subordinate legislation (eg the Misuse of Drugs Regulations 2001) has enabled the law to respond to changes in social mores and scientific understanding.

Prescription Only Medicines (Human Use) Order 1997 (SI 1997/1830)

This Order partially repealed the Medicines Act 1968 (see above) in matters relating to prescription-only medicines. This Order was largely revoked by later legislation (Human Medicines Regulations 2012), which is subordinate to the Medicines Act 1968.

Council Directive 2001/83/EC

This European Commission code consolidates EU provisions pertaining to the sale, production, labelling, classification, distribution and marketing of medicinal products for human use.

The Forensic Science Regulators' Statutory Code of Practice 2023

This code of practice is for forensic science activities related to the investigation of crime and the criminal justice system in England and Wales. It came into force on 2 October 2023. The requirement for a code of practice was established in the Forensic Science Regulator Act 2021.

Appendix C
Drugs and metabolites encountered in the criminal justice system

Chemical name (brand name)	Popular or other names	Section
Adrenaline	Epinephrine	1.13; 1.17
Alfentanil	Fentanyl	3.13.3
Alprazolam	Xanax, Xannies, Xan, Benzos, Bars, Footballs, French fries, Ladders, School bus, Xan, Z-Bars	3.5
Amphetamine, α-Methyl phenethylamine	Speed, Base, Billy, Whizz, Paste	3.2
Amyl nitrate	Ames, Amies, Amys, Pearls, Poppers	1.2; 3.11
Barbiturates	Barbs, Barbies, Bluebirds, Dolls, Downers, Goofballs, Sleepers	2.1.3; 6.1.2
Benzamides	Fake morphine, Pink	3.13.4
Brorphine	Synthetic opioid, Purple heroin	3.13.3
Buprenorphine	Big whites, Buse, Oranges, Small whites, Sobos, Stops, Strips, Sub, Subs	2.2.2; 3.13
1,4-Butanediol	1,4-BD	3.4.1
Butylone	Synthetic cathinone, Magic crystals	3.7
Cannabinoids	Weed, Grass, Pot, Hash, Bhang, Dope, Ganja, Resin	3.6
Cannabis	Cannabis, Dope, Grass, Green, Hash, Marijuana, Weed, Blow (also used to refer to cocaine), Ganja, Pot, Reefer, Resin, Skunk, Smoke, Broccoli, Bud, Haircut, Mary Jane, Jane	1.14; 3.6.1; 4.10
Carfentanyl	Fentanyl	3.12.3
Cathine	Norpseudoephedrine, NPE	3.7
Cathinones	Butylone, M1, Magic crystals, MDPV, Methylone, Monkey dust, Pyrovalerone	3.7
Chloradiazepoxide	Librium, Candy, Downers, Sleeping pills, Tranks	3.5.1
Cocaethylene	–	3.8

Chemical name (brand name)	Popular or other names	Section
Cocaine	Coke, Crack, Blow, Snow, Bump, Flake, Toot, Nose candy, Aunt Nora, Batman, Big C, Big rush, Candy, Charlie, Coca, Coke, Colombia, Pearl, Powder, Rail, Snow, Stardust, Stash, White girl, Dust, Sniff, Sugar	3.8
Codeine	Codis, Syrup, Codis500, Co-codamol, Sizzurp, Purple drank, Dirty sprite	3.12.1
Crack cocaine	Rocks, Crack, Dice, Garbage, Grit, Hail, Moon rocks, Nuggets, Sleet, Sugar block, Tornado, Trash, Trey, Yam, Yay, Captain Cody, Cody, Little C, Schoolboy	3.8
Cyclopropylfentanyl	Fentanyl	3.12.3
Desmethyldiazepam	–	3.1.5; 3.5.1
Dextromethorphan	DXM, Dexies, Dex, Dextro, Drix, Poor man's ecstasy, Red devils, Robo, Robotripping, Triple C, Tussin, X	3.10.1; 3.12.2
Diazepam	Valium, Vallies, Eggs, Jellies, Moggies	2.1.2; 2.1.5; 3.5.1
Dihydrocodeine	DFs, DFII8	3.13.2
Dimethyltryptamine	DMT, Dimitri, The rogan, The spirit molecule	3.10.4
Dopamine	Dope	1.13; 1.17; 2.2.1; 3.7
Ethyl alcohol	Alcohol, Booze, Bevvy, Ethanol	3.1; 4.3
Etizolam	Etties, Etizzy, Etty, Tizzy	2.1.5; 3.12

