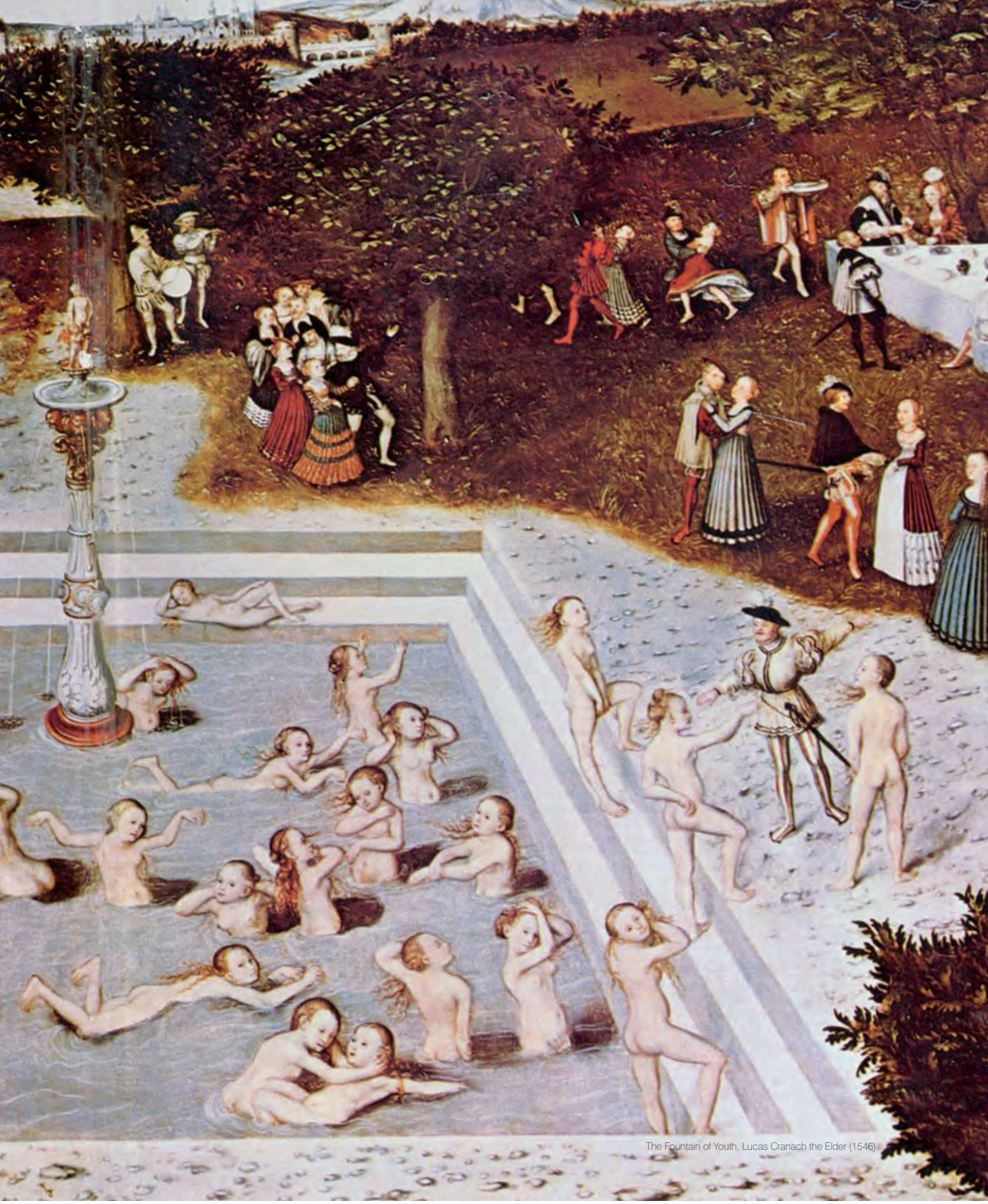

The Fountain of Youth, Lucas Cranach the Elder (1546)

Human Enhancement Drugs

The Emerging Challenges to Public Health

NorthWest Public Health Observatory

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Disclaimer

This report is intended to raise the profile of the emerging challenge to health from the self-directed use of drugs to enhance the human body, and to inform the development of approaches to understanding and tackling the problem. While every effort has been made to ensure that the information in this report is up-to-date and as accurate as possible at the time of publication, readers are advised to check the most current information that is available.

Most of the drugs discussed in this report are currently obtained from an illicit market, i.e. outside of government regulation. As such, without forensic analysis it is impossible to determine the composition and authenticity of such products. The inclusion of a drug product in this report, whether by generic or brand name, as well as example dosages are used for illustrative purposes only and are based on information published in the literature and in online communities. They are included in order to help inform healthcare professionals, researchers, commissioners and policy makers of the relevant issues discussed therein and should not be viewed or taken as a criticism or endorsement of any kind. The information provided in this report should not be used during any medical emergency, for the diagnosis, or treatment of any medical condition, or in relation to the self-directed use of such drugs. The case studies presented in this report serve to illustrate elements of this form of drug use. These were developed from sources that include academic research, online communities and media reports. They are not intended to refer to any particular person.

To the fullest extent of the law, neither the North West Public Health Observatory nor the authors assume any liability for any injury and/or damage to persons or property arising out of or related to any use of the material contained in this report.

April 2012

Foreword

It is more than 100 years since the British Medical Association raised concerns over unregulated enhancement 'potions', and exposed this profitable industry's tricks of the trade in their report Secret Remedies. Although much has changed since then, the drive for human enhancement has not diminished. Nowadays, it takes only seconds to find websites offering products purporting to enhance our strength and intelligence, help us shed excess weight and even delay the effects of ageing. There are many people who, unhappy with their bodies, their abilities or with the natural ageing process, are prime customers for such products, and there are plenty of manufacturers and retailers ready to exploit this demand.

The fact that some of these compounds sold can have genuine actions on the body's physiology including, in some instances, serious health threatening side effects, means that we need to review regularly whether we have adequate measures in place to protect people's health. As this report identifies, such drugs can cause ill health and sometimes even death. They may never have been tested for the purposes for which they are advertised; they may be products which are no longer used for their original purpose, due to unpleasant or harmful side effects, but which are still being marketed for their enhancement properties; and they may be manufactured without any of the quality assurance required for legitimate pharmaceuticals.

The increasing ease with which pharmaceuticals can be manufactured and distributed means this is likely to be a growing problem. It challenges the very concept of health and the expectations we place on health services. What should the limits of health service responsibilities be for an increasingly ageing population, many of whom wish to keep as much of the beauty and virility of youth for as long as possible? If a patient's doctor does not prescribe what they want, will the patient then access enhancement drugs online – only to return to the doctor for treatment of any subsequent adverse effects? Which enhancement drugs can safely be sold and advertised on the internet, and how could any form of regulation of such products work in a global market?

One of the core reasons the Public Health Observatories were established was to scan horizons for future health issues. Human enhancement drugs and how we live in a world where they are increasingly accessible is one such issue. I am delighted that this report has been written to shine a spotlight on some uncomfortable facts, and to encourage us all to face up to questions as fundamental as what health really means in a century where better strength, intelligence and looks can appear to be only a tablet away.

Professor Lindsey M. Davies CBE, FFPH, FRCP
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Executive summary

Public health faces a new kind of drug problem with the growing prevalence of so–called 'enhancement drugs' that have the potential to improve human attributes and abilities. The widespread availability of such drugs has generated a new and growing audience of users. People are seeking out enhancement drugs in a quest to improve their bodies and minds—to look younger and more beautiful, to be stronger, happier and more intelligent.[1–107] These types of drugs share a few similarities with recreational or addictive drugs—such as heroin, cocaine, ecstasy and 'legal highs'[108–135]—but also attract people who do not necessarily perceive themselves as 'drug users' and are vulnerable to cultural pressures to optimise their bodies.

Manufacturers and retailers around the world are tapping into the demand for such drugs by harnessing innovations in science and medicine, as well as improvements in transport and communication networks.[136–151] Significantly, in the case of illicit markets, retailers are able to circumvent national laws and regulation with creative and persuasive marketing strategies via the Internet. Often their customers are duped or remain unaware of the considerable harms associated with usage of these drugs, a situation that presents a threat to public health and throws up challenges for healthcare systems around the world.

The human condition

The age–old desire to be beautiful, fitter or more intelligent has marked human endeavour since the beginning of civilisation. Magic, religion, diet, exercise, education and surgery have all played a part, some woven together to form intricate rituals and lifestyles. Drugs too have been at the heart of these attempts—some of our ancestors sipped drinkable gold *aurum potabile* to make themselves young again. Others feasted on animal testicles to boost their strength and sexual prowess. Introspective Arab poets, meanwhile, chewed khat to stay awake for long periods, meditate on the soul and translate their experiences into poetry.[152–190]

By the 1880s there was huge growth in the commercial sale of medicines in the United Kingdom and other industrialised nations. This, along with the increasing development of potent synthetic drugs, provoked concerns amongst professional groups over the lack of market regulation.[190–210] Interestingly, this period saw the same use of dubious advertising techniques and circumvention of laws by retailers, as well as gaps in public scrutiny, that still concern healthcare professionals today (see §2 & §3). Most modern enhancement drugs are obtained from a thriving illicit market, which exploits people's insecurities about their looks, in an environment where the media and popular culture reinforce idealised body types on a daily basis (see Box I).

Box I: Drugs examined in this report are used to enhance:

Structure and function of muscle, such as anabolic steroids to get a 'six pack' or 'bulk up', or growth hormone to 'get toned and trim' (see §5)

Weight loss, such as rimonabant or sibutramine to suppress the appetite, or DNP to 'burn fat' (see §6)

Cosmetic appearance of the skin and hair, such as mercury–containing creams for 'healthy, lighter, more radiant skin', or melanotan II for that 'holiday tan' (see §7)

Sexual behaviour and function, such as sildenafil to 'get a better, stronger erection' and bremelanotide to 'get in the mood' (see §8)

Cognitive function, such as methylphenidate and modafinil to 'help study' (see §9)

Mood and social behaviours, such as paroxetine to be 'better than well' (see §10)[i]

All of these drugs can have potent effects.[ii] Some are licensed medicines that have been shown to be efficacious and/or effective in treating disease. Yet whether licensed, banned or untested, there is limited scientific evidence to support many of the claims made about their benefits when used by healthy people.

There is also the issue of over medicalisation, a phenomenon that blurs the distinction between normal life events and disease. Ageing, being overweight, sexual performance, hair loss, shyness, tiredness and being 'too' short are some of the events that have been redefined as medical issues and 'treated' with drugs (see §3.2).[2–4] This is causing more people to seek out such treatments, a growing number of whom appear to obtain them from the illicit market.

In the US, the fallout from over-medicalisation has seen the soaring diagnosis of childhood and adult attention deficit hyperactivity disorder (ADHD), where stimulants such as methylphenidate or amphetamine–based medicines are often prescribed. It is likely that the availability and awareness of such drugs (dubbed 'smart' drugs for their claimed ability to enhance concentration or memory) have fuelled usage in the healthy population, specifically among university students and school children (see §9.3).[18,74,218–222]

i While we know probably the least amount about these types of drugs, the potential market for the next generation of highly active mood enhancing drugs is considerable and will further blur our current definitions and limited understanding of recreational drug users and enhancement drug users.

ii Similar to other drugs and substances, placebo and nocebo effects are likely to play a substantial role in mediating some of the effects (including harms) related to these drugs.[211–217]

Benefits or harms?

All drugs whether licit or illicit have the potential to cause harm to individuals (see §4). To minimise risk to an acceptable level in countries such as the UK, medicines undergo a process of careful regulation including rigorous assessment and constant monitoring.[223–247] Failure in any of these aspects can cause serious harm—for example, the drug thalidomide, used to treat morning sickness in pregnancy, is reported to have not been sufficiently tested and led to serious birth defects.[248–276] While analysis of a broad range of drugs sold on the illicit market has found that some are genuine and licensed medicines, there are growing numbers of banned, untested, and/or adulterated drugs being detected.[e.g. 277–555] These include banned appetite suppressants such as rimonabant and sibutramine being taken to lose weight,[556–572] and untested drugs such as the synthetic hormone melanotan II being used to tan the skin.[573–587]

It is illegal to sell a medicine that is not licensed for use in the UK,[223–231] but many retailers ignore this or attempt to conceal the true nature of their products by advertising them as food or herbal supplements, cosmetics, 'research chemicals' and 'not for human consumption'.[i] In the case of food and herbal supplements—a market that has seen explosive growth—unscrupulous manufacturers and retailers exploit the common belief that 'natural' products are safer and healthier alternatives to synthetic drugs[588–590] and hide potent active substances in them (see §4.3).[e.g. 292–457] In some cases these products are sought out by consumers who have read about their rumoured effects on the Internet in discussion forums or reviews. Between 2005 and 2009 the Medicines and Healthcare products Regulatory Agency (MHRA) tested 138 unlicensed herbal products sold as treatments for erectile dysfunction.[ii] It found that 65% of the products contained active substances such as sildenafil, or untested analogues (see Box II), and lignocaine, a local anaesthetic. While the strength varied widely, in some cases there was enough active substance to cause an overdose.[296]

Similarly, products sold as muscle builders, fat burners, diet pills, sunless self–tanning sprays and cosmetics have all been found to contain potent active substances that are often banned or untested.[292–304,483] However, establishing the extent of the harms caused by these products is difficult, partly because most consumers are not aware that they are taking a drug. They may also be too embarrassed to admit that they have used such products, or simply do not know how to report any harms. In addition, consumers have no way of checking the quality, safety and efficacy of products sold on the illicit market. Instead they

i These two latter strategies are also commonly used in the 'legal high' market in order to circumvent regulation under medicine, food or consumer protection law.[123–135]

ii Overall, in the past six years, the MHRA has found more than 280 examples of 'all natural' products that contain undeclared potent synthetic active substances, although not all of these would have been intended for the 'enhancement' market.[296]

rely on anecdotes from online communities and other social contacts, wishful thinking and the misleading claims made by manufacturers and retailers (see §4.2).

Box II: Untested analogues found in 'food' or 'herbal' products

In the past 10 years, more than 40 untested substances similar to sildenafil, tadalafil and vardenafil (used to treat erectile dysfunction) have been found hidden in food and herbal supplements sold for 'sexual enhancement'. About half of these substances are frequently detected in products on the European market.[392] Most of these are not 'new' but by–products of the legitimate pharmaceutical drug–development process. It has been suggested that one of the reasons why these analogues have been used in illicit products is because they have different chemical signatures to 'known' drugs such as sildenafil. This makes them harder to detect by the authorities, which typically screen products for these 'known' drugs.

Most of these untested drugs have not been studied in humans so we do not know what effects and harms they can cause. However, a few appear to be capable of causing serious harms. In one case, a new designer drug, nitroso–prodenafil—a hybrid of a sildenafil–type substance with one that appears to be capable of releasing nitric oxide (a potent vasodilator)—was detected. Although it has not been studied in detail, this could be a potentially deadly combination as it might cause a sudden drop in blood pressure which could lead to a heart attack.[438]

The effects of these drugs often go undetected until reports of unusual and/or serious harms expose the problem. These vary from individual case reports and case series to outbreaks that involve tens or hundreds of people. Few systematic surveys of the level of use and harms caused by these drugs have been conducted, and studies in the UK are particularly limited. Despite this, it is recognised that substantial numbers of people across the globe have already been harmed in the last decade.

- More than 160 people in Japan suffered liver damage (with some estimates suggesting the figure was more than 800 injured) after using weight loss supplements containing hidden quantities of the untested drug n–nitroso–fenfluramine. Four of these subsequently died. In the UK at least four people suffered liver damage, one of whom subsequently died (see §4.3).[439–457]
- Globally, thousands of people have been harmed by the use of skin–lightening creams containing mercury compounds, hydroquinone and corticosteroids. This includes hundreds of cases of mercury poisoning. In the past two years, there have been five cases in the UK (see §7.3).[591–608]

- More than 220 people in Singapore and Hong Kong were harmed after using herbal remedies sold as sexual enhancement products and counterfeit erectile dysfunction drugs, which were adulterated with glibenclamide, a potent drug used to treat diabetes. Some suffered serious brain damage and 13 subsequently died (see §4.3).[548–555]

These reports are likely to be the tip of the iceberg—many more users will suffer a similar fate, particularly as it is difficult to stop the sale and distribution of harmful products once they have been identified on the market.[609–611] There are also hidden dangers when drugs are not properly labelled or manufacturers fail to provide guidance on how to use them safely (see §4.4). Where drugs need to be injected, poor manufacturing can lead to contaminated products that cause infections and other harm. There is also the risk that sharing injecting equipment can spread blood–borne viruses such as HIV (see §4.7). Equally, women of child–bearing age may be exposed to drugs that can harm the embryo or foetus (see §4.5), while routine screening of blood donors may fail to reveal that these drugs have been used. In both cases, if consumers have used a food, herbal or cosmetic product containing hidden active substances, they may be unaware to what they have been exposed (see §4.3). Some drugs may also cause dependence or impair the ability to drive.[612–649]

Access, availability and regulation

The biggest source of these drugs is the illicit market, which is vast, complex and global in nature.[277–555,650–653] During the past decade, this market has flourished as a result of low–cost manufacturing capacity in countries like China and India, the globalisation of free trade and the development of communication and transport networks, including the Internet, and cargo and postal services. While some drugs are sold or given away by friends, family and acquaintances, in many cases they are bought from the Internet and 'bricks and mortar' shops or dealers (see §3.4).

In 2010 alone, more than 8.5 million imported doses of counterfeit and unlicensed sildenafil (worth around £13 million) were seized. This included six million from freight deliveries at Heathrow Airport,[i] while 2.1 million doses were from orders placed online by consumers.[478] Supporting these findings, a recent large Internet survey of men from the UK, Germany and Italy, found that just over 3% of around 12,000 men have used drugs such as sildenafil in the last six months without a prescription, with around half of them buying the drugs online.[654] An older survey in 2003 found that 1% of 2000 people had ever bought medicines online without a prescription, often because it is the easiest way to get them and it costs less than a prescription (see §3.5).[655] While this included any type of prescription only medicine, monitoring data from this period supplied by the predecessor to the MHRA found that eight of the top ten medicines marketed over the Internet in the UK

i Some of these may have been destined for other markets as the UK is used as a staging post in the illicit trade in medicines.[651]

were also drugs that are commonly used for enhancement purposes.[655] Finally, a straw poll of 423 General Practitioners in the UK found that 25% had treated patients for suspected drug reactions after using medicines bought online. While it is unknown how many of these patients had bought them from a regulated pharmacy, comments by the GPs—e.g. 'Allergic response to fake Viagra'—suggested that at least some of the cases were linked to drugs bought from the illicit market.[656,657]

The decentralised and transnational nature of this illicit market makes it particularly difficult to control.[658] This is mainly because the legal regulation of the Internet is largely based on national law, whereas manufacturers, suppliers, retailers, website hosting and payment processing services[i] may all be based in different countries.[659] Effective control of these entities and services is limited by differences in national laws, policies and socio–cultural values (see §3.4).[660–662]

There are also broader issues associated with the illicit trade of enhancement drugs. The potential for huge profits has led to the involvement of organised crime.[650–653,661] Serious problems with the security of online 'pharmacies' can compromise the privacy of consumers. As a result of this and other scams, consumers may become victims of fraud, including identity theft.[296,663–671] In addition, the waste from the manufacture, use and disposal of these drugs can harm the environment, including contaminating drinking water supplies (see §3).[672–677]

The benefits or harms that these drugs bring could also intensify inequalities within society.[96–99,106,107] Access to advice on side effects, appropriate doses, quality assured products and health monitoring will only be within the reach of the wealthy through private medical consultations. This will allow them to maximise benefits while minimising the risk. By contrast, the poor will be left vulnerable to the conflicting and often misleading information on the Internet, as well as fraudsters selling untested, banned or adulterated drugs. One concern is that poorer people may expose themselves to harm after being coerced or manipulated into believing that enhancement drugs are their best option to 'fit in' or 'succeed' (see §3). With the growing interest in elite sport and the Olympics, it will also be important to examine if a 'win at all cost' mentality would encourage this form of drug use in those who try to emulate sports stars, particularly young people.

Pushing the boundaries

Enhancement drugs are forcing society to redefine health, well being and the boundaries of healthcare. They allow us to rethink how we view our bodies, how they work, how we can change them and what it means to be human. The value our society and youth–oriented culture place on 'better bodies'—in an increasingly medicalised environment—has persuaded many people that their bodies are

i Weaknesses in payment processing have been identified as a potential target to disrupt this trade.[659]

deficient in some way (see §3.2).[2–4] Our physical limitations, controlled by the genetics we inherit, the effects of our environment, and the natural ageing process, are no longer considered immutable. These types of drugs seemingly offer us a way to escape our fate.[96–99,106,107,678–682]

On a practical level, the Internet allows people to learn about drugs, as well as share experiences, advice and support, while a globalised world makes the drugs cheaper to manufacture, advertise and distribute. All of these factors make the trade particularly difficult to control, and also complicate the task of detecting harms to consumers. So far the response to this problem has been reactive—limited to enforcement activity to disrupt the trade in these drugs, and to investigations into cases of harms linked to their usage. Understanding this problem in the future, and developing policies to protect and promote public health, will require coordinated action at local, national, European and global levels (see §11).

This report is intended to raise the profile of this emerging challenge to health and to inform the development of approaches to understanding and tackling the problem. The report has been completed by the North West Public Health Observatory (PHO) as part of its 'health futures' horizon–scanning function[i]. There are a range of agencies and government departments that have a role in, and responsibility for protecting the public against drug harms. As the functions of the PHOs transfer to Public Health England (PHE), the evidence presented in this report will provide a basis to inform the public health workforce of this emerging threat.[683]

Key points

- This report raises the profile of an emerging threat to health. Growing numbers of people around the globe are using drugs to try to obtain a better body, empower themselves and increase their well being. The sociocultural value placed on these goals can powerfully shape our behaviour.
- Weak legal and regulatory systems in emerging economies, globalised communication and transport networks, corruption and organised crime help fuel the spread of these drugs. Increasingly, the Internet and express cargo/postal services play a central role by making it easy to learn about these drugs and buy them on demand. Such factors also make the trade particularly difficult to control.
- Many misleading and false claims are made about the 'enhancements' these drugs bring, and there is often no, or limited, scientific evidence to support them.

i Public health observatories (PHOs) were originally established in England in 2000 to provide knowledge, information and surveillance to support public health systems in improving health and reducing inequalities. In April 2013 PHOs will be absorbed into Public Health England, a new executive agency of the UK Department of Health.

- In some cases, substantial harm has already occurred, partly because some of these drugs are untested, banned and/or adulterated. Unknown to most consumers, some manufacturers add active substances to 'all natural' food, herbal and cosmetic products. In most cases these substances are not listed on the packaging/labelling. Overall, the ability to detect and prevent harms arising from usage is limited with current surveillance and reporting systems.

- This form of drug use may increase inequalities in health. The wealthy will have access to quality drugs, information and monitoring, which will allow them to maximise benefits while minimising harm. The poor meanwhile will be at the mercy of conflicting information on the Internet and fraudulent retailers.

- 'Next generation' drugs are already emerging on the illicit market. Research into advanced therapies, such as tissue–engineered products, somatic cell therapies and gene therapies, is advancing with some treatments already available. It is likely that these types of products will soon be sold on the illicit market.

- The new executive agency of the Department of Health, Public Health England, will need to work with partners at a national, European and international level to consider and co–ordinate action relating to the monitoring and surveillance, supply reduction, demand and harm reduction of this globalised drug problem.

1. Scope of the report

This report reviews the available information about the use of drugs by the general public to enhance the body (including the mind). It examines: 1. some of the historical context; 2. the reasons behind the increasing availability and use in the past few decades; 3. the general harms to public health and difficulties in detecting and preventing harms with current systems; 4. their effects on the body and the harms that they may cause; and 5. the research that is needed so that society can develop an effective and efficient response to protect and promote public health. While the focus of the report is the current situation in the United Kingdom, relevant global dimensions are also discussed.

This report has been produced by the North West Public Health Observatory on behalf of the Public Health Observatories in England. It is intended to raise the profile of this emerging challenge to health in the UK and inform the development of approaches to understanding and tackling it at a local and national level.

Box 1.1: Public Health Observatories (PHOs)

The public health observatories were originally established in England in 2000 to provide knowledge, information and surveillance to support the public health system in improving health and reducing inequalities, with each of the nine PHOs taking a lead nationally on specific topics. The North West PHO leads on drugs intelligence (as well as alcohol, violence and dental health) on behalf of the PHOs and this report is the product of ongoing monitoring and surveillance work on this issue. Public Health England (PHE) is due to be established in April 2013 as an executive agency of the Department of Health (DH) and will take on responsibility for leading on the design, delivery and maintenance of systems to protect the population against existing and future threats to health.[683]

There are a range of agencies and government departments that have a role in and responsibility for protecting the public against drug harms. The evidence presented in this report provides a basis for informing the public health workforce of this emerging threat and supporting work between public health and other stakeholders at a national level when considering and coordinating appropriate action. Here, we have reviewed the literature (including grey literature such as press releases from regulatory agencies), Internet sites (such as online communities and shops) and media reports to identify examples of drugs that are currently being used. These were then grouped according to the main reason for use, resulting in six categories:

- to enhance the structure and function of muscle (§5);
- to enhance weight loss (§6);
- to enhance the cosmetic appearance of the skin and hair (§7);
- to enhance sexual behaviour and function (§8);
- to enhance cognitive function (§9); and
- to enhance mood and social behaviours (§10).

Each of these forms a section of the report. They begin with a brief background, followed by a case study (or two) that highlights some of the issues related to the use of the drugs. These case studies were developed from sources that include academic research, online communities and media reports. They are not intended to refer to any particular person. The section then examines some of the types of drugs commonly being used, who uses them and why, and the harms that they can cause.

It is important to recognise that some of the drugs are used because they have multiple effects on the body. For example, while melanotan II is used mainly to get a cosmetic skin tan, it is also used as an aphrodisiac and as an appetite suppressant in order to help lose weight.[587,684] Anabolic steroids are used to increase the size and strength of muscle, but also to lower body fat, and to increase aggression that is used during training.[685–688]

The report concludes with a discussion on the research that is needed to enable an effective and efficient response to this problem. A detailed discussion of the ethical and environmental issues are outside the scope of this report. However we recognise their importance, particularly in developing an effective policy response, and refer where appropriate to existing reviews on these issues.

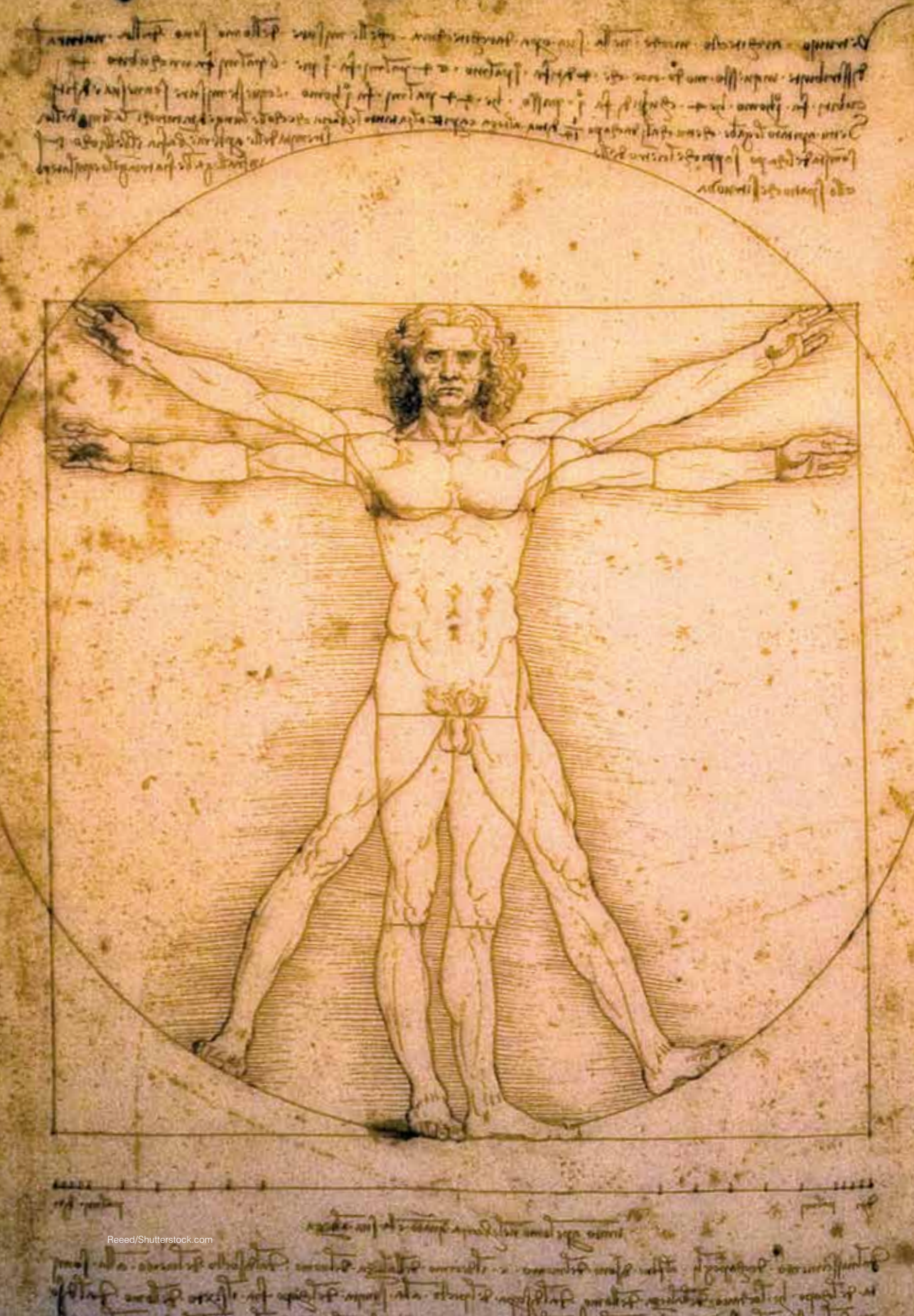
1.1 What do we mean by enhancement?