Chemical name (brand name)	Popular or other names	Section
Fentanyl	Lollipops, Fent, Apache, China girl, China white, Dance fever, Friend, Goodfella, Jackpot, Murder 8, Tango and Cash, TNT	3.13.3
Flunitrazepam	Rohypnol, Roofies, Benzo, Date rape drug, Forget-me pill, La Rocha, Lunch money, Mind eraser, Roofies	1.5; 3.5.1
Fluoxetine	Prozac, Wonder drug, Miracle drug, Happy pills, Bottled smiles	2.1.5
Flurazepam	Benzo, Trannie	3.5.1
Gabapentin	Gabas, Gabbies, Gabs, Johnnies	3.9
Gamma-butyrolactone	GBL, G, Gina, Liquid E, Liquid ecstasy, Liquid X	1.2; 3.4.1
Gamma-hydroxybutyrate	GHB, Liquid ecstasy, Easy lay, Juice, Geebs, Date rape drug, G, Geeb, Georgia home boy, Grievous bodily harm, Liquid E	1.2; 1.5; 3.4.1
Heroin, Diacetylmorphine	H, Smack, Brown, Dope, Junk, Black tar, Black pearl, Black stuff, Brown crystal, Brown rhine, Brown sugar, Brown tape, China white, Dragon, He, Horse, Mud, Scat, Skag, Skunk, Smack	2.1.5; 3.4; 3.13; 4.5; 4.10
Hydrocodone	Vics, Norco, Tabs, Vikes, Fluff, Scratch. When mixed with acetaminophen: Bananas, Dro, Hydros, Tabs, Vikes, V-itamin, Watson-387, 357s	3.13.2
Hydromorphone	D, Dillies, Footballs, Juice, Smack	–
Ketamine	K, KitKat, Special K, Blind squid, Cat valium, Green, Jet, K-Hold, Kay, Special K, Super acid, Vitamin K, Wonk	1.5; 1.18; 2.1.5; 3.4.2; 3.10.1
Khat	Abyssinian tea, African salad, Catha, Chat, Kat, Oat, Qat	3.7

Chemical name (brand name)	Popular or other names	Section
Isobutyl nitrite	Aroma of men, Bolt, Bullet, Climax, Hardware, Locker room, Poppers, Quicksilver, Rush, Snappers, Thrust	3.11
Lofentanyl	Fentanyl	3.13.3
Lorazepam	Ativan, Candy, Downers, Sleeping pills, Nerve pills	3.5.1
Lysergic acid diethylamide	LSD, Flash, Liquid acid, Smilies, Acid, Blotter, Dots, Sugar cubes, Yellow sunshine	3.10.2
Mephedrone	4-MMC, Bounce, Bubble, Charge, Drone, M-CAT, M-Smack, MC, Meow-meow, Meph, Miow, White magic	1.2; 3.7.1
Methadone	Mixture, Linctus, Green, Juice, Physeptone, Dollies, Dolls	3.13.3; 4.10
Methamphetamine	Chalk, Christina, Cookies, Crank, Cream, Crystal, Crystal meth, Glass, Ice, Meth, No doze, No stop, Pookie, Rocket fuel, Scooby snacks, Speed, Trash, Tweek, Wash, White cross	1.2; 3.2.2
3,4-Methylendioxymeth amphetamine	MDMA, Ecstasy, Molly, Beans, Pills, Love drug, E, X, Scooby snacks, Adam, Candy, Clarity, Dancing shoes, Disco biscuits, E-bomb, Egg rolls, Eve, Happy pills, Lover's speed, Peace, Rolls, Smartees, The vowel, Vitamin E, Vitamin X	1.7; 3.2.3
3,4-Methylenedioxyypyrovalerone	MDPV, Bath salts, Plant food, Research chemical, Synthetic cathinone	3.7
Methylphenidate	Ritalin: Kibbles and bits, R-ball, The smart drug, Vitamin R Concerta®: JIF, MPH, Pineapple, Skippy	1.16; 3.2.4
Midazolam	Benzo, Pills, Chill pills	3.5.1

Chemical name (brand name)	Popular or other names	Section
Morphine	Morph, God's drug, M, Miss Emma, Monkey, Morpho, White stuff	3.13.1
Nandrolone	Steroid, Arnolds, Gym candy, Juice, Muscle builders, Pumpers, Roids, Stackers, Weight gainers	1.1; 3.3
Nitrous oxide (Entonox)	Laughing gas, Balloons, Hippie crack, Buzz bomb, Whippets, Canisters, Chargers, Hippy crack, Loons, Nangs, N20, Whippets, Whipped	3.4.3
Ocfentanyl	Fentanyl	3.13.3
Oxazepam	Benzo, Nerve pills, Chill pills, Downers	3.5.1
Oxycodone	Oxy, Oxycet, Oxy, Hillbilly heroin, Percs, Berries, Ms, OC, Oxycotton, Ozone, Blue dynamite (when mixed with acetaminophen)	3.4; 3.13.2
Oxymorphone	Biscuits, Blue heaven, Mrs O, O bomb, Octagons, Stop signs	–
Phencyclidine (PCP)	Angel dust, Angel, Dust, Purple rain, Rocket fuel, Stardust, Water, Yellow fever, Zombie	3.10.1
Pregabalin	Prees, Pre-gabas, Pre-gabbies, Pre-gabs, Pregga	3.9
Pseudoephedrine	Chalk, Crank, Meth, Speed	3.13.2
Psilocybin	Magic mushrooms, Shrooms, Mushies, Liberties, Agaric, Liberty caps, Magics, Philosopher's stones, Alice, Boomers, Pizza toppings, Tweezes, Gooms	3.10.3
Remifentanil	Fentanyl	3.13.3
Sodium oxybate	Gamma-hydroxybutyric acid (GHB), Xyrem®	3.4.1
Sufentanil	Fentanyl	3.13.3

Chemical name (brand name)	Popular or other names	Section
Synthetic cannabinoid receptor agonists (SCRAs)	Amsterdam gold, Annihilation, Black mamba, Blue cheese, Bombay blue extreme, Clockwork orange, Devil's weed, Ecsess, Exodus damnation, K2, Krypton, Mary Joy, Tai high, Hawaiian haze, X, Fake weed, Genie, Moon rocks, Spice, Zohai	3.6.2; 3.12
Synthetic cathinones	Bath salts, Plant food, M-cat, Bounce, Bliss, Cloud nine, Flakka, Lunar wave, Scarface, Vanilla sky, White lightning	3.7
Temazepam	Benzos, Tems, Temazzies, Eggs, Green eggs, Jellies, Norries, Rugby balls	3.5.1
Testosterone	Arnolds, Juice, Pumpers, Roids, Stackers, Weight gainers	1.1; 3.3
Tramadol	Ultram, Chill pills, Trammies, Ultras	1.18; 3.13.3
Triazolam	Benzos, Candy, Downers, Sleeping pills, Tranks, Halcion	3.5.1
Zalepon	Z-drug, Downers, Tranks, Rope, Forget-me-pill, Sleep easy	–
Zolpidem	Z-drug, Zombie pills, A-minus	3.5.2
Zopiclone	Z-drug, Zimmers, Zimmies, Zim-zim, Zimmos, Zees	3.5.2

Appendix D
Descriptions of analytical techniques

High selectivity techniques

Infrared (IR) spectroscopy

IR spectroscopy is a highly discriminatory method. It measures the amount of IR radiation absorbed or emitted by a sample as a function of wavelength. The IR spectra of a pure molecular compound (such as a drug or a metabolite) provides a distinctive fingerprint that can be easily differentiated from the IR absorption pattern of other compounds, including those with the same chemical formula but a different arrangement of atoms in the molecule (isomers). IR spectroscopy can offer both qualitative and quantitative results for virtually all compounds.
Fourier transform infrared spectrometry (FTIR) uses a mathematical process to translate raw data into the actual spectrum and can be used on site to characterise chemical substances.

Mass spectrometry (MS)

MS is the most discriminatory drug testing technique and is the current gold standard in forensic drug analysis. It offers even greater specificity when combined with chromatographic separation, and together these two techniques can identify virtually any substance. Mass spectrometers separate and ionise compounds, then identify relevant ions based on their mass (m) and their charge (z), which are then used to calculate the mass-to-charge ratio (m/z) of a compound.