One common way of defining an enhancement is to view it as something that improves an attribute or ability 'beyond what is necessary to sustain or restore good health'.[689] However, the line between where medical treatment ends and enhancement begins is often blurred.[4,690] Many people would typically view the drugs discussed in this report as providing a functional enhancement to the user. That is they enhance some attribute, such as making them look younger, or ability, such as making them stronger or smarter. However, a closer look reveals that some people use the drugs for both enhancement and as a medical treatment.[690] For example, while some HIV–positive individuals use anabolic steroids to build up their bodies to prevent the deterioration of their condition or fight off HIV wasting

syndrome, they also use the drugs to enhance their physique and improve their physical appearance (and hence their body image satisfaction)[i] (§5.6).[691–697] Similarly the untested synthetic hormone melanotan II is used to get a cosmetic skin tan as well as to protect against UV–related skin damage (§7.2).[587] Some consumers may also be self–treating a problem (such as erectile dysfunction caused by performance anxiety or condom use)[698,699] or undiagnosed disease.[654]

Others may use these drugs because medicine currently offers no effective treatment for their condition, and, in desperation, they turn to unproven treatments including untested drugs (such as the use of melanotan II to self–treat rosacea).[587,684] The report takes this broad range of uses into account.

i However, this too may be related to the physical changes associated with HIV infection or medicines used to treat the disease.



2. The historical context

This section examines some of the historical context that is relevant to the current use of drugs by the public to obtain a better body. For practical purposes we will selectively focus on the 1880s onwards as this was a period that saw huge growth in the commercial sale of medicines, the development of potent drugs, and parallel concerns from professional groups over the lack of regulation of this market. Drawing on case studies of two drugs that were sold as weight loss products—Marmola and DNP (2,4–dinitrophenol)—we highlight some of problems faced by public health at this time. Indeed one of the main issues was that there was little, if any, regulation. You could buy these untested drugs off the shelves of many general stores and pharmacies, as well as by mail order. We also examine some of the harms that these drugs caused and the advertising techniques manufacturers and retailers used to sell them. There are remarkable similarities to the current trade in these types of drugs.

Medicines have been sold commercially for hundreds of years, and been used for millennia.[190–192] For various reasons, including the increasing regulation of opium and a reduction in stamp duty on medicines, there was a large increase in the number and types of products being sold during the late 1880s.[108,109] One big group of these were 'patent medicines' and 'secret remedies'. A telltale sign of many of these products was that their ingredients were a closely guarded secret. This was often because the ingredients used were ineffective and cheap (yet usually sold at a relatively high price), or, in some cases, harmful. They included treatments for epilepsy, diabetes, consumption (tuberculosis), fevers and 'kidney troubles'. Some of these remedies included cures for baldness, 'male weakness products' (their modern equivalents being treatments for sexual dysfunction, erectile dysfunction, penis enlargers and premature ejaculation), 'nerve tonics' ('pep pills', anti–depressants, anxiolytics, 'smart drugs'), 'reducing remedies' (weight loss drugs) and rejuvenating 'elixirs of life'.[193–207]

There was growing concern from professional groups, among others, about the sale of these products.[108,199,200] This was partly due to the harms they could cause (usually by delaying consultation with a doctor), but also because these products encouraged people to treat themselves rather than pay to see a doctor. The British Medical Association (BMA) raised their concerns in the early 1900s largely through the British Medical Journal (BMJ) and the publication of two books—*Secret Remedies* and *More Secret Remedies*—which exposed the tricks of the trade and provided details of the actual ingredients of the drugs.[194,195] (Figure 1) While the books were apparently popular, even with the general public (Secret Remedies sold 62,000 copies in less than two years),[201] it is not clear what impact these activities had in bringing an end to this trade. In fact the Parliamentary Select Committee set up to investigate the sale and use of these types of

Figure 1. Secret remedies What they cost and what they contain, 1909.

medicines[199] and remedies criticised the BMA because it accepted adverts for some of the products in the BMJ. This was a controversial relationship with advertisers that continued for many years. It even provoked criticisms from the BMA's sister organisations in the United States and Canada, which had also previously accepted such adverts. While the Select Committee had serious concerns over parts of the trade, the report was published on the same day that hostilities broke out among the Central Powers in Europe, signalling the start of First World War. The report was shelved.[200]

Similar concerns about patent medicines and secret remedies were voiced in other countries including the US.[203–207] However, there were many vested interests. The larger pharmaceutical companies were often intimately involved in this trade, either selling their own products or supplying the ingredients to smaller companies. The ingredients of the 'reducing remedy' Marmola, sold in the US and the UK, were sourced from such companies.[204]

The drugs were widely advertised to the public, particularly through the growing number of newspapers and magazines (Box 2.1).[199,208,209] In turn these publications relied heavily on the advertising revenue that was generated by the products.[199] The drugs were available on the shelves of general stores and chemists as well as by mail order. The advertising strategies were often similar to those used today: as well as playing on the insecurities of consumers, the effectiveness, quality and safety of the products were a cornerstone of any campaign (Figure 2). These were usually supported by testimonials from 'customers', which in some cases included the rich and famous. For products ordered through the mail, discretion was often guaranteed; some sellers even offered express delivery.[194,195,203,204] The growth in these types of drugs was largely unrestricted as there was little regulation. Typically, so long as the products contained no scheduled 'poisons' (substances such as opium, which were regarded dangerous under the law), then there was little that the authorities could do to prevent their sale.[108,198,199,204]

Figure 2. 'She was too fat'. Advert for Marmola which contained animal thyroid gland extract, 1933.

Box 2.1: 'Shed YEARS as well as FAT! So easy to reduce the 'Marmola' way'.

'When reducing, it is of paramount importance to use a scientific treatment which you know is really safe and sure. You will then not only lose fat to your heart's content, but feel fitter and look years younger … 'Marmola' has been used for 25 years—millions of boxes of it … Do Not carry that burden of excess fat when so many of the folks around you have found 'Marmola' the easiest way of all to reduce. Know once again the joy of a beautiful, slender figure and make Summer days happy days.'
Advert for Marmola in the Daily Mirror, 1937.[700]

Between 1908 and 1940 Marmola was advertised more than 200 times in the Daily Mirror.[i]

Some manufacturers, particularly those selling 'reducing remedies', tried as part of their sales pitch to closely associate their products with advances being made in medicine, physiology and pharmacology. In some cases this extended to using active substances that were emerging as therapeutic agents, such as animal thyroid gland extract in Marmola and DNP and in other 'reducing remedies'. However, most of these products were relatively innocuous and, aside from any placebo and nocebo effect they may have had, they were worthless. Some contained laxatives or alcohol presumably to disguise this.[194,195,203,204]

Despite the concerns raised, it was rare that any formal indication was given on how many people used these early types of 'enhancement drugs' in the UK.[199] In countries where there were greater efforts to control them, such as the US, some information was available from mailing lists of people who had previously bought these products—known as 'sucker lists'—as well as sales figures, and the number of products on the market. These give a general indication of how popular such products may have been. Overall, however, we know little about how many manufacturers and retailers made significant profits from their sale.[203,204]

In 1915 authorities in the US destroyed one sucker list that contained the details of 500,000 people. It had been seized as part of a court action against the fraudulent promotion of a 'lost manhood' or 'male weakness' product (its modern equivalents being treatments for sexual dysfunction, erectile dysfunction, penis enlargers and premature ejaculation). It was advertised as the 'surest–acting combination for the cure of deficient manhood and vigor failure ever assembled'[701] that would ensure 'once more the gusto, the joyful satisfaction, the pulse and the throb of physical pleasure,

i The ukpressonline.co.uk database of the Daily Mirror archive was searched on 12 March 2012 using the term 'marmola' between 01/01/1907 and 31/12/2010 which resulted in 239 hits. Marmola appears to have been first advertised in the Daily Mirror on Wednesday 2 September 1908. The last time it appears is on Friday 15 March 1940.

the keen sense of man sensation'.[702] In the late 1920s sales of Marmola reached $600,000 a year[703]—more than $7.5 million in today's money. Similarly, about a year after the first clinical reports on the use of DNP,[704] the Stanford Clinics in the San Francisco Bay Area of California had dispensed enough of the drug to treat an estimated 4,500 patients.[705] Meanwhile, more than 20 wholesale drug companies had begun selling products containing the drug causing great concern among some doctors (Box 2.2).[705,706] Despite the limited information it appears that there was a viable market for these kinds of products.

Box 2.2: The rapid spread of DNP in the US during the early–to–mid 1930s

'A little over a year ago, our first clinical report on dinitrophenol appeared in the Journal of the American Medical Association. The interest in and enthusiasm for this product were so great that its widespread use has become a matter of some concern in public health. The total amount of the drug being used is astonishing.' [705]

'As is usual with any drug used for cosmetic purposes, commercial interests have promptly entered the field of exploitation of dinitrophenol. There is not the slightest doubt that vast numbers of people are taking this preparation both with and without the advice of their physicians. At least two of the physicians who broadcast health information to the public through the radio and through the press have mentioned the use of this drug and have apparently failed to warn the public adequately concerning its dangers.' [706]

'Many of these remedies could be procured without prescription, and with no further directions than to take "one capsule three times daily after meals."' [707]

2.1 Marmola

As early as 1908 Marmola's advertising played on consumers' insecurities. Is 'fatness … a social offence?'[708] asked one campaign, while another noted that 'nobody loves a fat girl'.[709] Testimonials were also a popular advertising practice. One advert used the silent movie star, Constance Talmadge, who reasoned that 'the demand for slender figures is so universal that movie stars must have them. Not only beauty but good health and vitality argue against excess fat'.[710] According to the manufacturers, Marmola could provide the answer 'without hard exercise or starvation diet … the excess fat … simply slip[s] away revealing the trim and slender figure underneath …' 'Every over–fat person should try it. It's quite harmless and will take off as much as a pound of fat a day.'[708] While it contained seaweed and laxatives commonly found in many types of weight loss products at that time, the manufacturers also exploited scientific advances by incorporating dried animal thyroid tissue.[708]

This had been shown some years earlier to increase the metabolic rate,[711–721] causing weight loss in some cases. As well as mimicking the weight loss seen with hyperthyroidism (where the thyroid gland is over active), Marmola was linked to other harms such as palpitations and anxiety.[722] These types of harms were also reported in women after using similar products during the late 1960s which contained animal thyroid tissue and more recently synthetic thyroid hormone.[723–725]

2.2 *Dinitrophenol*

Marmola was not the only 'reducing remedy' to achieve 'fame'. In the 1930s products that contained DNP enjoyed brief success in the US as a similar type of remedy.[704–707,726–762] In the UK and some other European countries, products containing a structurally and pharmacologically related but more potent drug, dinitro-o-cresol, were also sold.[763–772] However, the extent of their use is unknown. The marketing strategy used for DNP products was similar to Marmola: 'here, at last, is a reducing remedy that will bring you a figure men admire and women envy without danger to your health or change in your regular mode of living'.[761] 'No dieting… No self-denial… No strenuous exercises… You can have the slender figure of Youth'.[749] Testimonies again played a supporting role: 'we feel much better and it has shown absolutely no ill effects', 'literally burning the fat away'. 'Sounds too good to be true? Yet it is true'[761] (Figure 3). The drug was also hidden in some weight loss products so consumers had no idea they were taking it.[760] DNP could cause weight loss, although it was not long before harms were reported (such as skin rashes, numbness and tingling in the legs and arms, loss of taste and a dangerous drop in the number of white blood cells that fight off infections). There were also at least 10 deaths, the first published just three months after the initial report of its clinical trial in humans.[i] In some cases this was because consumers had inadvertently overdosed on the drug because they were not satisfied with their weight loss. The drug was also found to be unpredictable: the toxic dose could be close to the therapeutic dose. Almost two years to the date from the first use of DNP, reports began to surface of cataracts linked to its use. Eventually more than 160 cases were identified.[704–707,726–773,ii]

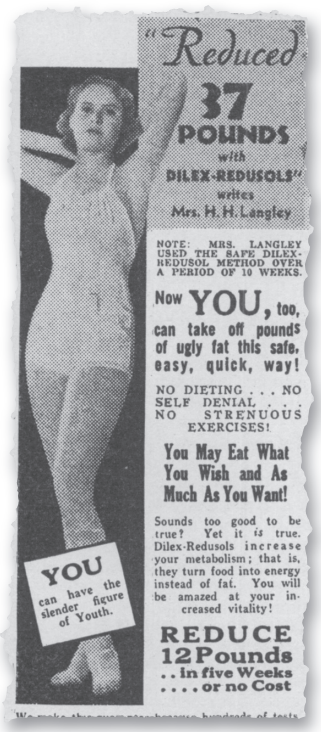


Figure 3. Advert for Dilux-Redusols which contained the metabolic poison dinitrophenol, 1936.

i 'The second death was a girl who bought the drug on her own responsibility from a druggist.'[705]

ii 'One hundred Los Angeles women were known to be blind or partly so with cataracts last week as result of taking dinitrophenol to reduce. That drug, whose weight–reducing properties were first cautiously utilized by San Francisco doctors (TIME, July 31, 1933), is illegally and secretly sold in California…'[753]

Over time the widespread advertising and sale of these types of products was prohibited as part of broader moves to tighten the regulation of medicines. Some products, such as DNP and dinitro-o-cresol,[740,741,754,771,i] were removed more rapidly from the market than others. Despite this there have been occasional reports of DNP being used for weight loss over the years, usually by 'enterprising' doctors using it in their weight loss clinics (in Belgium during the 1960s and in the United States during the 1980s for example) or by avant-garde bodybuilders.[760,774–777] Over the past 10 years or so the drug appears to have re–emerged.[778–796] In part this is driven by information available on the Internet about how to use it as a 'fat burner' and for weight loss.[797] It is also sold online (Box 2.3; Table 6).[798,799]

Box 2.3: The dangers of dinitrophenol

DNP is a metabolic poison. It stimulates metabolism by stopping the powerhouses of cells, the mitochondria, from making ATP (adenosine triphosphate).[801–803] This substance provides the energy needed for many cellular reactions. Instead DNP causes heat to be released from the mitochondria. This toxic effect is what causes weight loss. However DNP is highly unpredictable and the therapeutic dose can be close to the toxic dose.[804–806] These dangers are highlighted even further by the case of super–strength products sold on the illicit market, although consumers will be unaware of this.[782]

In 2003 the Food Standards Agency (FSA) undertook an investigation after information from the Finnish authorities that a bodybuilder had become seriously ill after consuming 'fat–burner' capsules containing DNP. These were sold through a website believed to be based in the UK. While the site listed the strength of the capsules as 200 mg, analysis by the Finnish authorities found about 380 mg per capsule—i.e. 90% stronger than advertised—although according to the FSA report there appeared to be significant variation in the amount the capsules contained. Based on the available toxicity data for DNP taking 3–4 capsules at once could have proved fatal.[782] Perhaps surprisingly this type of dose (and higher) is reported by users on Internet discussion forums. No studies have examined the composition or strength of DNP products currently on the market although this case from almost 10 years ago demonstrates the potential for serious harm with products that are of variable strength (particularly those that are over strength).

i The State of California in the United Sates made DNP a prescription only medicine on August 20 1934. Similarly in 1936 the UK had controlled both DNP and dinitro–o–cresol as scheduled poisons requiring a doctor's prescription.[740,741,754,771]

While there have been few studies that have looked at who and how many people use the drug, one Internet study found that 13% of 500 anabolic steroid users had used it.[800] Reflecting this, the use of the drug is a common topic on some fitness and bodybuilding discussion forums. However, its use is clearly not limited to just this group. The re-emergence of DNP has also seen a resurgence in poisonings.[778–796] Since 2002 there have been at least 18 cases, including 10 deaths (three of which were from the UK).[i] In 72% of cases the reason for using the drug was to lose weight or burn fat (just less than half of these were related to bodybuilders use of the drug); 22% were suicides; and in 6% the reason was unclear. Most involved young adults aged 17–32. In 10 cases the drug was bought from the Internet (n=9) or mail order (n=1), while in the remaining eight cases the source of the drug was not identified.

2.3 *The emergence of legal and regulatory systems*

Figure 4. Elixir Sulfanilamide. In the late 1930s the untested diethylene glycol used in Elixir Sulfanilamide killed 122 people, including 34 children, 1937.[ii]

It took many years for effective legal and regulatory systems for medicines to be put in place. Drug disasters between the late 1930s and early 1960s caused by the sale of untested drugs—such as Elixir Sulfanilamide (an antibiotic which used the toxic excipient diethylene glycol[ii], Figure 4) in the US, Stalinon (used to treat boils but contained a neurotoxic substance) in France, and particularly thalidomide (used to treat morning sickness in pregnancy but caused serious birth defects, Figure 5) in the UK and other European countries—were often the catalysts for reform.[248–266,807–815] These systems allowed authorities to prevent harm by restricting what drugs could be sold and to whom. However, not surprisingly, even after this some products remained on sale, albeit often illegally. Yet the public could also access a large number of drugs from the regulated, licit, market. Many of the 5.6 million and 4.8 million prescriptions for amphetamine issued in the UK in 1959 and 1968 respectively

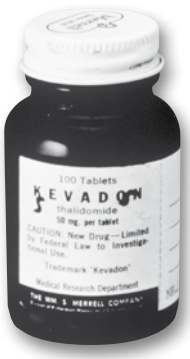


Figure 5. Thalidomide tablets. Based on anecdotes of its ability to reduce morning sickness, the drug was heavily promoted to pregnant women. The drug was untested and caused serious birth defects. Worldwide more than 10,000 foetuses were affected.

i Two of these deaths were apparently due to intentional overdoses.

ii The diethylene glycol used in Elixir Sulfanilamide killed 122 people, including 34 children.[248–250] This disaster led the US to introduce tougher laws designed to try to prevent such tragedies from happening again. More than 70 years later the toxin continues to injure and kill in countries with weak legal and regulatory systems. Sometimes present in over-the-counter medicines, such as pain–relief or cough medicines, it has seriously injured hundreds of people and killed more than 600 (almost half of these victims were children).[267–269] Most recently, 84 children in Nigeria died after they were given a 'teething formula' called 'My Pikin' that contained paracetamol dissolved in the toxin.[269]

were used as 'pep pills' and for weight loss. These appetite suppressants are the contemporary equivalents to 'nerve tonics' and 'reducing remedies' administered the secret remedy age.[816] Despite concerns raised at the time, it took a while for this widespread prescribing to stop, but not before much harm was done.[816–819] Similar prescribing patterns, particularly in relation to drugs that affect appetite and mood, have been repeated on many occasions since then.[75,820–829]

2.4 *Key issues*

- Drugs have been sold commercially and used to obtain a better body for many years.
- Getting hold of the drugs was easy. They could be bought 'off–the–shelf' in general stores and chemists or by mail order.
- Scientific research that led to the development of potent drugs allowed some manufacturers and other entrepreneurs to include these substances in products. At this time there were no laws to prevent untested drugs from being sold. In some cases this led to serious harms.
- There are remarkable similarities between the past and present day in the way that these drugs were advertised and sold, as well as the harms they caused.
- Products sold as 'all natural' weight loss supplements are still found with animal thyroid tissue, which is the same active substance that was used in Marmola. In the past decade DNP has re–emerged through its sale on the Internet, causing at least 18 serious poisonings, including 10 deaths.

Dmitry Kalinovsky/Shutterstock.com

3. The current context

Across the globe growing numbers of people are turning to potent drugs in the hope of getting a better body, empowering themselves, and increasing their well–being. Most of these drugs are obtained from a thriving illicit market. There has also been an explosive growth in products sold as 'all natural' food or herbal supplements aimed at the 'enhancement' market. Increasing numbers of these contain potent active substances hidden inside, including the appetite suppressants fenfluramine and sibutramine which have been banned, or sildenafil (used for erectile dysfunction) and untested analogues of these drugs[294–457] (Figures 6, 7, 8). Most consumers are unaware of this and the harms they are exposing themselves to. Overall in the last decade alone these pursuits have caused substantial harm. More than 160 people have suffered liver damage (with some estimating that the figure was 800 injured) and four died after using herbal weight loss products deliberately adulterated with a potent untested drug n–nitroso–fenfluramine, an analogue of the banned drug fenfluramine (§4.3).[439–457,i] Hundreds of people have been poisoned by skin–lightening creams containing mercury (§7.3).[591–608] While more than 220 people have been harmed, including 13 deaths, by 'sexual enhancement' herbal products and erectile dysfunction drugs adulterated with the potent drug glibenclamide which is used to treat diabetes (§4.3).[548–555] Analysis of the range of products currently being sold, as well as past experience of using untested and/or adulterated drugs on a wide scale, suggests that many more will suffer a similar fate.[248–661]

However, there are also broader issues related to this drug use. Realising the huge profits and with a limited chance of getting caught and prosecuted, organised crime has become involved in the trade.[650–653,661] This, along with scams from others involved in this trade, and poor security found on many online shops, will lead to consumers being the victims of fraud, or even having their personal information stolen or exposed.[296,663–671] The waste from the manufacture, use and disposal of these drugs can

Figure 6. 'Slimming orange juice' that contained the banned appetite suppressant sibutramine. Seized by the Danish Medicines Agency.

i Fenfluramine was banned in 1997 because it was linked to serious cardiovascular harms.[820–828] However, it remained on the market in China until 2009.[829] This may be one of the reasons why the drug was still available on the Internet and found hidden in 'food' and 'herbal' weight loss products.

lead to environmental harm, including contaminating drinking water supplies.[672–677] The benefits or harms that the drugs may bring could also increase inequalities in society.[96–99,106,107] Those who are wealthy will be able to access quality assured drugs, health information and monitoring through private medical consultations. This would allow them to maximise benefits while minimising harm. Wealthy people already have longer lives and better health. Yet in other situations (poorer) people may be pressured into using these drugs believing that they are their best option in order to 'stay in the game' or 'succeed'.

Figure 7. 'Fashion slimming milkshake' that contained the banned appetite suppressant sibutramine. Seized by the Danish Medicines Agency.

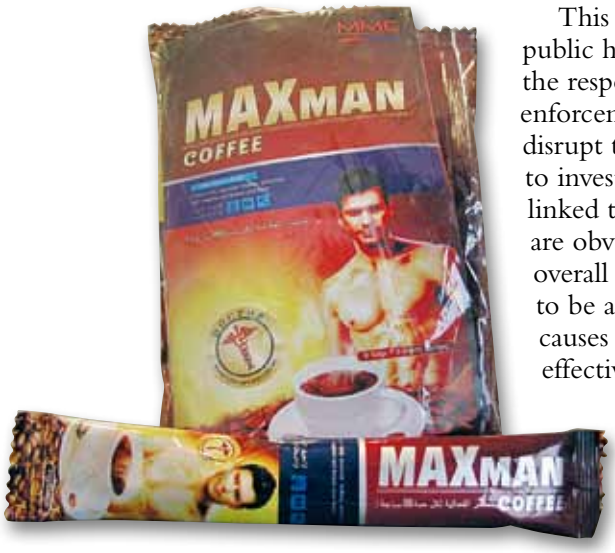


Figure 8. 'MaxMan coffee' that contained sildenafil - the active substance in Viagra®. Seized by the Danish Medicines Agency.

This globalised problem requires public health scrutiny. So far most of the response has been limited to enforcement activity, designed to disrupt the trade in these drugs, and to investigations into cases of harms linked to their use (Box 3.1). These are obviously critical parts to any overall response, but there also needs to be a better understanding of the causes and consequences so that effective and efficient policies[i] can be developed that protect public health.

i Which include policies designed to reduce the demand for these drugs.

Box 3.1: Just how big a problem are illegal skin lightening creams?

Over the past decade or so Trading Standards and the MHRA have made many seizures of illegal skin lightening creams containing hydroquinone, highly potent corticosteroids and mercury (§7.3). Some of the suppliers have also been prosecuted.[277–291] Despite this, the products remain widely available in 'bricks and mortar' shops and online. They are also regularly intercepted at EU borders.[i] This suggests that there is still demand for these products. While there have been case reports of harms linked to these drugs from patients in UK for almost 30 years, so far there have been no studies that have looked at how many people use these potent drugs, why they use them, how they are used and the public health implications. In the past two years, five cases of mercury poisoning linked to creams bought in shops or online have been reported in the UK.[602,606,607] These cases are likely to be the tip of a much bigger problem.

3.1 Overview

There is limited information about the spread of these types of 'enhancing' drugs. This reflects the fact that, for many, their use by the public has started relatively recently and so has escaped the attention of healthcare professionals, researchers, commissioners and policy makers. For example, sildenafil (used to treat erectile dysfunction, §8) and sibutramine (an appetite suppressant used for weight loss that is now banned, §6) have only been available as licensed medicines since the late 1990s,[560,830–838] while the illicit sale of melanotan II only came to the attention of regulatory authorities in 2007 although smaller numbers of people were using it for longer periods of time undetected (§7.2).[539,540,583,584,587,684,839] Similarly the issue of food and herbal products that contain hidden potent active substances has only come to the attention of regulatory authorities and researchers in the past 10 years or so.[292–457,528–532] In other cases, such as the use of skin lightening drugs (§7.3), they have largely been ignored (Box 3.1). There are a few drugs that are the exceptions to this rule. Some, such as anabolic steroids (§5), have been subject to more detailed investigation. Their use is relatively widespread, with about 52,000 people (mainly men) aged 16–59 in England and Wales using in the past year, while around 0.3% of boys and 0.1% of girls aged 11–15 have used the drugs.[840,841] Yet even in this case there are large gaps in our understanding, particularly on why and how people use them, and the harms they cause (Box 3.2).

i See: http://ec.europa.eu/consumers/safety/rapex/index_en.htm.

Box 3.2: Discovering that sildenafil, 'melanotan' & anabolic steroids were being used as 'enhancement' drugs

Sildenafil: A little over six months after sildenafil was licensed as a medicine in the UK, researchers found that some nightclubbers were using it as a 'recreational drug'. However, the drug was available both on private prescription and the illicit market before this. Studies then began to look at how the drug was being sold and used, although until recently these have largely been limited to small groups of users rather than general population surveys.[654,830–838]

'Melanotan' I/II: Reports by drug workers (particularly at needle and syringe programmes), observation of online discussion forums, enforcement activity by the authorities and case reports of harms played a key role in highlighting the use of 'melanotan' –usually claimed to be melanotan II–as well as generating widespread media interest.[539,540,583,584,587,684,839]

Anabolic steroids: Large numbers of studies have been published on anabolic steroid use since the 1960s, particularly in the US. This reflects the fact that they been used for much longer periods and have therefore come to the attention of researchers, healthcare professionals and public health agencies, as well as policy makers. It may also be due to political and societal concern over their use. In this latter case, this may stem from their use as doping agents in sport and the often cited, yet poorly defined, concerns over their links with aggression and violence. As a result a much richer set of data exists. However, even here there can be large gaps in our understanding, particularly on why and how people use them. We know little about the extensive range of drugs that users draw on both for their synergistic and additional effects to anabolic steroids, as well as those they use as treatments for harms linked to the drugs. Such limitations also extend to the changing patterns of drug use over the last 50 years or so. Despite the emergence of biosynthetic forms of growth hormone around 30 years ago (which has dramatically increased the supply of the drug on the illicit market) little is known about the spread and use of this drug, aside from in sub–groups of anabolic steroid users.[842–878]

Often much of what we know about the early stages of the diffusion[879] of these drugs relies on drawing together limited information from a range of sources, as part of the public health surveillance system. These include: anecdotes from users (including online discussion forums) and other people with a special knowledge of the drug or those using it; enforcement action that includes seizures of drugs; media reports (such as investigative journalism); reports of users attending health services (such as users attending needle and syringe

programmes in the case of melanotan II)[684]; and publications such as case reports describing drug use or harms. Together these sources play a valuable role in identifying new drugs, emerging trends and harms before formal epidemiological studies can be done. Sometimes, particularly given the multinational nature of many online discussion forums, these sources also demonstrate that the drug is being used in other countries, although the level of use, type of consumer, motivations for use, context and patterns of use may differ substantially.

Initially the drug is often limited to a relatively small group of individuals that share a common, albeit often broad, characteristic. These include groups such as bodybuilders (using growth hormone), students (using 'smart drugs'), nightclubbers and men who have sex with men (using sildenafil), among many others. Within these groups are a smaller number of 'innovators' and 'early adopters' who start using the drugs and can play an important role in helping them spread to the rest of the group, other groups, and eventually, the broader population. Drug use by 'innovators' and 'early adopters' may suggest drugs and patterns of drug use that may be adopted by broader, independent groups of people over time.[879] For example GHB (gamma hydroxybutyrate) which is a psychoactive drug, was first used to try to increase growth hormone secretion in bodybuilders (as a 'muscle builder' and 'fat stripper'), as well as an anti–ageing/life–extension 'treatment', before it became more widespread on the party scene as a recreational drug.[880–897] There may also be gender and ethnic differences in the use of some drugs. Anabolic steroids are predominately used by males, while, historically at least, the use of weight loss drugs has largely been skewed towards females. Skin lightening creams are mostly used by those with dark skin types; conversely, the skin tanning drug melanotan II is used more by those with lighter skin.

3.2 *Some of the causes*

Many factors drive the use of enhancement drugs.[1–107,136–151,663–671] Together they form a complex web, making it difficult to unravel the exact role they play and their importance. Some of those factors stem from changes in our sociocultural, economic, scientific, technological, legal and political environment, alongside those that play a role at an individual level (such as genetic or biological factors). In some cases there may be an evolutionary component (such as our maladaptive response to the obesogenic environment that predisposes us to obesity, §6);[898–906] or in part a response to our natural environment (such having light or dark skin colour, §7[i]). Some of these factors make us more open to the idea of enhancing ourselves, while others make it easier to learn about the drugs that are available to do this. In other cases, some of these factors help us form a positive opinion about enhancement drugs, and, ultimately, influence us to buy and (re)use them (Box 3.3).

i Which also has an evolutionary component.

Box 3.3: Some of the factors helping drive the use of 'enhancement' drugs

- Growing medical, scientific, popular, and political attention to the body, body dissatisfaction and enhancement. In part this is driven by the growing number of normal life events and problems that are medicalised. Sociocultural and demographic changes including gender roles, ageing populations, obesity, racism, discrimination (e.g. in the case of skin lightening, §7.3),[4] consumerism, focus on 'personal responsibility' and increasing disposable income.[4]
- Scientific and technological innovations, including the development of new drugs that have 'dual–use' potential as medicines and for 'enhancement'; globalisation that allows new ways of learning about these drugs (such as online); easier ways to buy them (such as online).[4]

To some extent society has always placed great value on 'better bodies' and how this can improve our well being.[1–107] These beliefs have become much more culturally dominant in the past few decades. How our bodies look and function are increasingly scrutinised by society, including our friends, family and peers. In our youth–orientated culture, bodies (or their parts) that are flabby, limp, wrinkled, weak, slow, tired, or old are seen as undesirable, abnormal or unhealthy. They may be ridiculed, stigmatised, and marginalised. Having the 'right body' allows you to fit in; it is highly prized and rewarded by society. These idealised body types are reinforced on a daily basis by the social networks we inhabit as well as by the media which regularly provides detailed 'do–it–yourself' instructions on how to achieve such a body. As a result these ideals have increasingly become linked to happiness, desirability and status (Box 3.4).

Box 3.4: Overweight, obesity & ageing: How should these problems be tackled?

This is not to say that some of these problems do not pose great challenges to society. Left unchecked the growing epidemic of overweight and obese people will cause serious health and economic harm, as will demographic shifts towards an ageing population that is linked to physical and mental functional decline. Society as a whole will have to decide which policy measures—at the individual, social or environmental level (or a mix)—should be used to tackle these problems.[96,97,99,106,107]

In some cases they can also be amplified by over-medicalisation.[2–4] The distinction between normal life events or problems and disease is increasingly blurred.[4,690] Ageing, being overweight, sexual performance and dysfunction, hair loss, shyness, tiredness, and being 'too' short—which can all fundamentally change how the body looks or functions—are just some of the things that have been redefined as medical problems, and 'treated' with drugs. The pharmaceutical industry, often in the hope of selling their next 'blockbuster drug' as the 'cure', has taken the lead in this process.[2–4] These types of drugs have become a multi–billion dollar industry, with companies increasingly focussed on extending these profitable markets. A cycle has evolved where new drugs are developed, requiring new diseases to be defined, or current definitions expanded to include more—and sometime almost all—of the population.[4,79–83] These include the highly controversial estimates of more than 40% of women affected by female sexual dysfunction or that 70% of men aged 40+ suffer from erectile dysfunction. The fact that for many this is linked to a temporary life event or normal problem is replaced by a single statistic that suggests that many of us are dysfunctional and in need of treatment.[4,79–83]

Some of these companies also use 'disease–awareness campaigns' to raise the profile of the problem and that it can be 'easily treated' with a drug.[4] However, policymakers, healthcare professionals, patient advocacy/support groups, the media and the general public have also supported and promoted this process.[4] Together, society's view of the 'normal' and 'healthy' body is being reshaped. Increasingly more aspects seem 'dysfunctional' and in need of fixing. In the process, some problems, such as female sexual dysfunction and erectile dysfunction, appear to be very common.[4,24,27,36,62,79–83] Redefined as a medical problem and coupled to 'simple' drug treatments, a seemingly perfect solution to these problems is provided that allows them to become an accepted and normal part of everyday life (Box 3.4).[4,24,27,36,62,79–83] It also increases the urge for more people to use these treatments that promise astonishing results: to transform our bodies, make them functional and desirable (again).[4,24,27,36,62,79–83] These messages are also mimicked and corrupted even further by the media, entrepreneurs, and other champions, including retailers on the illicit market. Given such an environment, it is little wonder that the general public have started to seek treatments out.

Box 3.4: The changing face of Viagra®?

A study that looked at Viagra® prescriptions in the US between 1998 and 2002 found that the fastest growing group of consumers were men aged 18–45, while the proportion of men with erectile dysfunction that were prescribed the drug actually decreased over the study period. This suggests that Viagra® may be used more for non–medical reasons. The study also found an increase in prescribing for young women.[907]

3.3 *A globalised, networked world*

It has become easier for people to learn about drugs that they can use to enhance their bodies, share these experiences, as well as provide advice and support to others.[136–151] Just a few years ago most people learned about them through the popular media and relatively small social networks. The drugs that were available at the time were bought mainly from local dealers, mail order or 'bricks and mortar' shops. Word of mouth and face–to–face communication were particularly important in their spread. These traditional types of social networks are still important in many cases; for some they appear to be the main way that their use is spreading. In the past decade or so thousands of websites, online communities and shops have sprung up making it easier for people from across the globe to access and share information, experiences, advice and support (Box 3.5). The growth of the Internet has also made it easier to advertise, sell and buy these drugs (Figure 9).

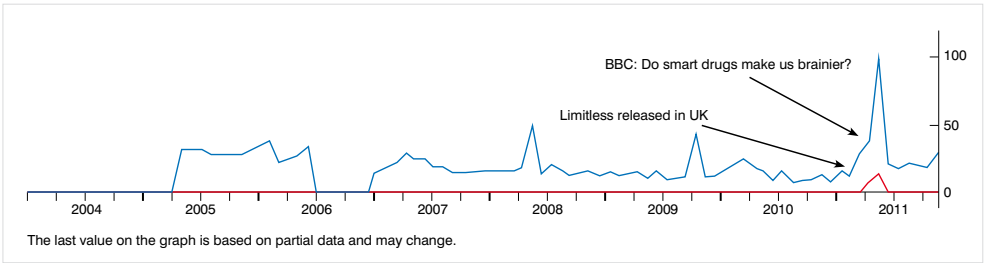


Figure 9. 'What if a pill could make you rich and powerful?' Searches on Google for 'smart drugs' (blue line) and 'buy smart drugs' (red line) from the UK. In 2011 there was a large increase in popularity for these terms around the time that the film 'Limitless' was on general release in the UK. The film was an action thriller about a writer who takes an experimental drug allowing him to use "100%" of his mind. During this period the media also ran related stories about 'smart drugs' (such as the BBC's 'Do smart drugs make us brainier').

Traditional and online social networks are not mutually exclusive; in many cases they appear to complement each other (although the importance one takes over the other may change over time). Of course these developments parallel innovations in science and medicine which have provided a growing range of drugs from consumers to draw on. Importantly the Internet allows cheap and easy access to drugs.[655] Here prescription only medicines, whose access by the public is meant to be tightly controlled in order to protect individual and public health,[223–247] are available alongside sought–after substances that are not available on the regulated market, such as untested and banned drugs (Figure 10).

Figure 10. Vials of the untested synthetic peptide hormone melanotan II bought from an Internet shop based in the UK. The substance is used as a tanning drug, aphrodisiac and appetite suppressant.

Box 3.5: Examples of how commonly asked questions start on Internet drug discussion forums

'I'm new to this, how do I…'	*'How much should I use?'*
'Which drugs should I use?'	*'Is it legal?'*
'Do they work?'	*'Why isn't it working?'*
'Is it safe?'	*'Need advice…'*
'What are the side effects?'	*'Should I be worried?'*
'Where can I buy…?'	*'How do I inject…'*

Consumers also learn about the drugs through the results of scientific studies. However, the findings are often miscommunicated, misrepresented and misunderstood (Box 3.6; 3.7).[85–94] They are reproduced, reinterpreted and spread around the globe by the popular media and online communities, and corrupted and manipulated by retailers on the illicit market, entrepreneurs, and others with a vested interest in the drug's success. As the information circulates it becomes more and more distorted. The limitations of the study—that it examined the effects of the drug on cells in a Petri dish, 10 or 20 rats or mice, a small number of healthy young men for a few days or hours, or even larger groups with a specific disease—are lost in translation or no longer matter. To some, the results are convincing enough to be seen as a 'breakthrough'—or certainly good enough for them to give it a try; their uncertain relevance, preliminary nature, limitations and harms often misunderstood, trivialised or ignored. In the haste to make a profit, retailers conveniently forget to mention that only a small number of untested drugs ever go on to be approved by medicine regulators which in many cases is because the harms they bring outweigh the benefits. While at the bottom of media reports there are the seemingly ever present search engine adverts (such as Google AdSense) that link through to retailers selling the untested drug. It is a retailer's dream come true.

Box 3.6: Growth hormone: the Fountain of Youth?

Can growth hormone prevent or reverse ageing? Research published in the world's leading medical journal claimed that daily treatment of older men with the drug for six months reversed the loss of muscle and build up of fat 'equivalent in magnitude to the changes incurred during 10 to 20 years of aging'. This captured the media's imagination. The results were grossly misinterpreted.[4,908–916] Headlines such as 'Human growth hormone reverses the effects of ageing' were repeated around the world.[917] For some the Fountain of Youth had been discovered. A huge market for growth hormone has developed globally as an anti–ageing therapy. Many companies selling quack therapies based on growth hormone quote and link to the paper to bolster their unfounded claims.[4,908–916]

Box 3.7: Media headlines that have misinterpreted the findings of research studies

'Want a tan without using sunbeds? Scientists develop implant that stimulates skin pigment production.'[918]

'Schools will soon have to ensure all pupils have access to brain–enhancing 'smart drugs', according to officially funded experts.'[919]

'It's a no–brainer – bring on the pills that will make us smarter.'[920]

'Biotech tan from a jab could put the heat on suntan salons soon.'[921]

3.4 The illicit market

The biggest source of these drugs is the illicit market. It is vast and complex; global in nature.[277–555,650–653,922–934] In some cases the drugs are bought from Internet, 'bricks and mortar' shops or dealers. In others they are sold or given away by friends, family, partners, or other acquaintances (Box 3.8). In both instances this can include prescribed medicines that are diverted to the illicit market. The size and scope of this market was simply not possible just over a decade ago. Increasing (low–cost) manufacturing capacity in countries such as China (Box 3.9) and India, the globalisation of free trade, communication and transport networks, such as the Internet and (express) cargo and postal services, have allowed more manufacturers, retailers and consumers to take part in the market.[68,136–151] It also allows consumers to buy a range of drugs that are restricted in the UK because of the harms they can cause. These include prescription only medicines, as well as banned and untested drugs.

Box 3.8: How do people obtain drugs such as sildenafil?

One of the few large–scale surveys that have looked at how consumers obtain drugs from the illicit market found that for drugs such as sildenafil (§8) the Internet was as popular a source as friends, partners, or other acquaintances.[654]

Recent seizures and prosecutions by authorities in the UK do suggest that there is a huge market for at least some of these drugs. In 2010 alone more than 8.5 million doses of counterfeit and unlicensed sildenafil, worth around £13 million, were seized. This included six million from freight deliveries at Heathrow Airport. While some of these may have been destined for other markets, as the UK is used as a staging post in the illicit trade in medicines, more than 2.1 million doses were seized in incoming international mail that were from orders placed online by UK consumers.[478]

Box 3.9: The falling cost of growth hormone

Although there is limited information, estimates of the cost of growth hormone (§5) on the illicit market in the UK during the 1990s suggested that it ranged from £6.58–£20 per IU (International Unit). Recent data drawn from a small convenience sample of products available on the illicit market in south east England in 2008 found a number of different products on offer that varied between £1–£8.33 per IU (see also Table 5). It appears that the cost of this drug has dramatically fallen over the past decade or so making it more affordable.[924] It is thought that much of this is from the increase in growth hormone manufactured in China. In a 1989 underground guide to steroid use from the US it was suggested that 'short term users (8 week duration) will spend up to $150 daily dosage.'[931]

The Internet appears to play a key role in the trade of these drugs (whether wholesale or retail). Some of the manufacturers, suppliers and retailers are not based in the UK and are rarely subject to UK law. However, in other cases the finished products are imported in bulk and then sold through Internet sites or other outlets.[465–482] Sometimes the ingredients are imported in bulk from countries such as China and the final product made in 'underground laboratories'.[932,933] Those involved in the illicit market range from cottage industries to large–scale operations some of which involve organised crime. The decentralised and transnational nature of this market makes it particularly difficult to control and reduce supply.[658] In part this is because there are few restrictions on consumers buying these drugs for their own use. It is also because the legal regulation of the Internet is largely based on national law. Manufacturers, suppliers, retailers, website hosting and payment processing services[i] may all be based in different countries.[659] Effective control of these entities and services are limited by differences in national laws, policies, and sociocultural values. In some of the countries where these drugs originate from, limited regulatory capacity and corruption can also limit their control.[660,661] In short, a globalised, networked market has made it easier and cheaper to manufacture, advertise, buy, and distribute a huge range of drugs. Moreover, like all communication and transactions conducted at a distance, the lack of physical face–to–face, contact between the consumer and retailer can make deception and fraud easier and more likely when there is little risk of being caught.

i Weakness in payment processing has been identified as a potential target to disrupt this trade.[659]

3.5 How many people buy drugs online?

There have been few detailed studies in the UK that have looked at how many people buy drugs online. In 2003 a nationally representative survey of 2000 people aged 15+ found that 1% had bought prescription only medicines online. Respondents said that it was the easiest way for them to obtain the drug and that it cost less than a prescription.[655] While this survey included any type of prescription only medicine, monitoring data from this period supplied by the predecessor to the MHRA found that eight of the top 10 medicines marketed over the Internet in the UK were also drugs that were commonly used for enhancement purposes (Box 3.10).[655] A more recent survey commissioned by the Royal Pharmaceutical Society of Great Britain found that 7% of 1950 adults had bought medicines online, and estimated 'over two million people across Britain now regularly purchase medicines via the web'. The respondents are likely to have included individuals with a prescription (and hence may obtain their medicines from a regulated pharmacy based in the UK), however of interest is that the most popular drugs purchased online were: fluoxetine (e.g. Prozac®), sildenafil (Viagra®), diazepam (Valium®), methylphenidate (Ritalin®), growth hormone (Serostim®) and modafinil (Provigil®).[934] These are all drugs that can be used for enhancement purposes.[i] Unfortunately only a few details of the study are available so caution is required when interpreting these findings.

Despite the limited data it appears that considerable numbers of people are buying medicines online without prescriptions. Further research is needed to get better estimates of both the number of people buying drugs online for enhancement purposes and details of the types of drugs.

Box 3.10: Top 10 prescription only medicines marketed over the Internet in the UK in 2003. Most of these are commonly used as enhancement drugs.[655]

1. Xenical® (orlistat used weight loss)
2. Proscar® (finasteride used for hair loss)
3. Propecia® (finasteride used for hair loss)
4. Viagra® (sildenafil used for sexual enhancement)
5. Uprima® (apomorphine used for sexual enhancement)
6. Reductil® (sibutramine used for weight loss)
7. Zyban® (bupropion used for smoking cessation)
8. Relenza® (Zanamivir used for influenza)
9. Phentermine (used for weight loss)
10. Merida® (sibutramine used for weight loss)

i Some consumers may have bought these drugs to self–treat a medical condition. In some cases, such as diazepam and methylphenidate, the drugs are also used recreationally.

3.6 Online marketing

The Internet is making it easier for more people to buy these 'enhancing' drugs in more situations.[68,141–151,478,654,655] Yet few studies have looked at how people buy drugs online, including how a particular retailer is chosen.[668–671] For some this may be based on personal recommendations from social networks. For others it may be from spam emails, online adverts or search engines. However, in the latter case how people access this information and the way it is presented is often manipulated.[659,663–666] Deception and fraud are key features of much of the illicit market,[296] although this is not to say that consumers will not always receive an order placed online. Many studies that have bought drugs online in order to study them have received at least some of them.[671] Online retailers use a range of strategies—known as 'spamdexing'[663,935]—in attempts to get their shop listed in the top results of search engines. These include 'keyword stuffing' as well as 'made–for–ads' websites that appear at first glance to simply provide information about a drug—although they focus attention on the 'benefits' and the ease of use, while ignoring the harms—but in reality are attempts to push consumers to a 'trusted' seller.[935] These forms of manipulation are critical because it appears that people tend to trust and select links that are highly ranked in search engines.[936] Some retailers also buy advertising space to ensure that the site is listed prominently on the top and bottom of search engine pages. The overall aim is to push more people to the sites selling the drugs. While the medium of manipulation may be new, such strategies to boost prominence have been used for many years. During the early 1900s the company that sold the weight loss drug Marmola planted stories in magazines in attempts to boost sales.[937]

The sales pitch online is often built around the drugs being of a 'high quality', 'safe' and above all 'effective' (Box 3.11). The harms are often manipulated, trivialised, or ignored. Some even advertise their products as manufactured according to international standards required by medicine regulators. Most notable in this respect are the growing number of synthetic peptide hormones such as melanotan II used for tanning and GHRP-6 used to stimulate the release of growth hormone. They quote scientific and medical literature, particularly published clinical trial data, that appears to support their claims. In the case of tanning drugs such as melanotan II or sexual enhancement drugs these are placed alongside pictures of (half)naked models that aim to reinforce the message (Box 3.12). 'Customer' testimonials are also used to praise the quality of the service and reliability of the retailer, as well as the quality, safety and effectiveness of the drug (not unlike the practices of those selling Marmola and DNP in the 1900s, §2). On the other hand, in order to avoid scrutiny by the authorities and circumvent medicine laws, some sites selling the drugs as 'research chemicals' and 'not for human consumption' limit such advertising activities. This is a similar ploy to that used by

retailers of so-called 'legal highs'. (In some cases such a marketing strategy may also give an air of scientific respectability for some avant-garde 'innovator' consumers.)[879]

Sites selling skin–lightening products (§7) often make no reference to the fact that the product contains a drug. In fact, similar to their sale in 'bricks and mortar' shops, they may be sold alongside normal skin care products and advertised simply as 'beauty creams'. Sites selling food and herbal products with potent active substances usually do not disclose these on the packaging/labelling, although in the case of some, such as muscle building supplements, they may be hinted at, yet promoted as simply 'safer'.

Box 3.11: 'Customer' testimonials from online shops selling the tanning drug

'BEST TANNING PRODUCT IN THE WORLD EVER!!! EVERYONE KEEPS ASKING ME HAVE I BEEN ON HOLIDAY!!! AND IVE LOST 3 KILO'S IN UNDER TWO WEEKS. ABSOLUTELY THIS IS A CANCER FREE WAY OF GETTING A GREAT TAN!!! THANKS …' Nicola

'We love this product!! My wife and I have used it for 8 months and I feel so good. It has actually helped keep our marriage can you believe! We're both got a great tan, lost weight and our sex life together has never been better. Who would have thought this product could be brilliant. MASSIVE THANKS … for saving our relationship, continuing to give good service and keeping your prices so fair.' Mike and Gill

'As a fitness coach I pay a lot of attention to my health and to having a vital and healthy appearance. Thanks to Melanotan 2 my body is nicely tanned. In my opinion, the greatest advantage of these injections is that they do not harm your skin and they do not cause premature skin aging [sic] like UV radiation does thanx.' Katie

'Last week was the first time I had bought from … (our former name) and I will definitately [sic] be a regular customer. I have been using MelanotanII for 2 years now and have noticed that I have sometimes felt ill shortly after injecting. However when using the MelanotanII from this website I experienced no negative side effects and acheived [sic] a deep golden tan within 10 days, using a 1mg per day dose. Delivery was superfast, [sic] and the product was with me within 3 days of placing the order. Excellent product and excellent service from the staff at … (our former name) also.' Danny Smith

Box 3.12: Other tricks of the online trade

Some sites selling melanotan II offer free 'starter kit' or discounts when you supply the retailer with 'before and after photos' for them to publish on their website. These are used to bolster the claims of the quality, safety and effectiveness of the product.

Other sites offer gift certificates, sale items, bulk discounts, customer loyalty programmes – such as points to redeem towards free products – online order checking, advice on the legal aspects of the products, a combination of different drugs at a discount, free gifts of drugs, or free shipping when a certain value is purchased.

In attempts to make the sites look legitimate and professional some use logos of pharmaceutical companies, healthcare providers, professional bodies, delivery companies and payment processing companies. In some cases fake certificates purporting to be from drug regulatory authorities or related professional bodies are used (Figure 11). Some sites also provide fake certificates of analysis of the products in attempts to deceive customers about the drug quality.

Many of these sites also 'offer' a convenient, reliable, and discreet service. They offer products delivered rapidly to your door to anyone who has access to a credit card, debit card or Internet payment account. Many offer express shipping or next–day delivery. Some also guarantee to replace the products or issue a refund if they are intercepted by customs agencies or found to be defective. Many sites also advertise customer privacy and data protection policies, although research has shown that out of 60 online pharmacies tested most did not provide adequate protection for their customers.[667] Products are delivered 'signed, sealed and private', the service is 'secure & discreet'. These features may play on consumers' embarrassment given the stigma attached to some of the uses for these drugs.[654] This is reflected in the common belief that the Internet provides anonymity for such purchases. Curiously one recent study that looked at drugs such as sildenafil (for erectile dysfunction) bought from the Internet found that just over two–thirds of men were not concerned about the privacy of their personal information in such transactions.[654]

Figure 11. 'Fake certificate used on an Internet shop selling drugs. It purports to be from the Royal Pharmaceutical Society of Great Britain and states that 'customers … can be assured that the products are of the highest quality and are purchases from reputable sources … We recommend using… for buying medicines on a regular basis'.

Unfortunately little is known about how consumers respond to these different types of marketing strategies.[668–671,938] Studies will be required to determine if they help legitimise the retailer and normalise drug use and if they think that the retailers are legitimate and supplying genuine drugs (or, indeed, if they care). Despite the lack of research on this issue, large numbers of sites use many of the marketing strategies that are found on popular e–commerce sites.

3.7 Key issues

- Growing numbers of people around the globe are using drugs to try to get a better body, empower themselves, and increase their well–being. The sociocultural value placed on these goals can powerfully shape our behaviour.
- Globalised communication and transport networks help fuel the spread of these drugs. Increasingly, the Internet and express postal services play a central role by making it easy to learn about these drugs and buy them on demand. This is facilitated by weak legal and regulatory systems as well as corruption in some countries involved in the manufacture and supply of these drugs. Such factors also make it particularly difficult to control.
- In some cases the drugs are also bought from 'bricks and mortar' shops or obtained from family, friends and other acquaintances.
- Many unfounded claims are made about the 'enhancements' these drugs bring, although there is often no, or limited scientific evidence to support them.
- There is often limited information about the use of these drugs, particularly in the UK. However, evidence suggests that a large illicit market does exist.
- Although online retailers use a range of marketing techniques likely to appeal to consumers, little research has been conducted on how they respond to this.

@iStockphoto.com/Dino

4. The harms to public health

This section examines some of the general harms that this form of drug use may cause. For a discussion of some of the specific harms the reader is referred to the individual sections on drugs.

4.1 The safety net

All drugs whether licit or illicit have the potential to cause harm to individuals. Widespread use of the drug, as well as the frequency, severity, duration and outcome of the harm, can more broadly harm public health. In order that this can be minimised to an acceptable level, the research, testing, manufacture, distribution, labelling, sale, supply, and advertisement of medicines are strictly regulated in countries such as the UK.[223–247] Failure in any of these aspects has caused serious harms.[248–276] All potent medicines that are licensed are subject to expert assessment and continuous monitoring to ensure the benefits they bring to those with disease outweigh the harms that they can cause.

This framework of 'quality, safety and efficacy' also includes a system of pharmacoepidemiology (that includes further safety studies of a drug after it has been licensed) and pharmacovigilance (that includes the detection and reporting of suspected reactions). These provide essential mechanisms for detecting and minimising harms in a timely manner, particularly after a medicine has been licensed. It was the bitter experience of the harms caused by a lack of regulation—culminating with the thalidomide disaster—that were the catalysts for this protective framework.

Licensed medicines can sometimes be recalled, restrictions placed on their use, or banned (such as in the case of the appetite suppressants rimonabant and sibutramine, §6).[556–572] Recalls may be due to a packaging error, such as a missing patient information leaflet, or because of a defect in the medicine, such as having the wrong amount of active substance or being contaminated in some way. Restrictions or bans may be due to a lack of efficacy or unexpected safety issues that cannot be identified during testing. This regulatory framework plays a critical role in protecting the individual and public health.

It is illegal to sell a medicine that is not licensed for use in the UK.[223–230] However growing numbers of retailers ignore this or attempt to hide their true nature by advertising them as food or herbal products or 'research chemicals' and 'not for human consumption' (in the case of those retailers based in the UK) or more simply they are based outside of the UK and hence not subject to UK law.

4.2 Circumventing the safety net

Increasingly, our globalised, networked society allows this safety net to be circumvented. The ability to manufacture potent active substances and drugs in countries with weak legal and regulatory systems has increased. The Internet and global cargo/postal systems have made it easier and cheaper than ever to advertise, sell, buy, and distribute them. Together these have made the control of this market much more difficult.

Box 4.1: How does regulation in other countries affect the UK?