Tandem mass spectrometry (liquid chromatography (LC)-MS/MS or gas chromatography (GC)-MS/MS) improves specificity even further through ion fragmentation. Two compounds with the same elemental composition, but different structures, may be distinguished by unique fragment ions produced using tandem mass spectrometry.

MS can detect drugs at extremely low concentrations with high specificity. MS results are usually interfaced with computers to allow comparison against drug databases and enhance drug identification processes. In many toxicology laboratories MS has replaced immunoassay screening due to the risks of false positive and false negatives and to the emergence of NPS (Section 3.12), which immunoassay tests struggle to detect and identify.

High resolution mass spectrometry (HRMS) features both high resolution and high mass accuracy and is a powerful tool that is helpful in the analysis and quantitation of large numbers of compounds, the determination of elemental composition and the identification of unknowns.

Resolving power differs between the various mass analysers referred to as 'high resolution'. Time-of-flight-based analysers generally have a resolving power of 20 – 40k, while Orbitrap analysers can reach 500k. The higher the resolving power, the more confidence can be assigned to accurate compound identification and quantitation. As a result, Orbitrap-based data are often used for creating confident mass assignments, and especially with metabolites having similar mass assignments. Quadrupole time-of-flight MS can offer particularly high-resolution qualitative results.

High resolution accurate mass (HRAM) systems characteristically detect very small differences in the masses of compounds that instruments with poorer resolution miss.

Nuclear magnetic resonance (NMR)

NMR spectroscopy is used to obtain structural information about molecules by analysing magnetic signals emitted by a drug or metabolite in the presence of a strong external magnetic field. All compounds have their own characteristic magnetic properties and can therefore be detected with the help of complex instruments. Advantages of NMR include sample reusability, high resolution and accurate structure determination. NMR is used in forensic science to determine the structure of bodily fluids for drug analysis, for post-mortem changes, for xenobiotic examination and to identify counterfeit products.

Raman spectroscopy

Raman spectroscopy works by shining a laser on a sample to identify patterns of scattered light after the light has interacted with a particular compound. Handheld Raman spectrometers have been optimised to detect drugs of abuse with a simple 'point and shoot' action. These devices may also search databases in real time to clearly indicate the substance(s) detected. Raman spectroscopy can be used to determine molecules with the same chemical formula but with different arrangements of molecules. This is important as many novel psychoactive substances are isomers, derivatives and analogues of many classic drugs of abuse. However, Raman spectrometers may have difficulty in identifying plant-based substances that exhibit strong fluorescence, such as heroin. This can be addressed by sample preparation, but analysis is not quantitative.

X-ray diffractometry (XRD)

XRD can be used to determine the cutting agents (adulterants) used in illegal drugs and analyse various types of trace evidence. XRD is useful in analysing suspected counterfeit pharmaceutical products. It can be performed on the crystalline form of a drug and requires no sample preparation. However, since many evidentiary materials recovered may not be powdered or form a flat solid disc, routine use may be limited[107].

Medium selectivity techniques

Capillary zone electrophoresis

Capillary zone electrophoresis identifies drugs and metabolites according to their charge/size ratio. Thus, it can be applied only to ionic or ionizable drugs with an appropriate control of the buffer pH. A particular application is in chiral separations where the efficacy, toxicity and pharmacokinetic properties of drug racemate are required (eg dextro vs levo amphetamine).

- Racemate is a drug that is composed of equal amounts of dextrorotatory and levorotatory forms of the same compound and is not optically active. Adderall is an unequal mixture of both amphetamine enantiomers.
- Chiral separation is a procedure used to separate the two isomers of a racemic compound. Various methodologies are used for chiral separation. For liquid chromatography a specialist chromatography column can be employed.

Chromatography

Chromatography separates and identifies the components of the tested substance, enabling drugs, their metabolites and contaminants in a mixture to be detected. Separation is achieved based on interactions between two ‘phases’: a non-moving stationary phase (typically in a column) and a moving mobile phase (or eluent). The eluent is commonly inert gas (GC) or a liquid (LC). Different component substances ‘peak’ at different points, enabling identification. A confirmation test often encompasses the use of GC-MS or LC-MS/MS to definitively identify the drug or drug metabolite and correlate that data to the positive results found in an initial screening. Even highly similar compounds such as amphetamine-type drugs can be separated from one another and identified.