The World Health Organization estimates that only 20% of Member States have well–developed medicine regulatory frameworks. Of the remainder, 50% have varying levels of development and operational capacity; while 30% have no regulatory authority or only limited capacity to regulate the market. These gaps in regulation allow the manufacture and global distribution of untested, banned and adulterated drugs.[660,661]

While analysis of a broad range of drugs sold on the illicit market have found that some are genuine, licensed medicines (whose use still requires medical supervision), growing numbers of banned, untested and/or adulterated drugs are also being sold.[277–555] Perhaps surprisingly some of the untested and banned drugs arise from consumer demand. In most cases consumers are unaware of the harms posed from these products. Consumers have no way of checking the quality, safety and efficacy of products sold on the illicit market. They rely on stories from online communities, other social contacts and the claims made by manufacturers and retailers. This latter group are able to exploit this to their advantage through misleading and fraudulent advertising.

While it is difficult to estimate the level of harm from these drugs, some indication can be inferred from pre-clinical and clinical studies of the substances; drug disasters that happened prior to contemporary regulatory systems; harms that occur in countries where there is weak legal and regulatory systems; case reports; drug alerts from regulatory authorities; and experiences that arise in countries such as the UK as a result of new safety information that requires restrictions or bans on a particular medicine.[248–276] However, in the case of untested medicines there is often little data to draw on.

A growing number of distributors and retailers have also started selling their own generic and branded drugs (Box 4.3) (Figure 12). There are a number of possible reasons for this: 1. it allows them to sell them as 'research chemicals' that are 'not for human consumption', (this is widely believed to fall into a grey area of medicine law); 2. it provides an opportunity to maximise profits by manufacturing cheaper products compared to selling genuine licensed medicines (which may also be more difficult to get hold of)

as well as marketing products for specific groups of people where there is no licensed equivalent (such as products containing sildenafil for women); and, critically, 3. it gives them the ability to offer products containing substances that are not available on the regulated market. In this latter case, this is because these substances are not licensed; or are sometimes in development as medicines (i.e. they may be in pre–clinical testing or pre–licensing clinical trials); or they may be substitutes to controlled drugs (§5.5)[e.g. 532] or medicines that have other restrictions placed on their use; others were never commercialised, often because they did not work as expected or were not safe;[e.g. 532] while in some cases, licensed products containing the active substances were banned (such as the appetite suppressants sibutramine and rimonabant) (Table 6)[556–572] because of concerns over safety.

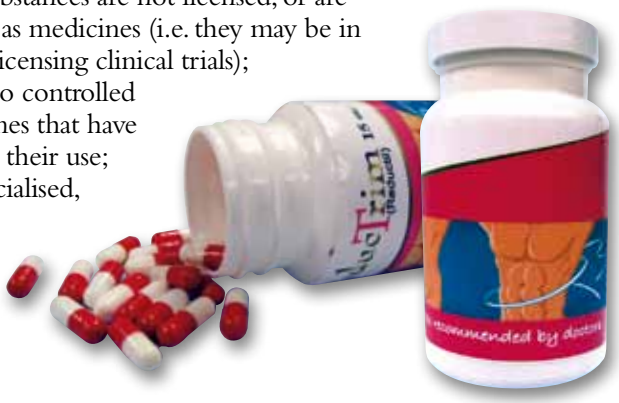


Figure 12. ReducTrim 'recommended by doctors'. The product contains the banned appetite suppressant sibutramine. 'It has been brought to our attention that some of our customers are concerned that this product has changed … Please be assured that the only change is the colour of the pill, and the manufacturer we deal with. This is still a genuine Sibutramine 15mg product.'

Box 4.3: Expanding the range of drugs

Drugs used to treat erectile dysfunction are not licensed for use in women, however, recently specific brands such as 'Pink Viagra' (counterfeit Viagra® product claimed to contain sildenafil), 'Pulse8 for Women' and 'Pink Lady for Women Capsules' (containing tadalafil) (Table 8) have started to be sold on the illicit market.

Other manufacturers capitalise on this by claiming to provide combinations of drugs at high strength. For example some anabolic steroids are being supplied as 'pre–made stacks' (combinations of different drugs) at strengths higher that those found in legitimately licensed products.

4.3 All natural products?

These problems run deeper. In order to capture some of the lucrative 'enhancement' market some manufacturers and retailers have deliberately added potent active substances to products sold as 'all natural', food, dietary, herbal and cosmetic products (Box 4.4, Box 4.5, Box 4.6).[e.g. 292–457] Here they exploit the common belief that 'natural' products are safer and healthier alternatives to drugs.[588–590] These creative marketing strategies are also designed to circumvent legal restrictions on the sale of medicines.

Anabolic steroids, progestins, growth hormones, aromatase inhibitors, drugs used to treat erectile dysfunction, melanotan II, stimulants, appetite suppressants, diuretics, laxatives, and mercury compounds, just to name a few, have all been detected. Some of these are untested, others are banned. Some of the untested substances appear to be used in order to avoid detection by the authorities (such as sildenafil analogues, Box II). In other cases it is because of the novel pharmacological effects they may have (such as melanotan II, §7.2). In some cases it may be due to poor manufacturing. However both the effects and the safety of these untested substances are largely unknown. Some of the active substances used have been banned because of safety concerns over their harmful effects (such as the appetite suppressants rimonabant and sibutramine). Most consumers are unaware of this adulteration. Nonetheless, in some cases (such as 'muscle builders' and 'fat burners') they intentionally buy them once they learn of rumours about their effects or true nature.

One example of this type of harm was the sale of weight loss products in Japan during the early 2000s.[439–457] Sold as 'herbal medicines' and 'dietary supplements', these products contained the untested substance n–nitroso–fenfluramine hidden inside. It shares some similarities with fenfluramine a popular weight loss drug that was banned in 1997 because it was linked to serious cardiovascular problems.[75,820–828] There were more than 160 cases of liver damage, four of which were fatal, linked with these products (some estimate that more than 800 people were injured). Similar cases were reported in China, Singapore, and the UK. In the latter country, four cases of serious liver damage were reported, one of which resulted in death. Despite an investigation by authorities it is still unclear why this substance was used.[439–457,939]

More recently, more than 220 cases of severe hypoglycaemia, causing serious brain damage in some consumers and 13 fatalities, were reported in Singapore, Hong Kong and Australia linked to the use of 'herbal remedies' and adulterated drugs that were sold as sexual enhancement products and treatments for erectile dysfunction. The products often contained huge amounts of glibenclamide, a potent substance used to treat diabetes.[548–555]

The public commonly view food and herbal supplements as safer than synthetic drugs. 'Natural' is often used as a synonym for 'good' and 'healthy'. Consumers may be more likely to use them believing that they will not cause harm—particularly when they are advertised as 'healthy' alternatives to drugs and 'free from side effects'.[588–590] Some consumers with underlying disease, or who are prescribed medicines that requires them to avoid certain drugs/substances, may inadvertently use such products in the belief that they are 'all natural'.[i] Many individuals do not inform their doctor that they

i While most products hide the fact that they contain potent drugs, a smaller number do not, although they do obscure it from the average consumer. Some list the substance using a chemical name. It is thought this is done to generate interest and rumours about true nature of the product while avoiding regulatory scrutiny. Analysis of these types of products has found that the actual drug that is present may not match that claimed by the manufacturer.

are taking food or herbal products, which can lead to harmful interactions with prescribed drugs and treatments. Some consumers also appear less likely to report a serious harm from a 'herbal medicine' (defined as symptom(s) that were 'worrying or alarming') compared to over–the–counter medicines. In one recent study 40% of consumers stated that they would not consult their GP for a serious harm linked to the use of a herbal medicine.[590] Consumers using herbal products may not associate a particular harm with its use. Importantly, as the consumer does not know that these products contain potent active substances it can delay correct medical treatment if they become ill (Box 4.6).

Box 4.4: 'Natural' & 'herbal' products in the UK

Since 2005, the UK medicines regulator has discovered more than 280 products sold as 'natural' or 'herbal' that contained varying quantities of undeclared potent active substances. Some of these contained banned or untested drugs. In some cases there was enough drug present to cause an overdose.[296]

Box 4.5: Ubertan. A 'natural blend?'

In 2011, the tanning product Ubertan was sold in the UK as 'a natural blend of melanin producing amino and fatty acids which is administered daily until the desired colour is reached … using the easy to administer nasal spray applicator.' It was found to contain the potent untested synthetic peptide hormone melanotan II that increases the amount of the pigment melanin produced by the body.[483]

Figure 13. 'Ubertan'.

Box 4.6: 'Herbal hide & seek'

In 2010 'herbal remedies' sold in New Zealand and Singapore for enhancing sexual performance were found to contain the prescription only medicine tadalafil (used to treat erectile dysfunction) hidden in the capsule shells in a deliberate attempt to avoid detection. This is presumably because in the past authorities have typically analysed the contents of the capsules rather than the shells.[505–507]

In the recent case in Hong Kong and Singapore where more than 220 people were seriously harmed by the use of herbal sexual enhancement products adulterated with glibenclamide only about 35% admitted use of the products. Three people were affected on two separate occasions by the adulterated products.[548–555]

4.4 *'Always read the leaflet'*

Drugs sold on the illicit market may not be supplied with adequate and accurate labelling and information about how to use them safely. (In the case of banned and untested medicines this information is impossible to provide by its very nature.) In licensed medicines this essential information covers the potential harms, including interactions/interference with other drugs, foods and herbs, as well as ingredients (including excipients) that can cause allergic reactions and anaphylaxis.[612–615] It also includes information on the effects of the drug in those with pre–existing disease and in specific populations such as older persons, children, and women of a childbearing age.[616,617] People with reduced liver or kidney function may have to avoid certain drugs to prevent a harmful build–up of the active substance in the body. Test purchases of drugs (such as the appetite suppressant rimonabant, §6) by researchers, have found that some are supplied loose in plastic bags or envelopes.[460] This means that essential information on using the drugs safely, including the correct dose to use, will be missing. It will also make it difficult for the consumer to actually identify what the drug is (assuming it is not already a counterfeit drug). The lack of child–resistant packaging in such cases could also lead to accidental poisoning in children.

4.5 *Fertility, pregnancy & breastfeeding*

Some of the drugs that are used may affect fertility (such as anabolic steroids which affect both males and females, §5).[878] Others can reduce the effectiveness of oral contraceptives which could lead to unplanned pregnancy (such as modafinil which is used as a 'smart drug', §9).[618] Growing numbers of the drugs that are used are untested so their effects in humans are unknown. Others, such isotretinoin (Table 7), which is used to self–treat acne (sometimes as part of general skin care routines) is a potent teratogen.[619] Mercury from skin lightening creams (§7.3, Table 7) can also act as a toxin to the embryo or foetus.[620] There are also concerns over the use of the anti–depressant paroxetine (§10, Table 10).[621–623]

Drugs can harm the embryo or foetus at any time during pregnancy. However, the first trimester is the most critical period of embryonic and foetal development.[617] Exposure to drugs during this time may lead to serious harm. From a public health perspective this is important if women of a childbearing age use these drugs as 30–50% of pregnancies are unplanned. This is usually caused by a failure or lack of contraception. About a third of these pregnancies proceed to birth. In such cases the embryo and foetus may be exposed to the drug before the pregnancy is recognised (4–6 weeks or longer post–conception) (Box 4.7).[624–627]

Similar concerns also extend to paternal drug use. Harmful drugs and metabolites may be transferred in the semen or other paternal-maternal contact.[628] Some drugs may also damage the sperm resulting in harmful effects in the embryo. Others, such as testosterone gel or skin lightening creams, which are applied to the skin, may be accidentally transferred to others including women and children.[608,629–633] Exposure can also happen by handling the drugs, such as crushed or broken tablets. The use of poor quality drugs can mean that protective mechanisms (such as special tablet coatings) may be absent causing those that handle them to be exposed (Box 4.8).[634]

Overall, such drug use, and more broadly, exposure, may not be detected by routine anti–natal screening, particularly if the woman was unaware of using drugs herself or her partner's drug use. This is particularly relevant in the case of food or herbal products that contain undeclared (hidden) active substances. Finally, in women who use these drugs during breastfeeding, the active substance or metabolite may be present in breast milk which could harm the baby.

Box 4.7: Are these types of drugs being used in pregnancy & breastfeeding?

There are no estimates of the number of women this may affect in the UK. It is unclear if routine anti–natal screening would pick up this type of drug use, particularly if the products are sold as food, herbal or cosmetics. There have been case reports of women using potent drugs for skin lightening and weight loss in the UK while pregnant. In one case the banned substance fenfluramine was hidden in a herbal weight loss product. The woman was breastfeeding at the time and was assured that the tablets were 'pure herbs' and could not harm the baby. After taking the drug for six weeks she discovered that she was also pregnant.[635]

Studies in Senegal, where use of skin lightening products (Table 7) in women is relatively common, found that some pregnant women continued to use products containing hydroquinone, corticosteroids and some of unknown ingredients during pregnancy and breastfeeding. The study also found that some started to use these drugs or increased their use during pregnancy.[608 636]

Box 4.8: Finasteride, male pattern baldness & exposure in pregnant women

Finasteride (Table 7) is used to increase hair growth and prevent further hair loss[i] (§7.4). It requires special precautions in its handling as exposure of the drug in pregnant women might lead to feminisation of a male foetus. In order to reduce the risk of exposure by women who are or who may become pregnant the tablets have a special coating. While finasteride is only licensed as 1 mg tablets for treating male pattern baldness, websites commonly promote and sell high–strength 5 mg tablets. In one recent case in the UK, a retailer promoted these high–strength tablets and suggested consumers use a pill cutter to divide the pill. This would have damaged the coating potentially allowing pregnant women to be exposed to the drug.[634]

4.6 *Hazards for children*

Children may be exposed to drugs through accidental transfer by those who are using them. Drugs obtained from the illicit market are not always sold in child–resistant packaging. In test purchases conducted by researchers, tablets have been supplied loose in an envelope or plastic bag.[460] Medicines are one of the most common causes of accidental poisoning in young children, and unsafe storage of medicines causes serious harm.[637] However, child–resistant packaging is the last line of defence in preventing poisoning and all medicines must be stored out of the reach and sight of a child. Similar measures should apply to injecting equipment. Such advice is not always present on drugs obtained from the illicit market.

4.7 *Hazards from injecting*

Drugs that are intended to be injected can cause serious harms through lack of sterility and other forms of contamination caused by poor manufacturing and distribution practices.[638] Similarly, harms also occur from inadequate infection control, injection technique, sharing and disposal of injecting equipment and other 'sharps'. Localised infection, particularly abscesses can result from this.[639–648] Sharing used injecting equipment leads to the spread of blood borne viruses such as HIV.[878] Limited information is available on injecting techniques and related practices for using enhancement drugs, particularly for those individuals who have just started injecting.

i It is also used clinically to treat benign prostatic hyperplasia (where there is an increase in size of the prostate gland without cancer being present).

4.8 Additional hazards

Some drugs have been linked to dependence (such methylphenidate which is used as a 'smart drug') (Table 9).[649] Some can affect the ability to drive and operate machines. Others may affect the ability to donate blood while using the drugs and for a period of time after treatment. This includes anabolic steroids (Table 5) and isotretinoin (Table 7). Routine screening of blood donors may not pick up such drug use, particularly if the individual is unaware of it as a result of using a food or herbal product containing undeclared active substances.

4.9 Detecting & preventing harms

Assessing the harm from this form of drug use is difficult when there is limited information on the number of people exposed to the drugs, the composition of the drugs, the regimens that are used, and number of people who experience harm.[238–241] Monitoring systems that can detect harms, such as the UK's Yellow Card Scheme, can be used by healthcare professionals and the general public to report suspected reactions related to any drug. However, few reports related to enhancement drugs are likely to be received through this system. In part this may be due to a lack of awareness of it, a belief that only harms linked to licensed medicines can be reported, and a reluctance of individuals to report such reactions (including embarrassment) (Box 4.9).[940–945]

Box 4.9: Reporting harms in the UK – the Yellow Card Scheme

The Yellow Card Scheme[940] provides a vital system for identifying harms caused by medicines. Recent studies have suggested that there could be some value in the public reporting harms that are linked to the use of medicines. There is little reason to believe that these findings would not apply to drugs obtained from the illicit market. However, the awareness of this reporting system in general by the public is poor. It is reasonable to assume that an even smaller number are aware that reports can be made for drugs bought on the illicit market. However, research will be required to determine how this reporting system can be optimised for reporting such harms (§11).[238–241,940–945]

While some drugs, such as the anabolic steroids, have been subject to a more systematic review of the harms,[878] most of what we know is limited to case reports or extrapolation of data from clinical trials. However, the usefulness of such data may be limited as unexpected safety issues cannot be identified before the drug is used for a sufficient period of time in large populations.[238–241] In the case of untested drugs (such as melanotan II, §7.2) there is often little or no data on the effects in humans and the harms they can cause. Assessing these relies heavily

on judgement and interpretation from other available data (such as in vitro or animal studies). Such data may have limited relevance and in some circumstances could provide false reassurances over the potential harms.[238–241] Moreover, identifying harms caused by these drugs may be delayed as neither their use nor the illicit market are subject to routine monitoring, with much of the data on harms collected through case reports published in the academic literature. Intrinsic delays in publishing means that it can be many months before this information is widely available.

Another concern is that if a harm is identified with a drug or particular product on the illicit market then it can be difficult to stop its sale and distribution (Box 4.10).[609–611] Tracing the products in the supply chain and at the level of the consumer can be difficult. Deliberate obstruction by the manufacturers and retailers may add to this complexity. This may be due to the fact that they are engaged in illegal activities and they may be reluctant to provide details of the supply chain etc., that incriminate either themselves or others, or because relevant details may not be available or retained. In some cases fictitious company names have been used on the product packaging (in the recent case where more than 220 people were harmed by sexual enhancement products adulterated with glibenclamide the company names were fictitious so the manufacturing source could not be determined).[554] Different company names have also been used for the same product.[609] There may also be a reluctance by consumers to provide information for fear of embarrassment. Overall this obstructs authorities in tracing the source of the product, points of sale, and, more broadly, makes estimating the degree of spread, including at the level of the consumer, extremely difficult.

Box 4.10: Removing products containing hidden active substances from the market can be difficult

Recently in the United States a product called Pai You Guo sold as weight loss capsules and tea was found to contain the banned substances sibutramine at more than twice the prescribed dose and phenolphthalein (a laxative) (§6). This led to a recall by authorities. A study of the effectiveness of this recall in one group of women found that none of them were aware of the recall and that 61% of those who had bought the product had done so after the recall had been announced. Some 85% of consumers reported at least one side effect (dry mouth, anxiety and insomnia were the most common).[611] These types of products have been sold in the UK and have caused similar types of harms.[301,302,304]

4.10 Key issues

- A globalised world allows medicine legal and regulatory systems to be circumvented. This allows almost unrestricted access to drugs that are otherwise tightly controlled in the UK. As a result untested, banned and adulterated drugs are widely available.
- Growing numbers of products sold as 'all natural', 'dietary' and 'herbal' are found with undeclared potent active substances. Such adulteration has caused serious harm.
- Drugs on the illicit market may not be supplied with adequate and accurate information about how to use them safely.
- Some of the drugs may affect fertility or reduce the effectiveness of oral contraceptives. Exposure in pregnancy may harm embryonic/foetal development. Exposure from breastfeeding may harm infants. Children may also be accidentally exposed to, or poisoned by these drugs.
- Drugs that are injected may cause harm to the individual through damage to the injecting site and infections. Sharing injecting equipment can spread blood borne viruses.
- Some of the drugs cause dependence or affect the ability to drive and operate machines.
- The ability to detect and prevent harms is limited with current surveillance and reporting systems.

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5. Drugs used to enhance the structure and function of muscle

This section examines the use of drugs to enhance the structure and function of skeletal muscle.[688,878] Typically they are used to enhance physical performance (for example to increase strength) and for their cosmetic effects (to increase muscle size and definition). Some are also used for their related effects in other tissues (to decrease the amount of fat, §6) (Table 5). However, there are a number of broader reasons why people use such drugs which may change over time. They include attempts to get that 'six–pack look', to help perform better in sport, to 'turn back the clock', 'get bigger' and 'stronger' for their job, or to treat injury or disease. From a historical perspective the reasons for use have also changed, broadening out from bodybuilders and professional sportspersons.[688]

The oldest and largest group of drugs (and hence their significance reflected in this section) are the anabolic steroids which have been used since at least the late 1940s.[688,946–952] However, the ability to manufacture biosynthetic human growth hormone in the last three decades or so, along with the more recent emergence of a number of novel untested substances, such as peptide hormones and the non–steroidal selective androgen receptor modulators (SARMs) (Table 5), have ultimately led to an increasing range of drugs that are sold on the illicit market.[484–490,953–1011] Alongside these, products labelled and sold as 'food' 'dietary', or 'herbal' supplements, which contain substances such as anabolic steroids, anti–oestrogens, aromatase inhibitors, progestins and peptide hormones, are increasingly available in gyms, fitness equipment and nutritional supplement shops, as well as on the Internet.[528–532,925] However little is known about their use as well as the harms they pose (Box 5.1).

5.1 Andrew, 19 years old

Andrew wants to 'bulk up' and 'get bigger and stronger'. He does strength training at the gym four times a week and plays rugby for his local club most Saturdays during the playing season. He describes himself as in very good health, thinks that he eats healthily, doesn't smoke or take recreational drugs, and drinks about 12 pints of strong lager a week, mostly over the weekend. For the past six weeks he has been using a 'dietary supplement' that he bought in a local fitness equipment shop that contains 'Superdrol' (see Box 5.1). The other day while training he got talking to Bob, an amateur powerlifter, about his lack of progress in building muscle.

Bob suggests that alongside changes to his diet and getting more sleep, anabolic steroids might help him achieve the gains he wants. Over the past six years Bob has tried 'almost every steroid there is … orals and injectables', as well as drugs such as clenbuterol, ephedrine, growth hormone, thyroxine, GHB, and insulin. He has also tried some of the 'new drugs' such as SARMs, melanotan II, GHRP–6 and MGF.

Bob has been training at gyms since his late teens. Six years ago he noticed that he was struggling to lift the same weight as some of the younger lads in the gym and decided to look into using anabolic steroids as part of his training regimen. He stresses that he has been careful not to 'abuse' the substances that he takes, and that, like his diet, he uses them to 'enhance' his training, and not as a 'short cut'. He spends a lot of time on the Internet researching their effects before trying them. He believes that he knows how to spot 'fake gear' (counterfeit/fakes), and always 'injects properly' using 'clean needles'. Aside from having to get used to the 'jabs' (injections), and feeling 'as horny as hell' most of the time when using steroids, he also gets a few 'minor' side effects 'every now and again'. These include 'a bit of acne', 'gyno',[i] and 'deca dick'[ii] which are 'easily treated' using isotretinoin, tamoxifen, and sildenafil. Occasionally he needs to use a drug called 'human chorionic gonadotrophin' to 'kick start' his body's production of testosterone after using steroids. While Bob admits these side effects are sometimes a 'bit of a hassle' he says that 'they come with the territory' and are 'easily treated' without having to go to his general practitioner—'at least I know the drugs are working and I don't have to worry about my GP having a moan!' GPs, suggests Bob, 'don't know what they are talking about' when it comes to these drugs. Bob believes that he has experienced 'big gains' from using the drugs and 'wouldn't change things for the world'.

Andrew has heard a lot about anabolic steroids causing 'roid rage' and asks if Bob has ever experienced it. Bob reckons that 'roid rage' is a 'load of crap', suggesting that it's just an excuse for 'nutters to lose their top'—particularly those that 'abuse' steroids. He says that the drugs can increase 'positive aggression' needed for training, but in his experience if someone is 'angry off steroids' they are 'angry on steroids'.

Bob suggests that to get the gains that Andrew wants he should start on his 'tried and tested basic cycle' of 1000 mg/ml of 'Sus' 'stacked'[iii] with 400 mg/ml of 'Deca' per week for 12 weeks, followed

i 'Gyno' (or 'bitch tits') is slang for gynaecomastia, the growth of the breast tissue in males. Caused by an imbalance in levels of oestrogen to testosterone, many of the drugs commonly used by this group (such as growth hormone, human chorionic gonadotrophin) have been linked to it. The use of anti–oestrogens (particularly tamoxifen, see Table 5), and, increasingly, aromatase inhibitors, which are taken to treat and prevent gynaecomastia, is relatively common in steroid users.[688,878,951]

ii 'Deca dick' is a slang term used to describe erectile dysfunction that users attribute to using the steroid nandrolone decanoate (Table 5). While erectile dysfunction is fairly commonly reported by steroid users during 'on' and 'off' cycles there has been very limited study of this problem.[688,878]

iii 'Sus' is slang for Sustanon 250, a drug that contains four different types of testosterone with different durations of action. Cycling is where steroids are taken for a period of time (for example 8–12 weeks) known as an 'on cycle', followed by a similar period of steroid–free training known as an 'off cycle'. This is done to prevent tolerance to the steroids, reduce the risk of side effects from prolonged use, and allow the body's hormonal systems time to resume normal function. Some individuals continue to use a lower dose 'maintenance' regimens of drugs during the 'off cycle'; a minority of individuals use the drugs on a continuous basis. Alongside cycling, users will typically take two or more different steroids at the same time in a practice known as 'stacking' which they believe will have synergistic effects. There is limited data to support this practice. The dose and regimen of the steroid(s) used in a cycle/stack may be manipulated throughout an 'on cycle' in an attempt to maximise positive effects, prevent tolerance to a particular steroid and minimise harms.[688,878]

by 8 weeks off the drugs. He introduces him to the gym manager, Dave, who can sell him everything he needs to get started. This includes the injecting equipment and any drugs that he might need to treat common side effects.[i] This costs Andrew about £40 per week (Figure 14). Bob shows him how to inject the first few times.

Figure 14. Anabolic steroids from the illicit market.

Since then Andrew has also been doing some of his own research on the Internet and joined a few discussion forums. He has bought a copy of the latest edition of a reference book specifically written for anabolic steroid users that includes 'detailed drug profiles', 'cycles', 'stacks' and how to spot counterfeit and fake drugs. The discussions and book mirror some of what Bob has already told him about the drugs, and his own early experiences.

Box 5.1: Comment on Andrew

Andrew may not be aware of this but he has been using an anabolic steroid for the past six weeks. Analysis of 'food supplements' containing 'Superdrol' found it to contain the anabolic methasterone. This was first synthesised in the late 1950s but was never commercialised. The reason for this is unclear. Data from studies in rodents found it to be a potent anabolic drug.[947] Information on the effects and harms of this drug is not available, however, 10 cases of liver injury linked with the use of Superdrol have been reported in the medical literature.[1011–1016] While Bob believes that he knows how to spot a counterfeit or fake, the reality is that apart from really obvious visible defects, the only way to tell is through detailed analysis of the product. This relates not only to what active substance is present and its strength but also whether there are any contaminants. In the case of injectable drugs this is particularly important given that they need to be sterile.

i Users will often take a combination of ancillary drugs. These include other performance–enhancing drugs (such as clenbuterol, growth hormone, and insulin) and drugs to combat steroid–induced side effects (such as tamoxifen and human chorionic gonadotrophin). Some may in addition use recreational drugs which may also function as performance–enhancing agents (such as cocaine, amphetamine).[688,878,951,952]

5.2 *Sarah, 38 years old*

Sarah wants to 'tone up and get trim', 'get some of that energy back that she had when she was in her early 20s' and 'get rid of those fine lines, creases and wrinkles' that have started to appear on her face. She trains at the gym three times a week and goes jogging at least twice. She describes herself as in 'good health', thinks that she eats healthily, doesn't smoke, drink alcohol or take drugs. Although she has never been overweight, Sarah often feels 'fat' and wants to get 'a flatter, toned, tummy and firmer arms, legs, and bum'.

Recently she read an article in a popular fitness magazine–'Forget plastic surgery, should we go for growth hormone?–that tells the story of Beth, a 46 year old business executive, who has been injecting 'low doses' of growth hormone over the past six years and has found that it has 'totally changed her life'. Beth mentions that she first got interested in growth hormone when she read an article about a study published in a leading medical journal which reported that over a period of six months the drug had 'reversed the effects of ageing by 10 to 20 years' in men in their 60s and 70s. Now Beth feels like she is back in her early-twenties. She is 'toned and trim' and her skin is 'smoother', with 'no wrinkles'. She feels less tired and is 'much better' at remembering things–all 'without any side effects'. Sarah decides to have a look on the Internet for some more information about the drug.

Sarah comes across a discussion forum where a group of women around her age are using the drug. Some of them keep an online 'log' (or diary) of their experiences, that include 'before–and–after' photos, and where other members can also comment on their progress. Sarah found that while many of the women were a bit worried about injecting the first time, they soon got used to it, helped by a video of how to inject posted to YouTube by a registered nurse. In fact the only side effect that most of them reported was a bit of pain at the injection site just after taking the drug.

One of the members, Joan, mentions a recent news report highlighting a clinical trial where young children who don't produce any growth hormone were given 'inhalers' of the drug, because it helped them stick to the regimens prescribed by their doctors. They all agree that when growth hormone is available in an inhaler they will switch to using this. They also believe a lot more people who are put off by injecting might be tempted to use the drug. 'Imagine being able to carry it around in your bag.'

Joan, who had been using growth hormone for the past two years, says that about six months ago she switched to a drug called 'CJC-1295' which 'stimulates' natural growth hormone secretion. She admits that the drug 'is still experimental' however, the shop she bought it from claimed that you only had to inject 'twice a week', compared to 'every day' with growth hormone. She also mentions that the shop said that

they got the drug from a 'leading' supplier in the EU that manufacturers it according to 'pharmaceutical standards'. Sarah decides to take the plunge and orders two vials of 'CJC-1295' for £86 that contains enough for a two–week course of treatment. The vials also come with a vial of bacteriostatic water to reconstitute the drug, two sterile wipes, and one needle and syringe (Box 5.2).

Box 5.2: Comment on Sarah

CJC-1295 is an untested drug. Its effects in humans are largely unknown, although studies with small numbers of people have found that it can stimulate the secretion of growth hormone.[1003–1007] As far as we know it is no longer being developed as a medicine. There is no evidence to support the claims made on online shops about its effects:

'Increases muscle mass (and physical strength if combined with moderate exercise). Reduces wrinkling of the skin and some other effects of skin ageing. Re–grows internal organs that have atrophied with age. It promotes lipolysis, which results in the reduction of adipose tissue (body fat). Strengthen the immune system.'

CJC-1295 is only available on the illicit market.[485] This means that consumers do not know what they are using and if it is sterile. Moreover, for each injection Sarah will need new sterile injecting equipment, otherwise she could develop an infection or damage the injection site (§4.7).

5.3 The emergence of anabolic steroids

Rumours of the use of anabolic steroids for 'muscle–building' effects date back to the late 1940s when it was suggested that some bodybuilders in the United States used 'various' forms of 'testosterone'. Most accounts suggest that by the early 1950s the drugs started to be used in weightlifting, after which their use became widespread in many other types of sport.[688] Use diffused beyond these small groups so that by the 1970s, data from the United States suggested that some collegiate and high–school athletes had also begun to experiment with the drugs. However the extent of this is unclear,[i] and a clearer picture is only available from the late 1980s onwards. Here a study found that 6% of male high school students in their final year[ii] had used the drugs at least once, with two thirds starting to use the drugs at age 16 or younger. Interestingly, just over 20% reported that they got the drugs primarily from either a doctor, pharmacist or veterinarian, however this was a time when the drugs were not classed as controlled substances.[1017]

i This is partly because it is unclear if a distinction was made between anabolic steroids and corticosteroids. Both are commonly abbreviated in the general population as 'steroids', and have been subject to mix–ups.

ii 12th Grade students. The ages ranged from <17 to 20, with 98.5% aged 18 or under.

The United States, with its emphasis on competitive sport at collegiate and even high school–level, may represent a rather unique social environment that facilitates anabolic steroid use compared to other countries. That said, school–based surveys in other countries have shown that between 0.4% and 5.8% of male adolescents have used the drugs at least once, with a much smaller number of females using the drugs. A small number of studies in both the United States and European Union have found a similar level of use in young females. It is unclear as to the accuracy and indeed the implications of these data. It has been suggested that a failure to discriminate between corticosteroids and anabolic steroids in the questionnaire (due to the common term 'steriods') may be the most reasonable explanation for these findings.[1018]

In the UK, up until 1992, reports about the use of anabolic steroids were largely anecdotal or informal and limited in scope.[842–863] However, concerns were noted during the mid 1960s that the use of these drugs was an accepted practice in weightlifting and bodybuilding, including at an amateur level. During the 1980s reports also began to appear about their use in 'health and fitness clubs'. These were supplemented by a small informal survey in a gym in the West of Scotland along with a series of investigative reports in The Times newspaper that highlighted a 'thriving' illicit market in 'buying and selling of anabolic steroids … in British gymnasiums and health and fitness centres'.[688]

In September 1987, the Government requested that the Advisory Council on the Misuse of Drugs (ACMD) examine the issue. In March the following year it concluded that there was insufficient evidence that the use of the drugs constituted a social problem— a key criteria which needs to be satisfied under the Misuse of Drugs Act 1971 before a substance can be brought under its control. Over the next few years the issue continued to be raised within Government, Parliament and the popular media, alongside further reports (both informal and formal) within the scientific literature.[688]

In October 1992, the Government asked the ACMD to re–examine the issue. This work coincided with the Department of Health commissioning the largest ever prevalence study undertaken in gyms in the United Kingdom, which found that 6% of men and 1.4% of women reported current use of anabolic steroids.[864] These data, along with evidence from a number of sources, led the ACMD in February 1993 to conclude that steroid use was now 'having or appeared capable of having harmful effects sufficient to constitute a social problem'. Subsequently, legislation was introduced in 1996 by the Government to control the use of steroids (along with clenbuterol, growth hormone and chorionic gonadotrophin which are often used as ancillary drugs) under the Misuse of Drugs Act 1971.[688]

5.4 *The emergence of growth hormone*

Up until the mid–1980s all human growth hormone (hGH) available on the market was obtained from cadavers.[924] This severely limited the amount of the hormone for medical use (limited to children with growth hormone deficiency, GHD) and research.[i] The development, and subsequent refinement of technology that allowed the hormone to be produced synthetically, radically changed the use and diffusion of hGH, opening it up to both licit and illicit markets. The new technology offered a mechanism for the large–scale production of growth hormone, which helped make important discoveries in basic and applied science, and the expansion of research outside of the treatment of young people with GHD. This included research into the role of the hormone in adults—such as its effects on body composition, particularly in ageing (Box 3.6)—and its potential for treating a range of conditions, including those with adult GHD.[924] The potential for biosynthetic growth hormone to increase height, coupled with its wider availability, was highlighted both by academics and in the popular media which raised concerns that some parents may use the hormone on their healthy children to increase their final height.[924]

Anecdotal reports suggest that growth hormone has been available in gyms for more than 25 years. However, it was not until 1992 that a more formal indication of this became available as part of a broader study examining anabolic steroid use in the UK. This Department of Health study examined use of the hormone in a group of 110 anabolic steroid users from nine locations in England, Scotland, and Wales. They found that three individuals had used growth hormone in the previous six months, which the authors understood to be essentially 'confined to those few who can afford it (ie. [sic] [drug] dealers and high standard bodybuilders)'. Since this report only a few other studies from the United Kingdom have looked at the use of the hormone. The most recent study recruited participants from 'hardcore' gyms in South Wales and found that out of 96 current anabolic steroid users, 24% were also currently using growth hormone. However, this does not reflect the level of use in the wider gym population. This is because these studies either recruited individuals already known to be using anabolic steroids or sampled people from 'hardcore' gyms[ii] where performance–enhancing drugs were more commonly used.[924]

In recent years the manufacture of biosynthetic growth hormone in China has made it cheaper and easier to buy. Facilitated by sale over the Internet, such manufacture is believed to have played a key role in the greater diffusion of this drug. Although there is limited information,

i Moreover, it was discovered that some growth hormone products were contaminated with the causative agent for Creutzfeldt–Jakob disease (CJD) causing the fatal neurodegenerative disease in some patients.

ii These are characterised by having predominantly heavy weight training equipment, competitive bodybuilders and relatively few female members.

Figure 15. Growth hormone from the illicit market, seized by Merseyside Police.

estimates of the cost of growth hormone on the illicit market in the UK during the 1990s suggested costs of £6.58 to £20 per IU (International Unit). Recent data drawn from a small convenience sample of products available on the illicit market in South East England in 2008 found a number of different products on offer that varied between £1 and £8.33 per IU (Box 3.9)[924] (Figure 15).

The use of growth hormone as an 'anti–aging therapy' or 'well–being' drug appears to be gaining popularity, particularly in the United States.[913–916] However, no studies from the United Kingdom have examined these reasons for use.

5.5 Emerging drugs

In the past few years a range of new but untested drugs have emerged on the illicit market. These are based on advances made by scientific research and in drug development. These include stimulants sold as food supplements,[134,1019] non–steroidal selective androgen receptor modulators (SARMs), CJC-1295, Mechano Growth Factor, GHRP–6, Examorelin (Hexarelin®), Long–R3–IGF–1, and PEGylated Mechano Growth Factor (Table 5). Little is known about how many people use these drugs, although discussion on online communities suggest that growing numbers are trying the drugs. In part this is likely to reflect their increasing availability through Internet shops. In some cases it may reflect the fact that they are not controlled drugs and hence easier to supply as 'research chemicals' for retailers, as well as being legal for consumers to possess (many of the commonly used anabolic steroids as well as growth hormone are controlled drugs in the UK, Table 5).[484–490,528–532,925]

5.6 Who uses and why?

In order to get a picture of who uses these types of drugs, it is useful to categorise individuals based on their main reason for use.[688] These should be viewed as a rule of thumb and users may fall into one or more categories. The main reason for use may also vary from person to person within any particular group, and within persons over time. With this in mind there appears to be four broad categories:

1. sports competitors (including elite bodybuilders) who use predominately to enhance their sporting performance;

2. occupational users, such as those in the security industry (e.g. door supervisors and security guards), prison officers and police officers whose major reason for use is to increase both muscle size, strength

and aggression to protect and intimidate others, there are also those in the entertainment industry, such as dancers and actors, who use to enhance their physical appearance as required by their occupation;

3. those who use predominately as treatments for disease, anti–ageing, short height; and

4. those who use predominately for cosmetic reasons to enhance their body image satisfaction.

Information on this form of drug use is limited. Overall, most of the surveys suggest that the majority of users are male (particularly in relation to anabolic steroid use),[864–878] however few studies have examined the use of growth hormone and new drugs.[924] Surveys in the general population often only look at basic measures of self–reported use, particularly in relation to 'anabolic steroids' (although surveys in some countries use terms such as 'doping', 'muscle–building hormones' or include examples of the substances). About 0.2% people (mainly men) aged 16–59 in England and Wales, equivalent to 52,000 people, used anabolic steroids in the past year.[840] Around 0.3% of boys and 0.1% of girls aged 11–15 had used the drugs.[841] Interestingly data from needle and syringe programmes in the North West of England have found that between 1991 and 2001 there was a sixfold increase in the number of new clients using anabolic steroids. This is a trend that appears to be continuing.[875,878]

More detailed studies of user groups have also focussed on those using anabolic steroids, particularly those self–identifying as 'bodybuilders' and 'strength trainers'.[864–875,878] Among other things, this research has explored why and how these drugs are used, as well as some of the harms. In the latter case these measures are largely restricted to subjective effects which limit the conclusions that can be drawn. While questions on the use of growth hormone has been increasingly included in such studies, this has usually been limited to a subgroup of those using anabolic steroids.[924] Information on the use of the newer drugs is largely limited to observations of Internet discussion forums.

5.7 *The illicit market*

There are some data to suggest an increasing number of 'off–label' (where a medicine is used outside the terms of its licence) prescriptions for anabolic steroids (largely testosterone) and growth hormone, particularly in the United States.[1020,2021] It is unclear how these prescribing practices affect this form of drug use, although it is possible that it makes the use of these drugs more normal and acceptable. While these practices allow access to quality assured products it is thought many individuals purchase the drugs they need from the illicit market.[925,959–983] In part this is because of national medicines policies that limit access to these drugs, but also because this market is the sole source of some of the drugs that are in high demand by users. This includes some anabolic steroids that are

no longer licensed (see 'methandienone', Table 5) or are only marketed as veterinary medicinal products,[925] as well as the newer untested drugs such as the SARMs (Table 5). While there is undoubtedly some diversion of licensed medicinal products to the illicit market, the range of products available appears to be mostly due to growing manufacturing capacities in countries such as China and India where regulatory capacity is weak (Box 4.1). An increasingly interconnected world also facilitates the transnational distribution, marketing and sale of such products. Here the Internet appears to be playing a key role as a 'hub' in the diffusion of these types of drugs.[925] This is thought to have led to underground laboratories in the United Kingdom that typically import the ingredients in bulk and produce the final drug product themselves.

Over the past decade or so there has been a trend of selling untested anabolic steroids, anti–oestrogens, aromatase inhibitors and progestins as food supplements (often labelled as 'dietary supplements'). More recently some peptide hormones and stimulants have also been detected in these products (Table 5).[484–490,528–532,925] They have been marketed in this way in order to circumvent the medicine laws. Here enterprising chemists have searched the medicinal chemistry literature for substances that were originally synthesised as part of pharmaceutical research programmes but were not commercialised (and in the case of the anabolic steroids or growth hormone analogues because such drugs may not be subject to controlled drug frameworks) or are currently being tested as medicines. Little is known about the effects and harms of many of the active substances in these 'supplements' or products sold as 'research chemicals'.

5.8 *Patterns of use*

Many individuals use a range of drugs in high doses.[864–875,878] This usage is based on the availability of the drugs, the user's personal goals and as a result of self–experimentation (informed by the user's social networks, genre literature and websites). Some individuals use a more limited range of drugs. Research from the United Kingdom suggests that the majority of users inject anabolic steroids.[878] Importantly, many of the new drugs are also injected (e.g. CJC-1295). The natural history of use of these drugs is not well understood.

5.9 *Do these drugs work?*

Doses of testosterone leading to supraphysiological levels in the blood significantly increase muscle mass and strength in healthy young men.[1022–1026] While it is reasonable to assume that similar effects are seen with other anabolic steroids as they are structurally related to testosterone, few have been subjected to the same rigorous study.[946–948,1027–1029] Alongside the empirically validated effects, many users also cite psychotropic effects such as an enhancement of mood and confidence, increased aggression and motivation for training, as well as ancillary ergogenic effects (such as a reduced recovery time between training), as additional and synergistic

reasons for use of these drugs. Data are limited on such reported effects, however we know that anabolic steroids can have powerful placebo/expectancy effects (i.e. when a person expects a given effect from a drug and this either unconsciously affects the outcome or causes them to report the effect they expect).[1030,1031] Moreover, the effects of training, among other things, may confound such reported psychotropic effects. Currently, there are little data available on the effects of growth hormone and many of the newer drugs.

5.10 What do we know about the harms?

Case reports and other studies have linked the use of these types of drugs, particularly the anabolic steroids, with harms. Direct harms include adverse reactions from pharmacotoxicological actions of the drugs, and, more broadly, those caused by adulteration.[878] One particular concern is the quality of the active substance (identity, strength and purity) and the presence of contaminant (including sterility) given that many drugs are injected. There are also indirect hazards from injecting (§4.7). These include inadequate infection control, injection technique and sharing of injecting equipment that can cause local and systemic infections. However these issues remain poorly studied. Part of the problem is that most of the drugs are obtained from the illicit market. Because the composition cannot be assured and the impact of this is not routinely quantified and assessed, then it is difficult to know if it is the effects of the drug that are being examined or some other factor.[925]

5.11 Acne

Acne is a common finding in questionnaire–based studies of anabolic steroid users, although the measures used have not been validated. There have been some case reports that documented severe forms such as acne conglobata or acne fulminans.[878]

5.12 Gynaecomastia

Gynaecomastia is a common finding in questionnaire–based studies. It is the growth of the breast tissue in males caused by an imbalance in the levels of oestrogen to testosterone. Many of the drugs commonly used by this group, such as growth hormone, human chorionic gonadotrophin and spironolactone (a diuretic), have also been linked with gynaecomastia.[878]

5.13 Liver

Many of the oral anabolic steroids have been linked with liver damage. Importantly, cases over the past few years have reported a link between the use of 'food' and 'dietary' supplements thought to contain anabolic steroids and liver damage, although the composition of the products were not analysed. There have been a small number of case reports of benign liver tumours, peliosis hepatis (blood–filled sacs in the liver) and liver cancer in individuals who have used anabolic steroids.[878]

5.14 Cardiovascular

Anabolic steroids have also been linked with a range of harms on the cardiovascular system although these remain poorly studied, with much of the data from studies being equivocal. While there are a number of case reports of cardiovascular harms it is unclear just how common these are. Differences in the study design, research participants and the drugs that are used could account for these different findings. The most consistent finding is a change in lipid metabolism, with a decrease of HDL cholesterol and an increase in LDL cholesterol which could increase the risk of cardiovascular disease, although this is not inevitable and depends on the specific drugs used, doses taken and the duration of use.[878]

5.15 Genitourinary

Many anabolic steroids when used at sufficient dose can suppress the body's production of testosterone and sperm. In some cases this can cause temporary infertility. While it is common for users to report increased libido during an 'on' cycle (and to a lesser extent decreased libido during an 'off' cycle), these effects have not been sufficiently researched. Some users also self–report erectile dysfunction during both 'on' cycles and 'off' cycles. Again these reports require further research. There has been a case report of prostatic cancer in an individual who was a long–term steroid user and a small number of case reports of renal cancers in individuals who reported use of anabolic steroids. The significance of these cases is unknown.[878]

5.16 Effects on behaviour and mood

While data from case studies and observational studies have linked anabolic steroid use with a range of effects on behaviour and mood (such as hypomania, mania, aggression, violence, depression, and, after ceasing use, suicide) these effects are poorly researched.[1032] However, these drugs are psychoactive, and it is important to note that a range of medicines that act on the central nervous system have also been associated with such effects.[1033,1034] More research is required into both the effects of these drugs on mood and behaviour and the public health implications of this. Self–reported data from observational studies suggest that anabolic steroids may be linked to psychological dependence. It is unclear if anabolic steroids have the potential to cause physical dependence.[878]

5.17 Growth hormone and emerging drugs

The harms from growth hormone use are likely to include those that mimic the symptoms of acromegaly (a disease where the body produces too much growth hormone) as a result of exposure to prolonged high doses of growth hormone. Limited research has been conducted on this. In relation to the newer drugs there is insufficient data to determine the harms to health. For those drugs that are injected there are indirect harms related to injecting practices, including damage to the injecting site, local and systemic infections.[924]

5.18 Specific concerns for young people

The use of these types of drugs could potentially disrupt the normal pattern of growth and behavioural maturation (for example the use of anabolic steroids could lead to virilization).[878]

5.19 Specific concerns for females

The use of anabolic steroids in females can lead to virilization which includes: hirsutism, deepening of the voice, problems with the menstrual cycle and fertility, clitoral enlargement, atrophy of breast tissue, and changes in libido. The impact of these effects can be pronounced, and, in some cases, permanent. Anabolic steroids and the other drugs discussed in this section can have harmful effects on the embryo and foetus. This is important both for women of childbearing age as well as men trying to father a child. Moreover, the active substances or metabolites may be present in breast milk which may harm the baby.[878]

Table 5. Examples of drugs used to enhance the structure and function of muscle.

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Anabolic steroids										
Testosterone Enantate	Analogue of testosterone	Injectable	Surveys of gym users. Enforcement/ Seizures. Internet forums	Prescription only medicine; controlled drug	'Scimex - 10ml / 250 mg per 1ml' for £55 = £0.02 per mg	Testosterone enantate 250 mg/ml, net price 1-ml amp for £13.33 = £0.05 per mg	1000 mg per week	✓	✓	✓
Nandrolone Decanoate	Analogue of testosterone	Injectable	Surveys of gym users. Enforcement/ Seizures. Internet forums	Prescription only medicine; controlled drug	'Scimex - 10ml Vial / 300 mg per ml' for £49 = £0.016 per mg	Deca-Durabolin® 50 mg/ml, net price 1-ml ampule for £3.17 = £0.06 per mg	400 mg per week	✓	✓	✓
Methandienone (Dianabol)	Analogue of testosterone	Oral	Surveys of gym users. Enforcement/ Seizures. Internet forums	Prescription only medicine; controlled drug†	'Danabol 10 mg' 60 tablets for £20.95 = £0.35 per tablet	N/A	160 mg per week	✓	✓	✓
Testosterone Cipionate	Analogue of testosterone	Injectable	Surveys of gym users. Enforcement/ Seizures. Internet forums	Prescription only medicine; controlled drug†	'Scimex - 10ml Vial / 250 mg per ml' for £55 = £0.02 per mg	N/A	600 mg per week	✓	✓	✓

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Growth hormone and substances that stimulate its secretion										
Growth hormone (Somatropin, rhGH)	Synthetic growth hormone	Injectable	Surveys of gym users. Enforcement/ Seizures	Prescription only medicine; controlled drug	'Jintropin 100 IU' vial for £309.97 = £3.10 per IU	Saizen® 3.33-mg (10 IU) vial for £73.20 = £7.32 per IU	6–7 IU per week	✓	✓	✓
CJC–1295	Stimulates secretion of growth hormone	Injectable	Internet forums	Untested	2 mg vial for £22 = £11 per mg	N/A	0.5 mg 1-2 times per week	✓	✗	Unknown. However, none of these products are licensed medicines
GHRP-6	Stimulates secretion of growth hormone	Injectable	Internet forums	Untested	5 mg vial for £18 = £3.60 per mg	N/A	0.1 mg 1-3 times per day	✓	✗	Unknown. However, none of these products are licensed medicines
GHRP-2 (Pralmorelin Dihydrochloride)	Stimulates secretion of growth hormone	Oral/Injectable	Internet forums	Not licensed in the UK‡	5 mg vial for £11.50 = £2.30 per mg	N/A	0.1 mg 1-3 times per day	✓	✗	Unknown. However, none of these products are licensed medicines
Examorelin (Hexarelin®)	Stimulates secretion of growth hormone	Injectable	Internet forums	Untested	2 mg vial for £21.50 = £10.75 per mg	N/A	0.2 mg per day	✓	✗	Unknown. However, none of these products are licensed medicines

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
IGF-1 and analogues										
rhIGF-1 (Mecasermin)	Synthetic IGF-1	Injectable	Surveys of gym users. Internet forums	Prescription only medicine	N/A, sites purporting to offer IGF-1 sell Long-R3-IGF-1	Increlex® 10 mg/ml, 4 ml vial for £605 = £15.13 per mg	0.05–0.1 mg per day	✗	✗	Unknown
Long-R^3-IGF-1	Analogue of IGF-1, enhances potency	Injectable	Enforcement/ Seizures. Internet forums	Untested	1 mg vial for £61	N/A	0.05–0.1 mg per day	✓	✗	✓
Mechano Growth Factor (IGF-1Ec)	Analogue of IGF-I	Injectable	Enforcement/ Seizures. Internet forums	Untested	2 mg vial for £18.61 = £9.30 per mg	N/A	0.4–0.8 mg post exercise	✓	✗	Unknown. However, none of these products are licensed medicines
PEGylated Mechano Growth Factor (PEG MGF)	Analogue of IGF-I, produced by underground labs	Injectable	Internet forums	Untested	2 mg vial for £37.90 = £18.95 per mg	N/A	0.4–0.8 mg post exercise	✗	✗	Unknown. However, none of these products are licensed medicines

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Others										
Aromatase inhibitors (Various: e.g. Anastrozole, Letrozole, Formestane)	Stops oestrogen being produced. Stimulates testosterone production	Oral	Surveys of gym users. Enforcement/ Seizures.	Prescription only medicine (some untested)	'Arimidex, Scimex' (Anastrozole) 30 × 1 mg tablets for £49 = £1.63 each	Arimidex® (Anastrozole) £2.50 per 1 mg tablet	Anastrozole: 0.25–1 mg per day	✓	✓	No studies
Anti-oestrogens (Various: e.g. Tamoxifen)	Blocks the action of oestrogen. Stimulates testosterone production	Oral	Surveys of gym users. Enforcement/ Seizures.	Prescription only medicine (for some)	'Nolvadex, Scimex' 50 × 20 mg tablets for £35 = £1.43 each	Tamoxifen citrate £0.09 per 20 mg tablet	Tamoxifen: 20 mg per day	✓	✓	No studies
Human Chorionic Gonadotrophin (HCG)	Stimulates testosterone production. Promoted as a weight loss drug	Injectable	Surveys of gym users. Enforcement/ Seizures.	Prescription only medicine; controlled drug	Human Chorionic Gonadotropin' 5000-unit ampule for £30 = £0.006 per unit	Pregnyl® 5000-unit ampule for £3.15 = £0.0006 per unit	500 units per day (post cycle)	✓	✓	No studies. HCG may be substituted for rhGH due to their similar appearance
Selective Androgen Receptor Modulators (Various: Andarine (S-4), Ostarine)	Synthetic non-steroidal androgens.	Oral	Internet forums	Untested	'30 ml 100mg/ml (SARMS S-4)' for £94.97 = £0.03 per mg	N/A	Anadrine (S-4) 20–75 mg per day	✓	✗	✓

Prices on the illicit market provide an indication only. Many sites offer considerable discounts when drugs are bought in bulk. Self-directed dose used by consumers provides an indication only. †Medicine/drug that is discontinued or no longer actively marketed, although it may be marketed in other countries. ‡Licensed in Japan.

Hartphotography/Shutterstock.com

6. *Drugs used to enhance weight loss*

This section examines the use of drugs to enhance weight loss. While concerns about body weight have been around for many years, they have become much more culturally dominant in the past few decades (Figure 16).[43–49,i] In part this is because of concerns over the growing number of people who are overweight or obese, as well as broader prevailing sociocultural preferences for thin women and lean, muscular men (§3.2).[47,49]

Figure 16. 'Slimex capsules'. The product claims to contain the banned appetite suppressant sibutramine. Seized by Merseyside Police.

Overall this has led to a multi–billon pound diet and weight loss industry. It is estimated that 95% of women have dieted at some stage in the lives, with 40% dieting at any one time.[45] One survey in 2004 found that 15% of adults in the UK were seriously trying to lose weight.[1035,1036] Lifestyle changes such as cutting out fatty foods, eating less, or exercising, are common methods that are used to achieve weight loss.[1037,1038] Recent years have also seen a large increase in the number of 'weight loss' food and herbal products aimed at this market. However, there is little evidence to support their use or effects. This is because either they have not been shown to work or because of the harms that they can cause (e.g. ephedrine and harms on the cardiovascular system).[1039–1042] There have also been various unlicensed drug treatments promoted by entrepreneurs, including doctors. These include the hCG 'diet'[ii] (where human chorionic gonadotropin, a hormone produced during pregnancy, is injected into the body)[1043,1044] and pills containing a mixture of stimulants, laxatives, sedatives and diuretics.[1045–1049] A parallel illicit market has also developed selling a range of potent weight loss drugs (Table 6). This has been joined by a growing number of food and herbal weight loss products that contain undeclared banned or untested active substances. Since December 2007 the US authorities have detected the banned appetite suppressant sibutramine (among other drugs) in more than 100 different products. While in 2011 medicine regulators in Europe found more than 40 with the substance. These included milkshakes, teas, coffees and fruit juices (Figure 6, 7 ,8).[e.g. 294–338]

i Smoking, as well as use of amphetamines and coffee, are just some of the substances that have been used to lose weight. Some of the other drugs discussed in this report are used for these types of effects. Anabolic steroids, growth hormone and clenbuterol are used as 'fat strippers', while melanotan II is used as an appetite suppressant.

ii Also known as the 'Simeons therapy'.

6.1 *Emma, 44 years old*

Emma wants to lose weight. She has a BMI of 25, and while not clinically overweight she feels 'fat'. She has tried dieting, exercising, and various herbal products that she saw advertised on the Internet. Despite this she is not happy with the amount of weight she has lost. While discussing this on a popular Internet forum, one of the members, Sue, mentions that she has been using 'Herbal Xenicol', advertised as a 'safe herbal' product. Sue mentions that she has had some palpitations and insomnia while using it, although she admits to doubling the dose 'every now and again'. The results have been 'so fabulous' she has put up with these side effects and plans to start using it again soon. She mentions that she bought it for £25 through a major online retailer. Emma decides to place an order for one month's supply (Box 6.1).

Box 6.1: Comment on Emma

Recently the MHRA warned consumers over the use of 'Herbal Xenicol' (which is named to sound like the licensed weight loss medicine 'Xenical®') after one patient was hospitalised and several others suffered from a range of side effects such as palpitations, severe gastritis and abdominal pain, as well as insomnia after taking the product. Analysis found it to contain more than twice the prescribed dose of the banned drug sibutramine.[294,295] These types of products have led to similar harms in a number of countries (Box 4.10).