107 Cappelletti, P, Graziano, S F and Bish, D L. (2023). X-ray diffractometry in forensic science. In: Mercurio, M, Langella, A, Di Maggio *et al.* (Eds.). *Mineralogical analysis applied to forensics* (pp 37-59). Springer. https://doi.org/10.1007/978-3-031-08834-6_2 (accessed 14 February 2024)

Ion mobility spectroscopy (IMS)

During IMS, ions are held stationary in a flowing buffer gas by an electric field gradient profile while the application of radio frequency potentials results in trapping in the radial dimension. It is the technique of choice for trace analysis of illicit drugs or explosives at security points. In addition, many prisons use IMS to screen mail and seized items (such as herbal mixtures, paper and food) for the presence of drugs, in particular SCRAs and other controlled substances. When deployed for the rapid detection of drug-infused papers, supported by up-to-date substance libraries, IMS is effective in identifying emerging threats as they arise.

Microcrystalline tests

Microcrystalline tests produce unique microcrystals when a given drug or metabolite is combined with a specific reagent. Several commonly abused substances can be identified, including cocaine, heroin, methadone, GHB, ketamine and methamphetamine. Microcrystalline tests require small quantities of reagent and simple instrumentation and are thus relatively cheap and quick to perform. Tests are highly characteristic and well suited to pure drug samples. They are, however, insufficiently specific for confirmatory tests, and samples are destroyed during the testing process.

Thin-layer chromatography (TLC)

TLC involves placing a sample onto a planar stationary phase then a liquid mobile phase is used to separate the compounds in the sample by simple capillary action. Components of the sample travel at differing rates depending on the component's size and affinity for the mobile phase. The result is a plate of spots (separated components of the mixture) that have moved various distances on the stationary phase. TLC can be used as a presumptive test.

TLC can detect numerous drug groups including barbiturates, BZDs, amphetamines, synthetic cannabinoids and most opiates, but not individual compounds. Novel psychoactive substances are particularly difficult to identify. TLC is rarely able to separate highly complex mixtures and has poor sensitivity. To increase specificity TLC must be used in conjunction with another technique such as Raman spectroscopy or colorimetric (colour-based) testing.

Macroscopic examination

This involves visual inspection and recording of the structure, taste, smell and touch of a substance, usually of a plant.

Microscopic examination

This may be used as a diagnostic technique to identify medicinal plants, crude drugs or small fragments, and detection of adulterants, substituents and authentic plants. This is achieved under a microscope to establish digital images of different magnifications. Numerous crime-scene micro-traces, including drugs, can be visually and chemically analysed with a scanning electron microscopy (SEM), which provides the most sensitive resolution for trace examination.

Low selectivity techniques

Colour (spot) tests (colorimetric tests) / presumptive testing

Various analytical colour techniques are available for screening tests. These are usually qualitative, semi-quantitative and/or non-specific and are typically used to detect or measure drugs in seized items or in bodily fluids and tissues. It is important to note that colour tests are not confirmatory tests but rather indicative of the substance present. Two examples are given below:

- The Mandelin reagent is composed of a mixture of ammonium metavanadate and concentrated sulfuric acid. Its primary use is for the detection of ketamine (deep red colour), para-methamphetamine (deep brown colour) and alkaloid drugs.
- The Marquis reagent is composed of a mixture of formaldehyde and concentrated sulfuric acid, which is dripped onto the substance being tested. For instance, heroin produces a purple colour and amphetamine/methamphetamine orange.

Colour tests are based on chemical reactions between analytes and indicators. The indicator chemically reacts with the analyte, generating a reaction that creates a certain colour stain depending on the analyte tested and which is compared against reference charts. Colour tests exist for most drugs of abuse including cocaine, various pharmaceutical opioids, amphetamines, LSD, cathinones, heroin and fentanyl. They have limits of detection in the microgram (µg) range depending on the analyte and the test utilised. Whilst colour tests can detect the presence (or non-presence) of a particular drug or class they are not always able to identify a specific substance.

Ultraviolet/visible spectroscopy (UV/Vis)

UV/Vis molecular absorption is used routinely to analyse narcotics. The presence of a drug can be confirmed from their absorption maxima (ie λmax) or by comparing the UV/visible spectra of these drugs with spectra of authentic samples. This is commonly undertaken within immunoassays and point of care tests.

Appendix E
Acknowledgements

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