6.2 *Who uses and why?*

Despite the current concern over the number of overweight and obese individuals, there is little research on the self–directed use of drugs in the United Kingdom in order to lose weight. As noted a survey from 2004 found that 15% of adults in the UK are seriously trying to lose weight,[1035,1036] while a survey of a 1000 internet users (aged 16+) in 2007 Suggested that 7% would 'take diet pills/appetite suppressants' or 'look for a herbal remedy' if they were trying to lose weight. Those who considered themselves 'quite a bit overweight' were twice as likely to suggest that they would take diet pills/appetite suppressants.[1050] A survey at a Welsh university in 2009 found that out of 505 students, around 1% had used prescription stimulants not prescribed to them to lose weight, similarly around 1% had used other types of prescription drugs not prescribed to them to lose weight.[929] Almost 5% of the 111 staff members who responded had also used prescription stimulants not prescribed to them to lose weight (the drugs used were not specified). While it is unclear if these findings reflected the wider population they did indicate that there was considerable interest in such products. More formal surveys from the United States have found that just over 15% of adults had ever used a weight loss supplement with almost 9% having used in the last year.

They also found that the highest use was among young women. In a similar survey that looked at the use of prescription only medicines, just over 2% of almost 16,500 individuals reported using these types of drugs. Over 50% obtained them from a healthcare professional (just over 10% from a doctor at a 'diet clinic'[75]), almost 16% got the drugs from family, friends or 'other', while about 19% did not know or refused to reveal the source.[1051–1053] Both these studies were done before widespread use of the Internet. Overall information on the number of people using food or herbal weight loss supplements is important given the growing number of products that contain undeclared active substances.

6.3 What do we know about the harms?

With the exception of Orlistat (Table 6), all other licensed drugs used to treat obesity (fenfluramine, sibutramine and rimonabant) have been banned in recent years because of serious harms linked to their use. For fenfluramine and sibutramine this is mostly due to serious cardiovascular harms; while rimonabant was linked to serious psychiatric harms (including depression, aggression, anxiety, and suicide).[556–572,820–829] These and other untested drugs continue to be sold widely on the illicit market (Box 6.2).

Box 6.2: Adverts for rimonabant on the Internet

'Why Rimonabant Acomoplia is called a Miracle Drug? Do you know, Rimonabant acomplia helps not only to lose weight as well as to reduce waist size and stop alcoholism also at some extent. Many of Teenagers (especially girls) are afraid to quit smoking as it might increase weight, but Rimonabant acomplia helps you to keep your weight in track for quick weight loss. Buy Rimonabant acomplia and start reducing weight and stop smoking now.'

'Rimonabant Acomplia was said to be well tolerated in early tests. The only relatively common side effects were mild GI side effects and dizziness, and these were said to be transient.'

The drug was banned in 2008 by medicine regulators over links with serious psychiatric harms (§3.6).[556–558]

Of great concern is the problem of 'food' and 'herbal' weight loss products that contain undeclared active substances, their untested analogues, laxatives, diuretics and anti–depressants (§4). Some also contain a combination of these substances that could cause harmful interactions. Overall these types drugs and products have already been linked to serious harms.[e.g. 497,520,i]

i Now that sibutramine and rimonabant have been banned, leaving only Orlistat as a licensed treatment for obesity, and economic constraints on the NHS limit the number of surgical treatments for obesity, one urgent research question is whether increasing numbers of patients will seek out these drugs and/or food and herbal products from the illicit market.

Table 6. Examples of drugs used to enhance weight loss.

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Sibutramine	Suppresses appetite*	Oral	Enforcement/ Seizures. Internet forums. Media reports	Banned†	'Sibotrim 15 mg' 30 tablets for £30 = £1 each 90 tablets for £65 = £0.72 each 'Merida 15 mg' 28 tablets for £119.99 = £4.28 each 112 tablets for £349.99 = £3.13 each	Reductil® 28 × 10 mg tablets for £25.00 = £1.12 each Price is from September 2008, before it was banned Reductil® 28 × 15 mg tablets for £25.00 = £1.12 each Price is from September 2008, before it was banned	15 mg per day	✓	✓	✓
Rimonabant	Suppresses appetite*	Oral	Enforcement/ Seizures. Internet forums. Media reports	Banned†	'Generic Acomplia 20 mg' 30 tablets for £101.17 = £3.37 each 90 tablets for £185.06 = £2.06 each 'Acomplia 20mg pills' 30 tablets for £30.69 = £1.02 each 120 tablets for £83.33 = £0.69 each	Acomplia® 28 × 20 mg tablets for £44.00 = £1.57 each Price is from September 2008, before it was banned	20 mg per day	✓	Unknown	✓

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Orlistat	Reduces absorption of dietary fat	Oral	Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine (Xenical®), Pharmacy medicine (Alli®)	'Xenical' 84 × 120 mg capsules for £86.50 = £1.02 each	Xenical® 84 × 120 mg capsules for £31.63 = £0.38 each	1 capsule three times a day	✗	Unknown	✓
Ephedrine	Increases metabolic rate	Oral	Internet forums	Prescription only medicine. Not licensed for weight loss	'Kaizen Ephedrine HCL 8 mg' 50 tablets for £11.48 = £0.23 each	Ephedrine hydrochloride 28 × 15 mg tablets for £8.15 = £0.29 each Ephedrine hydrochloride 28 × 30 mg tablets for £12.43 = £0.44 each	24–100 mg per day	✓	✓	✓
Liothyronine sodium (T3, 'thyroid hormone')	Increases metabolic rate	Oral	Surveys of anabolic steroid users. Internet forums	Prescription only medicine. Not licensed for weight loss	'Cytomel T3 25 μg' 30 tablets for £22 =£0.73 each	Liothyronine sodium 28 × 20 μg tablets for £26.15 = £0.93 each	20–200 μg per day	✓	✓	Unknown
Levothyroxine sodium (T4, 'thyroid hormone')	Increases metabolic rate	Oral	Surveys of anabolic steroid users. Internet forums	Prescription only medicine. Not licensed for weight loss	'Generic Synthroid 25 μg' 30 tablets for £9.03 = £0.30 each 'Generic Synthroid 100 μg' 100 tablets for £36.70 = £0.37 each	Levothyroxine sodium 28 × 25 μg tablets for £2.08 = £0.07 each Levothyroxine sodium 28 × 100 μg tablets for £0.99 = £0.04 each	25–300 μg per day	✓	✓	Unknown

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Clenbuterol	Increases metabolic rate. Also used as anabolic drug	Oral	Surveys of anabolic steroid users. Enforcement/ Seizures Internet forums suggest use. Media reports	Not licensed in the UK.†† Controlled drug	'Clenbuterol SOPHARMA' 50 × 20 mg tablets for £13 = £0.26 each 'Clenbuterol NIHFI' 30 × 20 mg tablets for £26 = £0.86 each	N/A	100 μg per day	✓	✓	Unknown
Dinitrophenol (DNP)	Increases metabolic rate	Oral	Case reports of harms. Internet forums	Untested	'Dinitrophenol' 100 × 100 mg capsules for £93.35 = £0.93 per capsule 'Dinitrophenol' 11 × 200 mg capsules for £43.51 = £3.95 per capsule	N/A	100–800+ mg per day	✓	✓	✓

Prices on the illicit market provides an indication only. Many sites offer considerable discounts when drugs are bought in bulk. Self-directed dose used by consumers provides an indication only.
*Acts on central nervous system. †Products containing this substance may be licensed in some countries. ††Products containing this substance may be licensed in some countries although not for weight loss.

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7. *Drugs used to enhance the appearance of the skin and hair*

This section examines some of the drugs used to enhance the appearance of the skin and hair (Table 7). Typically they are used to 'look younger', 'feel fresher', 'more beautiful', 'normal', and 'healthy' (§3.2). Some are used to get a 'skin tan'; others as 'skin lighteners'. Some are used to 'smooth' and 'soften' lines and wrinkles on the face, 'restore' sunken cheeks, or to give 'full plump lips'.[i] Others are to stimulate the growth of the hair or prevent its loss. There is little information about the use of these types of drugs in the United Kingdom. Most of what we know comes from seizures and legal action against suppliers, case reports of side effects, media reports, and observations of online communities.

7.1 Pete, 26 years old

Pete wants to get a skin tan before his wedding in Barbados in 10 weeks time. Although he has used sunbeds, he has become concerned after reading a news report about the damage this can cause his skin including increasing his risk of getting skin cancer. The report also mentioned a drug called 'melanotan' that is being developed as a medicine to treat certain skin diseases. Pete googles 'melanotan' and finds an online community where people discuss their experiences of using the drug, including where they buy it from, how they use it and its effects.

After reading some of the discussions he learns that there are actually two different types of 'melanotan': melanotan I and melanotan II. Both cause the skin to get darker, although some of the people on the site mention that they also use melanotan II as an aphrodisiac and appetite suppressant. Many of the posts on the site link to scientific papers detailing the results of clinical trials of the drug which look very impressive to Pete. He decides to try the drug and asks other members of the site where they buy the drug. A number of them respond with web links to shops where they have bought the drug in the past. When Pete tries to access the sites all but one no longer work. The one that does only accepts bank transfers as payment which Pete is reluctant to do.

He searches Google for 'buy melanotan' and selects the first shop that is listed. He recalls that many people from the online community use melanotan II because it is difficult to get hold of melanotan I.

i This section also discusses the use of dermal fillers despite the fact that they are regulated as medical devices in the UK. The use of these products is subject to many of the same concerns as the drugs discussed in this report. In part this is because they are injected. Serious harms from their use have been reported. Moreover, unlike prescription–only medicines, there are few restrictions on their supply and administration.[231]

He orders two 10 mg vials of melanotan II which he thinks should give him enough for two months' use. Because he wants to get started straight away he pays for special delivery. It arrives next day in a padded envelope. Inside are two unlabelled vials of a white fluffy powder, some sterile water, two insulin syringes (with needles) and two alcohol skin wipes (Box 7.1). He discovers that there is no information about how to prepare and use the drugs (Figure 17). However, after a quick look online he finds some instructions. As Pete has never injected before he also searches YouTube for a video of how to do this. He finds one posted by someone who has been using the drug for the past three years.

Figure 17. Melanotan II kit ordered from a UK website. The vial was supplied unlabelled and without instructions.

Box 7.1: Comment on Pete

While analysis of vials of melanotan II have shown it to contain the drug these studies have not looked at the overall quality, e.g. whether it contains any chemical or biological contaminants.[547] Moreover, just because the vials that have been analysed contain the drug there is no guarantee that other products on the illicit market contain the drug. Injectable drugs also need to be sterile to prevent infection. Two syringes and needles are only sufficient for reconstituting the drug and administering the first dose. After that a new needle and syringe will be required to prevent both damage to the site being injected as well as infections (§4.7).

7.2 *Drugs used to darken skin colour*

In the last few years products on the illicit market that claim to contain melanotan II (Table 7), and to a lesser extent melanotan I, have been sold and used to get a 'skin tan'.[573–587,684,1054–1081] Known in the media as 'tan jabs' they work by mimicking the action of the natural hormone, α–melanocyte stimulating hormone, which triggers the production of the pigment melanin in the skin, causing it to get darker. Melanotan I (also known as afamelanotide) is being developed as a medicine to treat some skin conditions that are aggravated by exposure to sunlight.[i] As far as we are aware melanotan II is no longer being tested as a medicine because of its side effects. However, it is used in animals to study the regulation of pigmentation, appetite, inflammation, as well as sexual function and behaviour. Little is known about the long–term effects and harms of these drugs.

i Melanotan I (also known as afamelanotide) is being developed as a medicine to treat some skin conditions that are aggravated by exposure to sunlight.

The first formal indication that these drugs were being used was in August 2007 when authorities in the United States took action against an online shop selling melanotan II.[539,540] This was followed by warnings in 2008 from regulators in the United Kingdom and other EU Member States, as well as an editorial that highlighted use in the UK, drawing on observations that some people were using drug services to get needles and syringes to inject the drugs.[684] However, it is not known how many people currently use these drugs. What information is available comes mostly from Internet sites, including online communities and shops selling the drugs. Limited information is also available on seizures: between 2005 and 2010 the majority of samples suspected to contain peptide drugs seized by the Norwegian police and border agency were found to contain either synthetic human growth hormone or melanotan II. While the Internet has played a key role in the diffusion of melanotan II, it has also been sold, and in some cases administered, in tanning and beauty salons, hairdressers, and gyms.[684]

One of the largest online melanotan II communities has more than 9,000 registered members. Since January 2009 there have been more than 3,000 new registrations.[684] Although not all of these will be using the drugs, it does provide some indication of the interest in them. The site was apparently set up in June 1999 with discussion forums added in January 2004. Discussions on this site suggest that people have been using melanotan II since at least 2004 and melanotan I since 2006.[583,587,1054] It also appears that most people use the drugs to get a cosmetic 'skin tan'. A smaller number use them as treatments for diseases such as rosacea and fibromyalgia after apparently becoming disillusioned with existing medical treatments.[684] Some also use melanotan II as an aphrodisiac (it can cause erections and appears to stimulate sexual desire) and as an appetite suppressant (§6, §8). Much of this type of use appears to be based on online discussions of small, preliminary, clinical trails of the drug. The drug's effect on weight loss has only been studied in animals.[582] Other Internet sites provide discussion forums for specific user groups, including bodybuilders and people with diseases such as rosacea and fibromyalgia.

The most commonly used drug appears to be melanotan II, although in recent months increasing numbers of Internet shops have started to sell products labelled as melanotan I (although the actual drug that is present is unknown). These are both injected, however some shops sell nasal sprays containing the drug. More recently, in an attempt to dupe consumers and circumvent the medicine laws, a nasal spray containing melanotan II was sold in the United Kingdom as 'a natural blend of melanin producing amino and fatty acids' (Box 4.5).[483]

The amount of the drug that is used is often determined through self–experimentation. Information on websites selling the drugs and social networks indicates usage typically includes a 'loading phase' where the drug is administered daily until the desired 'tan' is achieved, followed by a

Figure 18. 'Colouring you beautiful'. Melanotan II 'tanning kit'. Sold by a UK website, it contains the untested synthetic peptide hormone melanotan II, along with bacteriostatic water to reconstitute the drug and a leaflet on how to use it.

'maintenance phase' of one to three doses per week in order to maintain the tan. Some sites recommend using a tanning bed to achieve a 'quicker' or 'more even' tan (Figure 18). Much of this information appears to be based on the interpretation of early clinical trials of the drugs.

A number of discussions on the major online community describe harms linked to the use of these drugs.[587,1055] The most commonly noted appear to be short–lived nausea, facial flushing, fatigue and vomiting. These are similar to the effects reported in clinical trials of the drugs.[576–579,1060] Case reports describing harms have also been published (such as abnormal pigmentation and growths linked to the drugs, although in none of these cases were the products analysed to determine the active substance that was present).[1072–1081] However, overall, it is difficult to draw any firm conclusions from these. The long–term harms posed by the unregulated use of these drugs are unknown.

7.3 *Drugs used to lighten the skin*

Skin lightening drugs have a long history of use.[181] Products containing mercury compounds have been used for many years with case reports of harms dating back to at least the 1920s.[1082–1084] While the first formal reports of self-directed use of hydroquinone and corticosteroids date from late 1970s and 1980s, respectively, their use pre–date these studies.[1085–1094] Alongside lightening the colour of the skin some are also used to self–treat acne, blemishes or freckles. They are usually sold as cosmetic products in 'bricks and mortar' shops as well as on the Internet.[277–291,607] They largely work by blocking the production of the pigment melanin in the skin, and can cause patchy discolouration.[1082–1096] Despite seizures of products and prosecution of suppliers (Box 3.1 & 7.2),[277–291] and case reports of side effects for almost 30 years in the United Kingdom, it is not known how many people use the drugs, why they use them, how they are used, and the public health implications. While their use is mostly limited to those with darker skin types such as the Asian and Black communities, other groups may also use them.

Box 7.2: Skin lightening

'Stilman's freckle cream … for a clear spotless face' seized by UK authorities was found to contain 3.1% mercury by weight.[1097] Interestingly at the time of writing this report a product using the same name and similar packaging was being sold on amazon.co.uk through a third–party vendor.[1098]

'The London Borough of Southwark has been one of the most proactive enforcement authorities in the UK regarding illegal skin lighteners. Working with the MHRA over the last six years 23 defendants have been prosecuted with total fines, [sic] confiscations and costs in excess of £336,000.' [288]

The toxic effects of mercury–containing cosmetics have been noted for many years. These include damage to the skin (such as rashes), as well as to the kidneys and nervous system. Worldwide hundreds of people have been poisoned by these types of creams, including five cases in the UK in the past two years.[591–608,1099–1128] Drugs containing hydroquinone can also cause a range of side effects in the skin, including irritation and a bluish–black discolouration called ochronosis.[1096] Corticosteroids can cause thinning of the skin, suppress the immune system, and in severe cases cause high blood pressure, diabetes, Cushing's syndrome and adrenal insufficiency.[1095,1096,1129] Of great concern is the use of these drugs during pregnancy and breastfeeding[608] which in some countries is common (§4.5).[636,i]

7.4 *Drugs used to increase the growth of hair*

It is not known how many people use these drugs in the United Kingdom. One drug that is commonly found in seizures by the MHRA, as well as sold online, is finasteride (Table 7) which is used to treat male pattern baldness (Box 4.8). It blocks the production of a more potent form of testosterone, dihydrotestosterone, which is linked to hair loss.[1138] The drug cannot be prescribed through the National Health Service for hair loss (although a private prescription may be obtained from a GP).[1139,1140] While finasteride is only licensed in the UK for male pattern baldness as a 1 mg tablet, sites on the Internet commonly promote and sell 5 mg for this purpose (Box 4.8).[634] More recently, a prostaglandin analogue, bimatoprost, used to treat glaucoma is being used for 'eyelash rejuvenation' as one of its side effects is the growth of the eyelashes. It is not licensed for this indication, although may be prescribed 'off–label'. However, it is illegal to promote a prescription only medicine to the public and the MHRA has recently warned companies in the UK for illegally promoting its use for cosmetic purposes.[1141,1142]

i See references 1130–1137 for further studies that have researched the burdens on health from the use of these drugs around the world.

7.5 Drugs to change the shape/contours of the skin

It is not known how many people in the United Kingdom use drugs such as botulinum toxin or dermal fillers to change the shape/contours of the skin. However, since January 2010 there have been more than 200 cases where the MHRA has warned companies (such as beauty salons, rejuvenation clinics and dental practices) which have illegally advertised botulinum toxin products to the public.[1143–1161] This, along with media reports and interest, suggests that there may be considerable interest in using these types of products.

7.5.1 Botulinum toxin products

Botulinum toxin products are used to treat wrinkles and lines on the face. Injected into muscle botulinum toxin products block the signals from the nerves to the muscle, so that it can no longer contract; the muscle relaxes, and the wrinkles relax and soften. The effects last about three to four months.[1162] Tests of botulinum toxin products obtained from the illicit market have found many did not have the potencies that were stated on the labelling. Some were found to contain no toxin, others were under–potent, while others had potencies greater than that listed on the labelling. This included two products from separate studies which both had a measured potency of more than 350% of that stated on the label. In at least one case no information was provided on recommended dosages. Over–potent products pose a serious hazard and have led to severe, life–threatening harms through poisoning (Figure 19).[533–537]

Figure 19. 'Botulinum toxin products sold on the illicit market[534]

Some of these products also contained gelatine although the source and type were unidentified. As this is not a recognised component of licensed botulinum toxin products, the harms this poses are unknown, although allergic reactions to gelatine have been reported. It is also possible that some of the products contain excipients of human origin. Use of unregulated sources from animal products used in these drugs could pose a risk of transmission of spongiform encephalopathies (such as 'mad cow disease'). While those from human sources could pose a risk of transmission of blood borne viruses and other infections.[534]

7.5.2 *Dermal fillers*

Dermal fillers are injectable products made from a range of synthetic, animal and human products. They can contain absorbable and non–absorbable substances.[1163–1166] Most of them work by bulking out the skin. They are used to reduce the appearance of wrinkles or folds, and smooth the skin, but can also be used to 'plump out' the lips. The effects of some of the commonly used products last for around six to 12 months. Concerns have been raised after untrained people have administered these products as improper injecting technique can cause damage and infections (§4.7).[i] While there has been little study of the composition and safety of products on the illicit market, untested and adulterated products have been sold. In some cases these have caused serious harm. Similar to botulinum toxin products found on the illicit market, the use of unregulated sources for products derived from animals or humans in dermal fillers also poses a risk of serious infections. Other harms include chronic inflammation, allergic responses, as well as distortion and migration of the filler.[1163–1166]

i In 2010 the president of the British Association of Aesthetic Plastic Surgeons suggested that members of the Association 'have seen an alarming number of patients with clinically significant harm from injection of fillers into the wrong site', although the figures have not been published.[1167] For a discussion of the regulation of medical devices in the United Kingdom, see references 231 and 1168–1172.

Table 7. Examples of drugs used to enhance the appearance of the skin and hair.

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated Drugs detected
Drugs to lighten skin colour										
'Cosmetics' containing mercury compounds (sold as 'beauty', 'bleaching' or 'freckle' creams)	Blocks the production of melanin in the skin	Topical	Case reports. Enforcement/ Seizures. Internet forums. Media reports	Untested. Banned in cosmetics	POP Popular Facial Cream 4 g £2.77 (1% mercury, approximately 3% mercury compound)	N/A	Applied as required	✓	✓	✓
'Cosmetics' containing hydroquinone (sold as 'beauty' or 'lightening' lotions/creams)	Blocks the production of melanin in the skin	Topical	Case reports. Enforcement/ Seizures. Internet forums. Media reports	Untested. Banned in cosmetics	Carolight Cream Jar 300 ml £9.00 Hydroquinone (max, 2%)‡ Skin Light Cream 500 g £12.00‡‡	N/A	Applied as required	✓	✓	✓
Corticosteroids	Blocks the production of melanin in the skin	Topical	Case reports. Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine. Not licensed for skin lightening	Clear white cream (Clobetasol propionate 0.05% cream) 100 g for £4.50 = £0.05 per g Dermotyly (Clobetasol propionate 0.05% cream) 30 g for £5.00 = £0.16 per g	Clobetasol propionate 0.05% cream 30 g for £2.69 = £0.09 per g	Applied as required	✓	✓	✓

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated Drugs detected
Drugs to darken skin colour										
Melanotan II (MTII)	Increases the production of melanin in the skin*†	Injectable/ Nasal	Case reports. Enforcement/ Seizures. Internet forums. Media reports	Untested	10 mg vial for injection for £21 = £2.10 per mg 20 mg nasal spray for £50 = £2.50 per mg	N/A	1mg per 100 kg of bodyweight per day 4 sprays of nasal spray (1 mg)	✓	✓	No studies. However, none of these products are licensed medicines
Drugs used to increase the growth of hair										
Bimatoprost (prostaglandin analogue)	Increases the growth of the eyelashes	Topical eyedrops	Enforcement/ Seizures. Internet forums	Prescription only medicine	Bimatoprost' 3 ml eyedrops (300 μg/mL) for £16.66–£33.29 = £5.55–£11 per 1 ml	Lumigan® 3 ml (300 μg/mL) for £10.30 = £3.43 per 1 ml	1 drop	Unknown	Unknown. Adverse reactions reported from therapeutic use	✓
Finasteride	Increases the growth of scalp hair	Oral	Enforcement/ Seizures. Internet forums	Prescription only medicine. Only 1 mg tablets are licensed for treating hair loss	Finasteride' 30 × 1 mg tablets for £19 = £1.57 each 'Finasteride' 30 × 5 mg tablets for £24 = £0.80 each	Propecia® 28 × 1 mg tablets for £26.99 = £0.96 each	1-5 mg per day	Unknown	Unknown. Adverse reactions reported from therapeutic use	✓

Name	How it works	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated Drugs detected
Drugs to change the shape/contours of the skin										
Botulinum toxin products	Causes muscle relaxation that results in wrinkles relaxing and softening	Injectable	Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine. Not licensed for cosmetic use	'Botox' 100-unit vial for £207–268 = £2.07–2.68 per unit	Botox® 100-unit vial for £138.20 = £1.38 per unit	N/A. Unit doses are not interchangeable between products.	✓	✓	✓
Dermal fillers	Bulks out the skin, reducing wrinkles	Injectable	Internet forums. Media reports	Medical device	£55+ (depending on product)	N/A	N/A	Visual inspection only	✓	✓
Others										
Isotretinoin	Reduces sebum secretion. Used to treat acne	Oral	Internet forums	Prescription only medicine. Special restrictions placed on prescribing as it is a teratogen	'Isotretinoin' 30 × 10 mg capsules for £24–£47 = £0.80–£1.56 each 'Isotretinoin' 30 × 20 mg capsules for £30–£54 = £1.00–£1.80 each	Roaccutane® 30 × 10 mg capsules for £14.54 = £0.48 each Roaccutane® 30 × 20 mg capsules for £20.02 = £0.66 each	20-80 mg per day	Unknown	Unknown (Adverse reactions reported from therapeutic use)	✓

Prices on the illicit market provide an indication only. Many sites offer considerable discounts when drugs are bought in bulk. Self-directed dose used by consumers provides an indication only.
*Acts on the central nervous system. †Also used as an aphrodisiac and to suppress appetite. ‡EU recalled product of 120ml contained 4.67% of hydroquinone. ‡‡EU recalled product contained 4.3% of hydroquinone.

8. Drugs used to enhance sexual function and behaviour

This section examines some of the drugs being used to enhance sexual function and behaviour. They include drugs to enhance (normal) erectile function as well as aphrodisiacs that increase sexual arousal and desire (Table 8). Little is known about the use of these types of drugs in the United Kingdom.

8.1 Overview

Up until 1998 the only available treatments for erectile dysfunction were penis pumps, prosthetic implants and surgery. The only approved medicines were penile suppositories or had to be injected into the penis. These treatments were not widely accepted by men or their partners.[1173–1178] The situation changed in March 1998 when sildenafil (marketed by Pfizer under the trade name Viagra®) was approved in the United States to much media fanfare on both sides of the Atlantic. The drug was the first effective oral therapy for treating erectile dysfunction.[1179–1192] It rapidly became a social and cultural phenomenon[27,62,830–832,1189] (in the decade after the launch of the drug, the word 'Viagra' has appeared in the Daily Mirror on average once a week[i]), with its use extending beyond medical treatment by an increasing number of men (Box 8.1). The drug was licensed in the European Union, including the UK, seven months later. Even before this there were media reports of its sale on the illicit market, including its recreational use in nightclubs, where Coke and 'poke' [Viagra] apparently made 'a great combination'.[1188] Some private clinics providing the drug on private prescriptions noted that they were 'overwhelmed' by the response to the drug. Subsequently, two further drugs tadalafil and vardenafil have been approved that work in a similar way to sildenafil. Together these drugs are known as phosphodiesterase type 5 inhibitors (PDE5i). Tadalafil has earned the nickname of 'the weekend pill' or 'le weekender' because its effects can last up to 36 hours compared to four to eight hours for sildenafil and vardenafil.[1193] These drugs do not act as aphrodisiacs and require sexual stimulation to work.

i The ukpressonline.co.uk database of the Daily Mirror archive was searched on 26 February 2012 using the term 'viagra' between 1 January 1998 and 1 January 2008 which resulted in 575 hits. The first was from 29 April 1998, entitled 'Men's sex pill 'miracle'', while the last was from 10 December 2007 'Inside Strictly'.

Box 8.1: Is Viagra® used as an enhancement drug?

A study that looked at Viagra® prescriptions in the US between 1998 and 2002 found that the fastest growing group of consumers were men aged 18–45, while the proportion of men with erectile dysfunction prescribed the drug decreased over the study period. This suggests that Viagra® may be used more for non–medical reasons. The study also found an increase in prescribing for young women.[907]

In the past few years a number of untested drugs, such as melanotan II and bremelanotide, with suggested effects on sexual behaviour and function, have been sold on the illicit market. These have been sold for injection and as nasal sprays. There is limited data on the effects of these drugs in humans. There is some evidence to suggest they cause spontaneous erections as well as increase sexual desire and arousal.[573–587,1194–1211]

8.2 Steven, 22 years old

Steven is a third–year student at university. Over the past six months he has been using 'Viagra' occasionally to enhance his sexual performance. He finds it particularly useful after a drinking session when, combined with using condoms, he has had trouble getting and keeping an erection. However, he knows very little about the drug. Most of what he knows comes from discussion forums on dance music websites. Here other users claim that the drug is 'really safe'.

Figure 20. 'Kamagra' purported to contain sildenafil which is the active substance in Viagra. Seized by Merseyside Police.

His friends are aware that he uses the drug, and of the glowing reviews that he gives it. He occasionally sells it to them as well. Recently he came across a site selling 'Kamagra' (Figure 20) which is far cheaper. He did some research on the drug and found that it is a generic product made in India. The site selling the drug offers significant discounts when it is bought in bulk. Four tablets cost £6.50 each, but if he buys 200 they work out at £0.74 each. Steven suggests to his friends that they all chip in and buy 200 tablets to share (Box 8.2).

Box 8.2: Comment on Steve

Because Steven is buying the drugs from the illicit market he has no way of knowing what they actually contain. Many studies have shown that these types of drugs are commonly adulterated. In some cases this has led to severe, life–threatening illness and death.[548–555]

8.3 *Who uses & why?*

Despite limited study, there appears to be great interest in the use of these types of drugs. Shortly after sildenafil was licensed in the UK, surveys found that it was used recreationally by men who have sex with men and by nightclubbers (including women) (Box 8.3 & 8.4).[830–832,836–838] These drugs appear to be more popular as time goes on.[837,838] Recently a large Internet survey of men from the United Kingdom, Germany and Italy found that just over 3% of around 12,000 men had used the drugs in the last six months without a prescription (the average number of tablets purchased was 13). Just over 50% had obtained the drugs from Internet sites, similarly just over 50% had obtained them from friends, partners or other acquaintances (multiple answers were possible). Two of the most common reasons why they obtained the drug without a prescription was because they were too embarrassed to speak with a doctor or thought that buying them online would be the cheapest way to get hold of them (see Table 8 for prices; see also §3.4). Unfortunately it is not clear from this study why these men were using the drugs (was it purely 'enhancement' reasons or as self–medication to treat erectile dysfunction?). The survey estimated that this could mean more than six million men in the EU got these drugs from the illicit market, however it is not known if the respondents were representative of the general population.[654] Nonetheless, recent seizures and prosecutions by authorities in the UK do suggest that there is a huge market for these drugs (Box 3.8). Tellingly, these types of drugs are the most counterfeited group of medicines seized by customs agencies in the EU.[500–504]

The reasons why people use these drugs have not been studied in detail. However, surveys in other countries found that they were used because of curiosity, peer pressure, to increase sexual confidence, erection quality, prevent premature ejaculation, increase pleasure and for better sexual performance. Some of these reasons may have included reversing temporary erectile dysfunction caused by condom use, prescribed drugs, alcohol or other recreational drugs.[1212–1226] It is likely that many of these reasons apply to people using them in the UK. There has been little research on the benefit in healthy individuals.[699,1227]

Aside from anecdotal reports on Internet discussion sites, media reports and medical case reports, there is no information on how many people use drugs such as melanotan II and bremelanotide nor their reasons for using the drugs. However, it appears that the main reason for use of melanotan II is to get a 'skin tan' (§7.2).

Box 8.3: 'Viagra' use in men who have sex with men in London

Just over six months after sildenafil was licensed in the UK a survey in London gyms of 677 men found that almost 15% had used the drug. Most of these had used it more than once, with many using it in combination with other drugs. Some 83% used the drug 'recreationally'.[836]

Box 8.4: 'Viagra' use in readers of Mixmag

An annual survey of the drug habits of readers of the Dance music magazine Mixmag found that between 1999 and 2003 there was a year–on–year increase in the number of participants who reported ever using 'Viagra' (sildenafil), as well as those who had used in the previous month. In 1999 just over 3% and 1% of males and females, respectively, had ever used the drug, while in 2003 it was almost 17% and 13%. Use in the last month in 1999 was around 1% and 0.2% in males and females, respectively, while in 2003 it was around 6% and 2%. Despite limitations in the design of the survey, it appeared that 'Viagra' was becoming more popular in this group.[837,838]

8.4 What do we know about the harms?

Sildenafil, tadalafil and vardenafil have well–established safety profiles when prescribed within their approved indications. However, there are specific cautions and contraindications.[1128,1129] They are contraindicated in HIV positive individuals being treated with the anti–retrovirals saquinavir and ritonavir. This may be of importance given the high prevalence of erectile dysfunction reported by HIV–positive individuals and the relatively high usage of these drugs by men who have sex with men.

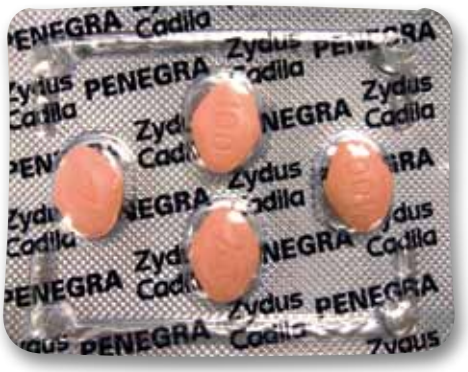

Figure 21. 'Penegra' purported to contain sildenafil which is the active substance in Viagra. Seized by Merseyside Police.

These drugs are also contraindicated with volatile nitrates/nitrites, such as poppers, which are used recreationally as well as nitrates used as a medical treatment.[1230] Studies have shown that these drugs are used together for recreational reasons. This can cause serious harms. One of the greatest risks is from the use of adulterated and untested drugs bought from the illicit market (Figure 21, 22).[459] Importantly, this market appears to be an important source of the drugs in the UK.[654] More recently there has been a large growth in the number of food and herbal supplements sold as sexual enhancement products. Many of these have been found to contain untested analogues of sildenafil, tadalafil and vardenafil.[390,392] These are not declared on the packaging/labelling. In 2009 adulterated 'herbal supplements' as well as counterfeit tadalafil, sold in Singapore and Hong Kong, caused serious harm in more than 220 people, 13 of whom subsequently died (§4.3).[548–555]

Figure 22. 'Viagra' seized by Merseyside Police

The harms posed by drugs such as melanotan II and bremelanotide are unknown because of their limited testing in humans. Because these products are injected, consumers could be at risk from harms including infections caused by unsterile drugs and from poor injecting practices (§4.7).

Table 8. Examples of drugs used to enhance sexual function and behaviour.

Name	Overview	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Phosphodiesterase type 5 inhibitors (PDE5i)										
Sildenafil citrate	Increases blood flow to the penis causing erection	Oral	Surveys. Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine	'Generic Viagra' 10 × 100 mg tablets for £13.31 = £1.33 each	Viagra® 4 × 100 mg tablets for £23.50 =£5.88 each	1 tablet 60 minutes before sexual activity	✓	✓	✓
Tadalafil	Increases blood flow to the penis causing erection	Oral	Surveys. Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine	'Generic Cialis' 10 × 20 mg tablets for £42.41 = £4.24 each	Cialis® 4 × 20 mg tablets for £26.99 = £6.74 each	1 tablet 30 minutes before sexual activity	✓	✓	✓
Vardenafil hydrochloride	Increases blood flow to the penis causing erection	Oral	Surveys. Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine	'Levitra' 10 × 20 mg tables for £41.33 = £4.13 each 'Levitra' 120 × 20 mg tables for £339.01 = £2.82 each	Levitra® 4 × 20 mg tablets for £23.48 = £5.87 each	1 tablet 25-60 minutes before sexual activity	✓	✓	✓

Name	Overview	Route of administration	Evidence of use	Legal status	Price on illicit market	Price in British National Formulary	Self-directed dose	Sale on illicit market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Analogues of α-MSH										
Melanotan II	Causes spontaneous erections and acts as an aphrodisiac.* Main reason for use appears to be for cosmetic 'skin tan'. Also used as an appetite suppressant	Injection Nasal	Enforcement/ Seizures. Internet forums. Media reports	Untested	10 mg vial for injection for £21 = £2.10 per mg 20 mg nasal spray for £50 = £2.50 per mg	N/A	1 mg per 100 kg of bodyweight per day 4 sprays of nasal spray (1 mg)	✓	✓ (related to use in order to get a skin tan)	No studies
Bremelanotide (PT-141)	Causes spontaneous erections and acts as an aphrodisiac*	Injection Nasal	Internet forums. Media reports	Untested	10 mg vial for injection for £21 = £2.10 per mg 20 mg nasal spray for £50 = £2.50 per mg	N/A	0.5–2 mg injected 2-3 hours before sexual activity 4 sprays of nasal spray (1 mg)	✗	✗	No studies
Others										
Yohimbe/ Yohimbine hydrochloride	Increases blood flow to the penis causing erection. It is also used for weight loss or to 'burn' fat	Oral	Surveys. Enforcement/ Seizures. Internet forums	Prescription only medicine	'Yohimbine - 5mg 100 capsules' for £26.99 = £0.27 each	N/A	2.5–60 mg	✓	✓	No studies

Prices on the illicit market provide an indication only. Many Internet sites offer considerable discounts when drugs are bought in bulk. Self-directed dose used by consumers provides an indication only.
*Acts on central nervous system.

Lightspring/Shutterstock.com

9. Drugs used to enhance cognitive function

This section examines the use of drugs to enhance cognitive function. Often called 'smart' or 'study' drugs these substances are used to enhance a range of functions including memory, concentration, perception, comprehension and alertness (Table 9). In the words of those using them, they 'increase mental energy', help with 'word finding' and 'hard thinking', 'help study', 'concentrate' or 'write a term paper', and they offset the effects of 'jet–lag'.[1231]

9.1 Overview

People have tried to enhance their cognitive functions using drugs for many years.[96,97,106,107,169] Caffeine, often in the form of coffee, energy drinks or pills, are often cited as a typical example. A broad range of herbal and food supplements are also used, most of which have little evidence to support their effectiveness in healthy people.[1232] The use of amphetamine as medicine in the United States from the 1930s onwards spread rapidly into the healthy population when university students started to use it as a 'study aid', particularly when 'burning the candle at both ends'.[819] Today it appears that stimulant medications for attention deficit hyperactivity disorder (ADHD)[218,219] as well as the wakefulness–promoting agent modafinil are becoming the 'smart' or 'study' drugs of choice (Table 9). However, little is known about the use of these types of drugs in the United Kingdom.

Box 9.1: Quotes from media interviews with UK students using 'smart' drugs

'I read an article in the student press on them,' says [Student A], a third–year arts student at Sheffield Hallam University. 'It was criticising them, but I thought they sounded great.' [Student B], similarly, found out about smart drugs through the media. 'I read an article in Nature on them,' he says. 'They seemed a pretty good idea.'

'Once I've taken a pill I can stay up all night without stopping. It just works so well,' says [Student C]. 'I need it."

—Newspaper interviews with UK students using 'smart drugs'

9.2 Julie, 20 years old

Julie is a second–year student at university. Her end–of–year exams are two months away. The pressures of student life—keeping on top of coursework alongside a hectic social life—have left her little time for revision. She is chatting with friends about her worries of failing her exams when Samantha, who is studying philosophy, suggests that she try 'modafinil'. She learnt about the drug during a lecture on 'cognitive

enhancement'. The lecturer had mentioned that it was widely regarded as a safe drug by most researchers and had been used in 'numerous' studies 'with really good effects'. 'Some of the professors I know use it on a fairly regular basis,' he had quipped. After the rest of her friends have left, Samantha admits to Julie that she has been using the drug 'on and off' for the past six months. 'Why not? It's safe and it works really well'. She buys the drug from an Internet shop based in the UK which is popular with other students. She found the site by googling 'buy modafinil'. She follows the shop on her Twitter feed to keep up to date with when the drug is in stock and any special offers that the site runs. Samantha says that she initially started with 100 mg per day, gradually increasing the dose to 400 mg. She wonders how she ever managed without it. Based on her experiences, she suggests that Julie try 200 mg per day for the next week and sells her seven days' supply for £20. 'After that if you like it then start using 400 mg'. One week later Julie is delighted as she has sailed through her revision timetable. They agree that in order to get a discount they will pool their money and buy a year's supply when Samantha next places an order (Box 9.2).

Box 9.2: Comment on Julie

While modafinil is commonly regarded as a 'safe' drug by those promoting its use as a cognitive enhancer, a recent review of its safety by the European Medicine Agency led to its restricted use as a medicine after links with serious skin reactions and psychiatric harms.[618] Moreover, there is currently little evidence to suggest that modafinil has any 'real world' benefits as a 'smart' drug.[1233]

9.3 *Who uses and why?*

In the past few years concern has been raised in the United Kingdom over the use of 'study' or 'smart' drugs. These include stimulants such as methylphenidate (Ritalin®) and the 'wakefulness promoting agent' modafinil (Provigil®). Aside from straw polls (Box 9.3)—which may provide snapshots of use but are not representative of the wider population—only one survey, conducted at a Welsh university in 2009, has examined the use of these drugs in the United Kingdom. It found that out of 505 students, around 1% had used prescription stimulants not prescribed to them to stay awake, while just over 0.5% had used them to study (the drugs that they used were not specified).[929] These findings, along with media reports, appeared to indicate that the drugs were being used by some individuals and that there might have been broader interest in using them (although this remains to be confirmed by formal research). There are seemingly 'natural' user groups for these kinds of drugs, as indicated by the focus of the media (and of researchers in other countries) on university students, and, more recently, on school children (although it is difficult

to see who could not benefit from them). However, while some of these drugs have shown some positive effects in highly controlled trials and laboratory test situations, their 'real world' benefits are largely based on personal anecdotes.[219,1233] It is also possible that while some improve performance in certain tasks, they may reduce performance in others; in some cases they may even lead to overconfidence in performance. Similarly, while some drugs may increase short–term memory, they may impair episodic memory.[219,1233] However, it appears that some people are not waiting for the verdict on whether these drugs bring real benefits to their everyday life, nor if they are safe (Box 9.4).[219,1231,1233–1235]

Box 9.3: Straw polls. Do people use 'smart drugs'?

'A Varsity survey, completed by 1,000 students [out of 5,000], had revealed that one in 10 Cambridge students had taken drugs such as Modafinil, Ritalin and Adderall. Meanwhile one–third of respondents admitted that, given the opportunity, they would take concentration–enhancing medication.'[1235]

'Look who's doping'

'Nature ran its own informal survey. Some 1,400 people from 60 countries responded … One in five respondents said they had used drugs… to stimulate their focus, concentration or memory… The most popular reason for taking the drugs was to improve concentration. Improving focus for a specific task (admittedly difficult to distinguish from concentration) ranked a close second and counteracting jet lag ranked fourth behind 'other' …'

Our question on frequency of use… revealed an even split between those who took them daily, weekly, monthly, or no more than once a year. Roughly half reported unpleasant side effects, and some discontinued use because of them… one–third of the drugs were purchased over the Internet. The rest were obtained from pharmacies or on prescription. In the few respondents from Britain that answered this question (n=14), all but one reported the Internet as their source.[1231]

Box 9.4: Selling 'smart' drugs – marketing material used on Internet shops selling modafinil

'Modafinil is being subscribed [sic] by many physicians to millions of people for 'off–label' or 'lifestyle' uses, including: Fatigue experienced by people who need to be awake and alert for extended amounts of times such as soldiers, truckers or students cramming for finals.'

'FOX NEWS confirms study shows DOCTORS perform better surgery when using Modafinil' — Tweet from an Internet shop selling modafinil in the UK.

'Wake up to increased alertness and concentration with Modafinil… Time to improve your memory – SAFELY

In countries such as the United States there is little doubt that the fallout from over-medicalisation—such as soaring diagnosis of childhood and adult ADHD where the principal therapy is potent stimulants such as methylphenidate or amphetamine–based drugs—is fuelling use of 'smart' drugs. The informal and formal trade particularly between university students and school children leads to widespread diversion of these drugs.[218,219] It is unclear if a similar situation is emerging in the United Kingdom. There are rising rates of ADHD diagnoses and some indication from grey literature reports and the media that diversion is occurring.[923] While these observations need to be confirmed, diversion is likely to be an important source of these drugs as the stimulant drugs such as methylphenidate are controlled drugs both in the UK and internationally. This may limit their sale, particularly on the Internet. It is also unclear to what degree diverted drugs in the UK are used as study drugs or recreationally, although, in common with other countries, there is likely to be some overlap.[218,219]

9.4 What do we know about the harms?

There have been few studies of the long–term effects of these types of drugs when used as 'smart' drugs.[219] Much of what we know is based on their use as medicines. Amphetamines, for example, have well established physical and psychiatric harms including the potential to cause dependence.[819] Similar concerns apply to methylphenidate (§4.8).[649] As the drug is not licensed for use in adults, we know little about the safety of the drug with this age group. In some cases, such as atomoxetine (sold online as 'Ritalin equivalent' or 'generic Ritalin'), there is a link with increased risk of suicidal thoughts, psychosis and mania.[1236,1237] Modafinil is commonly regarded as a 'safe' drug by those promoting its use as a cognitive enhancer. However, a recent review of its safety by the European Medicine Agency led to its restricted use after links with serious skin reactions and psychiatric harms were reported (§4.5).[618] Monitoring of the use of 'smart' drugs will be required to better understand the harms from their non–medical use.

Table 9. Examples of drugs used to enhance cognitive function.

Name	How it works	Route of administration	Evidence of use	Legal status	Price on black market**	Price in British National Formulary	Self-directed dose	Sale on black market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Modafinil	Promotes wakefulness*	Oral	Internet forums. Media reports	Prescription only medicine	'Modalert 200 mg' 10 tablets for £24.99 = £2.49 each 'Modalert 200 mg' 30 tablets for £26.82 = £0.89 each	Provigil® 200 mg 30 tablets for £105.21 = £3.51 each	200–400 mg per day	✓	Unknown. Adverse reactions reported from therapeutic use	Unknown
Methylphenidate hydrochloride	Stimulant*	Oral	Internet forums. Media reports	Prescription only medicine. Controlled drug	'Ritalin (Generic) 10 mg' 90 tablets for £123.74 = £1.37 each 'Ritalin Novartis 10 mg' 90 tablets for £149.34 = £1.66 each	Ritalin® 10 mg 30 tablets for £5.57 = £0.19 each	10–20 mg per day	✓	Unknown. Adverse reactions reported from therapeutic use and recreational use	Unknown

Name	How it works	Route of administration	Evidence of use	Legal status	Price on black market**	Price in British National Formulary	Self-directed dose	Sale on black market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Atomoxetine hydrochloride	Blocks uptake of the neurotransmitter noradrenaline*	Oral	Unknown. Internet shops selling it as 'Ritalin equivalent' or 'generic Ritalin'	Prescription only medicine	'Axepta 10 mg' 10 'tablets' for £3.20 = £0.32 each 'Strattera 25 mg' 60 'pills' for £46.32 = £0.77 each	Strattera® 10 mg 7 capsules for £15.62 = £2.23 each Strattera® 25 mg 7 capsules for £15.62 = £2.23 each	Unknown	✗	Unknown. Adverse reactions reported from therapeutic use	Unknown
Adderall® (mixture of amphetamine salts)	Stimulant*	Oral	Unknown. Surveys in the United States report diversion to illicit market for recreational and for enhancement reasons.	Not licensed in the UK.† Controlled drug	'Adderall 30 mg' 60 tablets for £107.46 = £1.79 each	N/A	30–60 mg	✓	Unknown. Adverse reactions reported from therapeutic use and recreational use	Unknown

Prices on the illicit market provides an indication only. Many sites offer considerable discounts when drugs are bought in bulk. Self-directed dose used by consumers provides an indication only.
*Acts on the central nervous system. †Licensed in the United States and Canada.

10. Drugs used to enhance mood and social behaviours

This section examines the use of drugs to enhance mood and social behaviours. Such attempts are not new. Drugs such as alcohol, cannabis, tranquillisers, MDMA and 'legal highs' have all been used for these types of effects. The effects and harms linked to these drugs have been reviewed extensively elsewhere.[121,122] With the availability of a range of drugs, such as the Selective Serotonin Reuptake Inhibitors (SSRI), which include fluoxetine and paroxetine, people are finding new ways to enhance their 'mood', increase 'happiness', blunt feelings of disappointment, relieve anxiety, be 'more able to cope', and be 'better than well' (Table 10).[96,107] However, little is known about the non–prescription use of these types of drugs in the United Kingdom.

10.1 Steve, 56 Years Old

Steve is a graphic designer. Because of the recession, there have been job losses at his company. A key part of the business is pitching to clients, which is something that he has always tried to shy away from. However, his line manager has told him that as part of the restructuring he will have to give more presentations in the future. This worries Steve as even in small meetings with colleagues he tends to get quite nervous. When he has presented to larger audiences in the past he has ended up shaking, sweating and feeling like his heart was going to burst out of his chest. This has bothered him so much that he become unable to get his words out. It has shattered his confidence. Recently he read a magazine article about 'extreme shyness'. The article explained that doctors now thought that quite a large number of people suffered from a 'crippling' form of shyness called 'social anxiety disorder'. It then discussed the treatment options that were available to people who suffered from the condition. 'That's me,' Steve thinks. He goes to see his GP who suggests that he initially has some counselling to help deal with his anxiety. Steve is not convinced by this, in part because the article mentioned that there were 'good drug treatments' for the problem, but also because he doesn't want to discuss these problems with a stranger, 'face–to–face'. He does some research on the Internet and finds an online community where people with the problem discuss the drug treatments they use. He prints out a list of the drugs to take to his GP. However, she believes that he should try counselling first. Despondent, he decides to try the drug paroxetine which many people online say work well for them. He googles 'buy paroxetine' and finds a large number of sites selling the drug. The first site does not need a prescription to buy the drug. He decides to buy thirty 20 mg tablets to try over the next month.

Box 10.1: Comments on Steve

As Steve bought the drug from the illicit market he had no way of knowing if he was actually taking paroxetine. However, adverse reactions are reported with the drug. These commonly involve neurological, psychiatric and gastrointestinal problems. The drug can also cause erectile dysfunction and problems with ejaculation. Withdrawal from the drug can be severe. As Steve did not have this drug prescribed to him he might not have been aware of these effects. Nor may he have volunteered this information if he became ill and needed medical treatment (Box 4.6)[1238].

10.2 Who uses & why?

Around the world the over-medicalisation of mood and social behaviours has led to increasing numbers of people being treated with drugs such as SSRIs.[4,1239] It is has been suggested that growing numbers of these have no discernible disease.[1239] As with other drugs, such as sildenafil, over-medicalisation is likely to encourage more people to seek out these types of drugs. However, currently there is little information on people who are using these drugs to enhance themselves rather than being prescribed them as part of medical treatment. Moreover, there is little known about the effects of these drugs in 'healthy' individuals. Aside from media reports, a survey in 2010 found that out of just over 2,000 adults, 4% had shared drugs such as anti–depressants with other people.[928] While a study in 2009 at a Welsh university found that out of 505 students just over 15% had used prescription medicines not prescribed to them to help sleep, almost 9% to relieve anxiety, while just over 1.5% had used them to relieve depression. Meanwhile out of 111 staff, just over 12% had used them to help sleep, around 5% to relieve anxiety, while just under 1% had used them to relieve depression. Few of the drugs (around 4% in total for both students and staff) were bought from the Internet. Most were obtained from friends, housemates or other acquaintances.[929]

It is likely that this group of drugs has the potential for wide appeal to the general population.[96,106,107] While there is little evidence regarding the current extent of their use or of any dominant characteristics of their users, the potential market for the next generation of drugs to 'enhance' mood and social behaviour is likely to be considerable. It will further blur our current definitions and limited understanding of recreational drug users and enhancement drug users.

10.3 What do we know about the harms?

The harms posed by these types of drugs have been reviewed extensively elsewhere.[121,122] They include a range of physical and psychiatric effects including a risk of dependence (§4.8). Some are also linked to an increased risk of suicide. However, there have been few studies examining the effect in 'healthy' people. Much of what we know stems from their use as medicines to treat problems such as depression, social anxiety disorder, panic disorder, obsessive-compulsive disorder and anxiety. Monitoring of the use of these types of drugs will be required to better understand the harms from their non-medical use.

Table 10. Examples of drugs used to enhance mood and social behaviours.

Name	How it works	Route of administration	Evidence of use	Legal status	Price on black market**	Price in British National Formulary	Self-directed dose	Sale on black market confirmed by analysis	Harms from self-directed use	Adulterated drugs detected
Selective Serotonin Reuptake Inhibitors										
Paroxetine	Selective Serotonin Reuptake Inhibitor*	Oral	Internet forums. Media reports	Prescription only medicine	'Generic Paxil (Paroxetine) 20 mg' 30 'pills' for £33.07 = £1.10	Paroxetine 20 mg 30 tablets for £2.25 = £0.08 each	20-60 mg per day	✓	Unknown. Adverse reactions reported from therapeutic use	Unknown
Sertraline	Selective Serotonin Reuptake Inhibitor*	Oral	Internet forums. Media reports	Prescription only medicine	'Zoloft 50 mg (Low Dosage)' 60 tablets for £47.99 = £0.80	Sertraline 50 mg 28 tablets for £1.71 = £0.06 each	50–200 mg per day	✓	Unknown. Adverse reactions reported from therapeutic use	Unknown
Fluoxetine	Selective Serotonin Reuptake Inhibitor*	Oral	Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine	'Generic Prozac 60 mg' 30 tablets for £49.14 = £1.64 each	Fluoxetine 20 mg 30 capsules for £1.42 = £0.05 each	20-60 mg	✓	Unknown. Adverse reactions reported from therapeutic use	✓
Anxiolytics										
Diazepam	Reduces anxiety*	Oral	Enforcement/ Seizures. Internet forums. Media reports	Prescription only medicine	'Generic Valium' 10 mg 30 tablets for £84.22 = £2.80 each	Diazepam 10 mg 28 tablets for £0.84 = £0.03 each	15–30 mg per day	✓	✓	✓

Prices on the illicit market provide an indication only. Many Internet sites offer considerable discounts when drugs are bought in bulk. Self-directed dose used by consumers provides an indication only.
*Acts on central nervous system.

Losevsky Pavel/Shutterstock.com

11. Discussion

11.1 Overview

Across the globe, growing numbers of people are using a broad range of drugs to try to get a better body, empower themselves and increase their well being. Most of these drugs are obtained from the illicit market. Consumers risk serious harms from the potent effects that these drugs have, and, in the case of injectable drugs, from the way that they are administered (§4). This is magnified by the growing number of untested, banned or adulterated drugs as well as food, herbal or cosmetic products that contain active substances hidden inside them.[292–457] Little is often known about the risks untested active substance or drugs can have. However in some cases, such as n–nitroso–fenfluramine (§4.3), we know that they can cause serious harms,[439–457] while hidden active substances mean that consumers and healthcare professionals treating them will not be aware of their use. In the case of banned substances, we know that they pose unacceptable risks to health.[556–572] Some of the drugs and products that are adulterated, have caused serious injury and deaths (§4.3).[548–555]

These drugs can also harm our environment and increase inequalities in health (§3.1).[96–99,106,107,672–677] There is limited scientific evidence to support many of the claims made about the 'real world' benefits of these drugs in healthy people. Yet this vacuum has been filled with personal anecdotes, wishful thinking, hype and scams. Most consumers are unaware of the risks they face.

This phenomenon requires close public health scrutiny. Currently, there are large gaps in our understanding of this problem and our ability to respond to it. So far the response has largely been reactive, focussing on disrupting the supply of drugs and investigating outbreaks of harms linked to their use. Yet their availability is widespread and reports of harms continue to grow.

In part people are turning to these drugs because of the huge pressure they often face to improve themselves, to fit in, get a better body, to increase their well being and be 'better than well' (§3.2).[1–107] Growing (low–cost) manufacturing capacity in countries such as China and India, the globalisation of free trade and communication and transport networks, such as the Internet and express postal services, play a critical role in their spread by making it easy to learn about them and buy on demand.[136–151,668–671] The global nature of this market makes it particularly difficult to control and reduce supply.[658] In part this is because existing legal and regulatory systems are largely based on national law and are inadequate in a globalised, networked world (§3.3). Weak legal and regulatory systems in some countries involved in the trade of these drugs, as well as corruption and the involvement of

organised crime, exacerbate the problem.[650–653,660–662] Adding to this complexity are the minimal restrictions on importing and possessing these drugs for personal use.[i]

New drugs and related technologies continue to emerge all the time. Those involved in the illicit trade are quick to seize upon these innovations and sell them to their customers. This is reflected in the growing numbers of untested drugs that are sold (see for example 'selective androgen receptor modulators', §5.5, Table 5), as well as in the formulations that make them easier to use (such as tablets rather than injections) and consequently more acceptable to greater numbers of people.[ii] Recent examples include food supplements containing a potent growth hormone releaser,[484] and the synthetic tanning hormone, melanotan II, in nasal sprays.[483] Prior to these 'innovations' both had to be injected. In some cases these have even been disguised as 'all natural' products so that consumers will not be aware that they are even taking a drug (Box 4.5). Those involved in the illicit market will go to almost any length in order to boost their sales.

11.2 Next steps

From April 2013 Public Health England (PHE) will be responsible for leading on the design, delivery and maintenance of systems to protect the population against existing and future threats to health.[683] PHE will be working alongside other agencies and government departments which have a key role in preventing drug harms, such as the MHRA and the Home Office. Clarity of roles and responsibilities will be critical to ensure effective co–ordinated action to tackle this drug issue.

Three key areas for action are discussed below.

11.2.1 Understanding the nature and extent of the problem

Research is required to better understand this group of drugs. We need to know how many people are using the drugs, and what drives this behaviour (§3.2). Specific gaps in research are highlighted in Box 11.1.

Healthcare professionals including doctors, nurses and pharmacists need to be aware of this form of drug use and should be provided with guidance on how to deal with the issues raised in this report. This will include measures that will allow healthcare professionals to engage with

i Restrictions usually apply to most controlled drugs or small number of specific substances. In the latter case an order can be made under the Medicines Act 1968 that makes it illegal to import the substance. Usually such an approach has been used for herbal substances linked to serious harms (such as Kava Kava and Aristolochia which have both been used in weight–loss products).[1240,1241]

ii This is one of the lessons learnt from the availability of oral therapies, such as sildenafil, for erectile dysfunction (§8.1). Prior to 1998 the drugs that were used for this condition were either penile suppositories or had to be injected into the penis.[1173–1178] These were not widely acceptable as medical therapies. Not surprisingly they did not diffuse widely either as enhancement drugs. After sildenafil was licensed, growing numbers of men and women around the world have used these drugs to enhance their sexual performance (§8.2).[830–838,907,1212–1225]

patients to identify, treat, and report harms caused by these drugs. Much of this responsibility is likely to fall on primary care services, such as General Practices. Inevitably some will also fall on secondary care services (such as emergency and urgent care). More broadly we will need to find ways of engaging with other stakeholders including consumers, parents, teachers, and social workers to inform them of the issues and what they can do to minimise harm (Box 11.1).

11.2.2 Supply reduction

There are few restrictions on consumers buying these drugs (and importing them) for their own use.[223,224] Most are obtained from online shops, 'bricks and mortar' shops or dealers, as well as sold or given away by friends, family, partners, or other acquaintances. Enforcement action in the UK against retailers, or measures that aim to reduce the number of drugs that are diverted from prescriptions, may help reduce the overall supply. Yet these will only apply to the illicit market that is based in the UK. Increased manufacturing capacity in emerging economies, globalised free trade, communication and transport networks, such as the Internet and postal services, and demand from consumers, have allowed a global market to thrive. Its regulation is often beyond the UK's legal jurisdiction.[658]

Careful consideration will need to be given on whether bilateral, multilateral and international agreements, though difficult to accomplish, may be required to help stem the tide of these drugs. However, countries with inadequate legal and regulatory systems will always remain the weakest link.[660,661] These systems must be strengthened and corruption tackled if there is to be any useful progress. In this respect there are obvious overlaps with the broader illicit trade in medicines. However, significant barriers must be overcome at the international level, including the lack of consensus on how best to tackle this trade in general.[i] Failure to tackle this issue will also have a knock–on effect on policies designed to achieve the rational use of medicines across the globe. The irrational use of medicines places huge economic and health burdens on countries.[1242,1243]

Consideration will also need to be given as to whether the current legal and regulatory system for medicines and medical devices in the UK (harmonised under EU law) can respond effectively to this problem. Whether a product is legally classed as medicine, and therefore its manufacture, advertising and supply can be regulated, is decided on a case–by–case basis.[223] This administrative process is slow to respond to the growing numbers of drugs being sold and the creative strategies employed by retailers, such as selling drugs as 'research chemicals', 'not for human consumption' or as 'food' or 'herbal' supplements. In this

i This is all the more difficult with the emergence of new technologies that differ in their legal classification from country to country. For example dermal fillers are regulated as medicines in the United States while in the EU as medical devices.

respect there are similarities with the way in which new psychoactive substances (so called 'legal highs') are marketed in order to circumvent regulation under the medicine, food and consumer protection laws.[123,127,128,131] Interestingly, while many of these new psychoactives are used recreationally, some are also used for enhancement purposes as 'designer fat burners' in order to lose weight.[134,1019]

11.2.3 Demand & harm reduction

How do we deal with the pressures to be 'normal' or 'perfect'? How is this done while ensuring that the scientific communities and pharmaceutical/biotechnology companies continue to innovate and develop new medicines which are required by society, yet may also find 'dual uses' as enhancement drugs? How can the misinformation which stems from research studies, the media and online discussions be prevented? How can fraudulent claims made by retailers on the illicit market be counteracted?

What are the responsibilities of pharmaceutical/biotechnology companies to ensure that medicines are marketed and advertised appropriately? Inappropriate practices have, directly and indirectly, driven demand for some of these drugs both inside and outside of healthcare systems. Practices such as the illegal advertising of botulinum toxin products by private treatment centres, beauty salons and dentists are also likely to exacerbate the demand for these types of drugs (§7.5).[1144–1161] More generally we also need to know the impact of indirect advertising (e.g. 'look younger, feel fresher, rejuvenate…'). While these issues may be a particular problem in countries that allow direct–to–consumer marketing of medicines (such as the United States and New Zealand), the Internet is reducing barriers to this direct to consumer marketing for consumers in other countries. Research on this type of advertising suggests that 'more advertising leads to more requests for advertised medicines, and more prescriptions'.[1244] Advertising also appears to increase the early use of new drugs.[1244] What is not clear yet is if such advertising may affect self–directed drug use.[926]

How can the harms caused by these drugs be identified and reduced? What role can existing surveillance/monitoring systems and other data sources play? Pharmacovigilance systems,[i] as well as related early warning systems, could all play essential roles. Similarly, data from the National Poisons Information Service and Hospital Episode Statistics could also provide useful data. Consideration will need to be given as to how these systems can be optimised for this purpose, including how to overcome barriers to reporting by consumers and healthcare professionals. More broadly, a specific early warning system

i Such as the Yellow Card Scheme in the UK, EudraVigilance at the EU–level and Vigibase at the international level.

for this form of drug use may be required allowing new drugs, harms,[i] and trends to be identified by drawing together data from existing systems and other sources such as treatment centres, forensic and toxicology labs, law enforcement, literature reports, key informants, consumers and media sources (Box 11.1).

New ways of effectively communicating with consumers and the general public will need to be found in order to spread prevention and harm reduction messages as well as alerts on recalls and other harms once they have been identified (Box 4.10). Consideration should be given to the role of new media, including social networking sites, for the delivery of these messages.

11.3 Where do we draw the red line?

These drugs are forcing us to redefine health, well–being and the boundaries of healthcare. To rethink how we view our bodies, how they work, how we can change them and what it means to be human. People have always strived to enhance themselves. It is part of what makes us human.[96–107] However, despite the harms that have been highlighted in this report, it is possible that enhancement through drugs could benefit humanity. The key issue is how society can harness these benefits while minimising the harms. Ultimately, it is for society, informed by evidence, among other things, to decide if this form of drug use should be allowed. Such a debate would also have to include discussions on how we regulate drug use, and how we reduce the harms. These are not easy questions to answer, particularly since the use of drugs in healthy people to enhance themselves is a new science. Our existing legal and regulatory frameworks governing medicines and related technologies are not designed to address these kinds of 'enhancement' questions nor regulate their supply to the public. In this respect, consideration will also need to be given to how the different stakeholders view the risk posed by these substances—currently, in the case of medicines used to treat disease, regulators, healthcare professionals and the public often view the risks very differently.[1245–1247] Moreover, if there is a shift in the role of medicines from their primary roles as curative and palliative agents to one that is about providing an 'optimal', 'enhanced' life then there will be massive cost implications, some of which may fall on government or third–party insurers.[678]

While today much of the science does not match the hype, new technologies will continue to emerge that could provide significant benefits as well as serious harms. Demand for such technologies are likely to be high. It is also going to become easier for people to buy and use them. Already 'next generation' drugs and advanced therapies,

i Importantly in this respect pharmaceutical companies could play an essential role in making relevant data available to regulators and other public health agencies on the effects and harms of old, new and failed products that have emerged on the illicit market.

such as tissue–engineered products, somatic cell therapies and gene therapies are being tested and in some cases used. The claims made about these, particularly from illicit retailers, are likely to be even more misleading than those made about the drugs that are currently being used (such as CJC-1295 which stimulates the release of growth hormone (§5.2) and rimonabant which acts as an appetite suppressant) (§6). Huge profits will be made through these scams, while many consumers are likely to be seriously harmed.

Discussions will also be needed on how the inequalities caused by this drug use can be prevented. Will the poor be particularly affected? What about those who choose not to use these drugs? Will we end up with a two–tier society of 'non–enhanced' and 'enhanced'? Will this be the cause of (greater) discrimination? What do we do about this?

More urgently, what should clinicians and other prescribers do if faced with requests for these types of drugs tomorrow? Should they give in and prescribe them if the alternative is that people would turn to the illicit market with its banned, untested and adulterated products, lack of unbiased information and medical monitoring? It is worth noting that the current rationing of drug treatments for erectile dysfunction (such as sildenafil) on the NHS could possibly lead to consumers buying them from the illicit market.[678–682,1248,1249]

Both the interest in human enhancement and the use of drugs to achieve this are likely to continue to increase in the future. Currently there is limited research on this emerging issue. However, the market for such drugs and the harms reported from their use continue to grow. Society has many difficult questions to answer in this respect, including whether such drug use should be allowed, or even facilitated. Ultimately, the challenge to public health will be how to ensure that any benefits are equitable while the harms from such drug usage can be effectively and efficiently minimised in order to protect and promote health.

Box 11.1: Gaps in research

Research is required to:

- help us better understand this broad user group, including how many people are using these drugs; who is using; the motivations for use; the patterns of use; how people learn about the drugs; and where they buy them from
- examine the causes of this phenomenon, including the role of sociocultural and demographic changes (such as over-medicalisation, globalisation, and the media)
- identify the consequences of this form of drug use, including the harms to users, the impact on the environment and inequalities, but also the potential benefits
- allow the development of prevention programmes and harm reduction measures
- measure the impact and effectiveness of legislation, and more broadly, regulatory systems (as well as gaps therein) in both the UK and internationally
- assess how a drugs early–warning systems can reduce harm. This includes how drugs can be rapidly identified, trends in use tracked over time, as well as timely information exchange between regulators, policy makers and other stakeholders. Such systems can also be used to identify harms and disseminate them through rapid alerts. This will include studies that:
  - examine the structure of the illicit market and how it functions, including systematic test purchases of products along with detailed forensic analysis in order to develop profiles of the harms they pose; as well as monitoring of prescriptions and diversion of drugs to the illicit market
  - examine a system for identifying, reporting and monitoring harms caused by the use of these drugs. This will include how best to link the work of pathologists, toxicologists and analytical laboratories
  - identify drugs and related technologies in the early stages of development which may also be in demand for enhancement purposes


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Glossary

Acne conglobata
A severe form of acne characterised by abscesses and irregular scars.

Acne fulminans
A rare but severe form of cystic acne associated with sudden onset and fever.

Acromegaly
A chronic disease where the body produces an excess of growth hormone.

Adderall®
Brand name of amphetamine salts-based stimulant used to treat attention deficit hyperactivity disorder (ADHD).

Adenosine triphosphate (ATP)
A substance that is produced in the body that provides energy needed for cellular reactions.

Adrenal insufficiency
A condition where the adrenal glands do not produce enough of the hormone cortisol (and in some cases aldosterone). Also known as Addison's Disease.

Adulterated
Incorporates a range of defects in a drug (medicine) that may make its use harmful. It includes drugs that contain too much or too little active substance, the wrong active substance, contaminants or impurities (e.g. biological and chemical), or inactive or dangerous ingredients.

Amphetamine
A powerful stimulant of the peripheral and central nervous system.

Anabolic steroids
Synthetic substances related to the male sex hormones (androgens), capable of producing a range of effects including growth of skeletal muscle and the differentiation, growth and maintenance of the sexual characteristics in males.

Analogue
A compound that has similar structure to that of another one. While they share structural similarities their effects on the body may be very different.

Anaphylaxis
A potentially life-threatening allergic reaction that can affect multiple systems of the body.

Androgen
A natural or synthetic hormone that stimulates/controls the development and maintenance of male characteristics.

Anti-depressant
A drug used to treat depression.

Anti-oestrogen
A substance that blocks the effect of the hormone oestrogen in the body (such as tamoxifen). It is used in the treatment of breast cancer but also self-administered by anabolic steroid users to prevent or minimise the development of breast tissue (gynaecomastia).

Anti-retroviral
A drug used to treat infection by retroviruses, such as HIV.

Anxiolytic
A drug used to treat anxiety (such as the benzodiazepines e.g. diazepam).

Aphrodisiac
A substance or food that stimulates sexual desire and/or behaviour.

Aromatase inhibitor
A substance that blocks the production of oestrogen in the body (such as anastrozole). It is used in the treatment of breast cancer but also self administered by anabolic steroid users to prevent or minimise the development of breast tissue (gynaecomastia).

Atomoxetine
A selective noradrenaline uptake inhibitor used in the treatment of attention deficit hyperactivity disorder (ADHD).

Attention deficit hyperactivity disorder (ADHD)
A condition in which an individual may, amongst other symptoms, find it difficult to pay attention, have overactive behaviour, be impulsive or have all of these symptoms together.

Banned drugs
A drug that was licensed for use in the United Kingdom but has since been banned. Usually, this is because of safety concerns over the harmful effects of the active substance(s) it contains. It is illegal to manufacture, advertise or supply a banned drug in the United Kingdom.

Benign prostatic hyperplasia
An increase in the size of the prostate gland without cancer being present.

Bimatoprost
A prostaglandin analogue used to treat glaucoma. It is also used for 'eyelash rejuvenation' because one of its side effects is the growth of the eyelashes.

Biosynthetic
A product derived from processes conducted in the cells of a living organism.

Botulinum toxin product
A product containing botulinum toxin that is used to treat wrinkles and lines on the face. After it is injected into the muscle, it blocks the signals from the nerves so that the muscle can no longer contract. The muscle relaxes and so the wrinkles soften.

Bremelanotide (formerly known as PT-141)
A metabolite of melanotan II which is reported to cause spontaneous erections and act as an aphrodisiac.

Cannabis
Psychoactive preparations of the marijuana (hemp) plant, Cannabis sativa.

CJC-1295
A drug that stimulates the secretion of growth hormone in the body. It is not being developed as a medicine and its effects in humans are largely unknown.

Clenbuterol
A drug prescribed as a decongestant and bronchodilator. It is not licensed for use in the United Kingdom. It is also used by bodybuilders, among others, as an anabolic agent and weight loss drug.

Clinical trials
A type of research study that compares one treatment or drug with another.

Cocaine
A drug derived from coca leaves, which is used medically as a topical anaesthetic and illicitly for its euphoric and stimulant effects.

Corticosteroids
Synthetic version of the hormone cortisol, used in the treatment of inflammation.

Cortisol
A hormone produced within the adrenal glands and released in response to stress.

Cushing's syndrome
Hormone disorder caused by high levels of cortisol. This can be caused by taking a corticosteroid drug (such as in some skin lightening products).

Cycling
Practice where steroids are taken by users for a period of time (e.g. eight to 12 weeks), known as an 'on cycle', followed by a period of abstinence, known as an 'off cycle'.

Dermal fillers
Classed as medical devices, dermal fillers are made from a range of synthetic, animal and human products, and injected to bulk out the skin in order to reduce the appearance of wrinkles or to 'plump out' the lips.

Designer drug
A synthetic drug produced outside of the formal pharmaceutical industry and sold often with the purpose of circumventing detection and/or legal control by authorities.

Diazepam
A drug in the class of benzodiazepines, used in the treatment of anxiety.

Diethylene glycol
A toxic substance used as an excipient that has been found in inadequately tested and adulterated drugs.

Dihydrotestosterone
A potent androgen made in the body from testosterone. It is linked to male pattern baldness.

Dinitro-o-cresol
A drug structurally and pharmacologically related to DNP, but thought to be more potent.

Diuretics
Drugs used to increase the excretion of urine.

Dinitrophenol (DNP)
An untested drug sold on the illicit market for weight loss. It stimulates metabolism by stopping the powerhouses of cells, the mitochondria, from making ATP (adenosine triphosphate). This substance provides the energy needed for many cellular reactions. Instead DNP causes heat to be released from the mitochondria. This toxic effect is what causes weight loss.

Drug
Any substance or combination of substances that may be used with a view to exerting a pharmacological, immunological or metabolic action. For the purposes of this report, the term 'drug' and 'medicine' are used interchangeably.

Ecstasy
Common term for 3,4-methylenedioxymeth-amphetamine, (MDMA), a synthetic amphetamine analogue used illicitly for its mood-enhancing and mild hallucinogenic properties.

Elixir Sulfanilamide
An antibiotic medicine sold briefly in the late 1930s that used the untested excipient diethylene glycol which is toxic.

Ephedrine
A drug used to treat hypotension (low blood pressure) in anaesthesia, a decongestant and a treatment to widen the airways. Bodybuilders, among many others, also use it as a stimulant, appetite suppressant and concentration aid.

Erectile dysfunction
Persistent inability to achieve or maintain an erection for satisfactory sexual intercourse.

Ergogenic
Enhance physical performance or recovery.

Excipient
A pharmacologically inactive substance that is used in formulating a medicine.

Fenfluramine
An appetite suppressant that was banned in 1997 because of its link to serious cardiovascular harms.

Fibromyalgia
A rheumatic condition typified by muscular or musculoskeletal pain with stiffness and localised tenderness.

Finasteride
A substance that inhibits the enzyme in the body that converts testosterone to dihydrotestosterone (DHT). It is used to treat benign prostatic hyperplasia and male pattern baldness.

Fluoxetine
A selective serotonin reuptake inhibitor (SSRI) used to treat, among other conditions, depression. It is commonly known by the general public by the brand name Prozac®.

General Practitioner
A physician who is trained to provide primary health care within the community.

Gene therapy
Emerging treatments that use DNA to treat or prevent disease.

Genitourinary
Related to the system of reproductive organs and the urinary system.

GHB (gamma hydroxybutyrate)
A naturally occurring compound that was originally synthesised for use as an anaesthetic. It is used recreationally for its sedative and anaesthetic effects and used by others in an attempt to promote the release of growth hormone to enhance the structure and function of muscle.

GHRP-6
A substance used to stimulate the release of growth hormone in the body.

Glibenclamide
A substance found in some medicines that are used to treat diabetes.

Gynaecomastia
The growth of the glandular breast tissue in males thought to be caused by hormone imbalance between oestrogen and testosterone. It is a common side effect in those who use anabolic steroids.

Herbal Xenicol
Advertised as a safe herbal product and named to sound like the licensed weight-loss medicine Xenical®. Products labelled as 'Herbal Xenicol' have been found to contain the banned appetite suppressant sibutramine.

Heroin
A drug derived from morphine. Heroin is one of the most widely used illicit opioids because of its potency, availability, solubility in water and the speed with which it crosses the blood-brain barrier.

Hexarelin®
Brand name of examorelin, a synthetic peptide capable of stimulating growth hormone release in the body.

High-density lipoprotein (HDL)
Also known as 'good cholesterol', HDL carries cholesterol away from the cells and back to the liver, where it is either broken down or passed out of the body as a waste product.

Human chorionic gonadotrophin (hCG)
A hormone produced by the body during pregnancy. It is also sold as a weight loss product and used by anabolic steroid users to stimulate testosterone production in the body.

Human growth hormone (hGH)
A peptide hormone involved in the regulation of a diverse number of physiological processes including growth and fat metabolism. A biosynthetic version is known as recombinant human growth hormone (rhGH).

Hydroquinone
A topical bleaching agent used in treatment of melasma (a common skin condition of adults in which light to dark brown or greyish pigmentation develops, mainly on the face), but also self administered without a prescription as a skin lightening agent.

Hyperthyroidism
Condition where the thyroid gland is overactive. It can increase the rate of metabolism and cause a rapid heart beat.

Hypomania
A milder form of mania, often including symptoms of over-active, excited behaviour and irritability.

Illicit market
A market that functions outside the formal economy regulated by the State.

Insulin
A hormone produced by the pancreas and essential to the control of blood sugar and the metabolism of fat and carbohydrates.

Isotretinoin
An anti-inflammatory agent derived from vitamin A that is used to treat acne by decreasing the skin's production of the oily substance sebum.

Kamagra
Brand name for a range of medicines that contain sildenafil that is used in the treatment of erectile dysfunction. These medicines are not licensed in the United Kingdom.

Khat
The leaves and tender stems of the plant Catha edulis that are chewed or brewed as a drink to produce a stimulant effect.

Laxative
A substance that stimulates bowel movements.

Low-density lipoprotein (LDL)
Commonly known as 'bad cholesterol', LDL carries cholesterol from the liver to the cells. If there is too much cholesterol for the cells to use, it can build up in the artery walls, leading to disease of the arteries.

Licensed medicine/drug
A medicine that has been approved for marketing in the United Kingdom.

Licit market
Lawful, legitimate provision of goods within the formal economy regulated by the State.

Lignocaine
A local anaesthetic.

Lipid metabolism
The processes by which the body synthesises, utilises or breaks down lipids.

Marmola
A weight loss product sold from the mid-1910s until the early 1940s. It contained dried animal thyroid tissue as its active substance.

Mechano Growth Factor (MGF)
An untested analogue of insulin-like growth factor-I (IGF-I), used by bodybuilders, among others, to promote muscle repair and growth.

Melanotan I (afamelanotide)
A synthetic peptide that increases the levels of the pigment melanin in the body resulting in skin tanning.

Melanotan II
A synthetic peptide that increase the levels of the pigment melanin in the body resulting in skin tanning. It is also used as an appetite suppressant and aphrodisiac. It is an untested drug.

Metabolism
The chemical processes by which the body synthesises, utilises or breaks down substances.

Metabolites
Chemicals formed as part of the natural biochemical process of degrading and eliminating chemical compounds.

Methandienone/methandrostenolone
A commonly used oral anabolic steroid.

Methasterone
Anabolic steroid first synthesised in the late 1950s but never commercialised. Chemical analysis has identified it in 'dietary supplements' sold as 'Superdrol'.

Methylphenidate
A central nervous system stimulant used in the treatment of attention deficit hyperactivity disorder (ADHD) in children.

Mitochondria
The site for the production of high-energy compounds, such as ATP, in the cell.

Modafinil
A wakefulness promoting agent used in the treatment of narcolepsy. It is also used as a cognitive enhancer ('smart' drug).

Nandrolone decanoate
A commonly used anabolic steroid, administered by injection.

Nitroso-prodenafil
A designer drug containing both a sildenafil-type substance and a vasodilator.

N-nitroso-fenfluramine
An analogue of the banned appetite suppressant fenfluramine.

Nocebo
A harmful effect on health produced by psychological factors following the administration of an inert or active substance.

North West Public Health Observatory
A specialist team of analysts and researchers, providing high quality health intelligence to support policy makers and practitioners in improving the health of the population and reducing inequalities.

Obesogenic
Capable of causing obesity.

Orlistat
Licensed treatment for obesity. It works by stopping the body absorbing dietary fat.

Paroxetine
A selective serotonin reuptake inhibitor (SSRI) used to treat, among other conditions, depression. It is commonly known by the general public by the brand name Seroxat®.

Patent medicines
A range of medicines often of questionable quality and effects, particularly associated with the 18th to early 20th century.

PEGylated Mechano Growth Factor (PEG-MGF)
A modified form of Mechano Growth Factor with prolonged action. It is untested.

Peliosis hepatis
A rare condition where blood-filled sacs occur in the liver.

Pep pills
Pill that contains a stimulant, such as amphetamine.

Petri dish
A shallow dish used for the culture of microorganisms such as bacteria.

Pharmacoepidemiology
The study of the use and the effects of drugs in the population.

Pharmacotoxicological studies
Investigation and assessment of the toxic effects of drugs.

Pharmacovigilance
System that includes the detection and reporting of suspected adverse reactions to drugs.

Phenolphthalein
A form of laxative.

Phosphodiesterase type 5 inhibitor (PDE5i)
A group of drugs containing either sildenafil, tadalafil or vardenafil that are used to treat erectile dysfunction by increasing blood flow to the penis causing erection.

Placebo
A beneficial effect on health produced by psychological factors following the administration of an inert or active substance.

Progestin
Hormone found in oral contraceptives.

Prostaglandin
A fatty acid compound with hormone-like effects.

Provigil®
See modafanil.

Prozac®
See fluoxetine.

Psychoactive drug
A substance that when ingested affects mental processes, e.g. cognition or mood.

Psychotropic effect
An alteration in a person's perception, emotion, or behaviour.

Recreational drug
Psychoactive drug used to create or enhance pleasure or leisure activities.

Rimonabant
Banned appetite suppressant used for weight loss.

Ritalin®
See methylphenidate.

Ritonavir
An antiretroviral drug used in the treatment of HIV infection.

Roid rage
Term used to describe aggressive or violent behaviour in anabolic steroid users.

Rosacea
A condition where the blood vessels in the face can enlarge, giving a flushed appearance to the nose and cheeks.

Saquinavir
An antiretroviral drug used in the treatment of HIV infection.

Selective Androgen Receptor Modulator (SARM)
Synthetic non-steroidal androgens.

Selective Serotonin Reuptake Inhibitor (SSRI)
A class of antidepressant drugs including fluoxetine.

Serostim®
See human growth hormone.

Sibutramine
Banned appetite suppressant used for weight loss.

Sildenafil
A substance found in some medicines that are used to treat erectile dysfunction, for example Viagra®. It is a Phosphodiesterase type 5 inhibitor.

Smart drug
Common term to describe drugs used to enhance cognitive function.

Somatic cell therapy
Treatment involving the insertion of a gene into a non-reproductive cell in a patient causing the production of a naturally occurring protein/substance that was either missing before or did not function properly. Can also be used to over-produce the protein/substance.

Spironolactone
A diuretic, used to increase the excretion of urine.

Spongiform encephalopathy
A group of progressive conditions that affect the brain and nervous system, such as Creutzfeldt–Jakob disease and 'mad cow disease' (bovine spongiform encephalopathy, BSE).

Stacking
Practice where steroid users will typically take two or more different steroids at the same time.

Stalinon
A drug from the 1950s used to treat boils but was found to contain a neurotoxic substance.

Stimulant
Any substance that activates, enhances, or increases neural activity.

Superdrol
See methasterone.

Supraphysiological levels
Amounts greater than normally found in the body.

Sustanon 250®
A common anabolic steroid administered by injection, containing four different types of testosterone with different durations of action.

Synthetic drugs
A drug made by chemical synthesis.

Synthetic peptide hormone
Manufactured hormones such as melanotan I and melanotan II.

Systemic
Relating to or affecting the entire body.

Tadalafil
A substance found in some medicines that are used to treat erectile dysfunction, for example Cialis®. It is a Phosphodiesterase type 5 inhibitor.

Tamoxifen
An anti-oestrogen used in the treatment of breast cancer but also self administered by anabolic steroid users to prevent or minimise the development of breast tissue.

Teratogen
An agent or factor that causes malformation of an embryo or foetus.

Testosterone
A hormone that stimulates development of male secondary sexual characteristics, produced mainly in the testes.

Thalidomide
Drug used to treat morning sickness in pregnancy but was not sufficiently tested and caused serious birth defects.

Therapeutic dose
Amount of drug required to provide the correct effect.

Thyroxine
Hormone produced by the thyroid gland, involved in regulating metabolism.

Tissue-engineered products
Products derived from living cells or tissues, which may be used for the regeneration, repair or replacement of tissue.

Toxicological actions
Poisonous effect of a substance.

Tranquillisers
A drug used to reduce tension and anxiety and promote relaxation.

Unlicensed drugs
A drug that has not been licensed for marketing in the United Kingdom.

Valium®
Brand name of diazepam, a benzodiazepine used in the treatment of anxiety.

Vardenafil
A substance found in some medicines that are used to treat erectile dysfunction, for example Levitra®. It is a Phosphodiesterase type 5 inhibitor.

Vasodilator
A drug which widens the blood vessels resulting in a decrease in blood pressure.

Viagra®
See sildenafil.

Virilization
The development of male physical characteristics (such as muscle bulk, body hair and a deep voice) in a female, or precociously in a boy, typically as the result of excess androgens.

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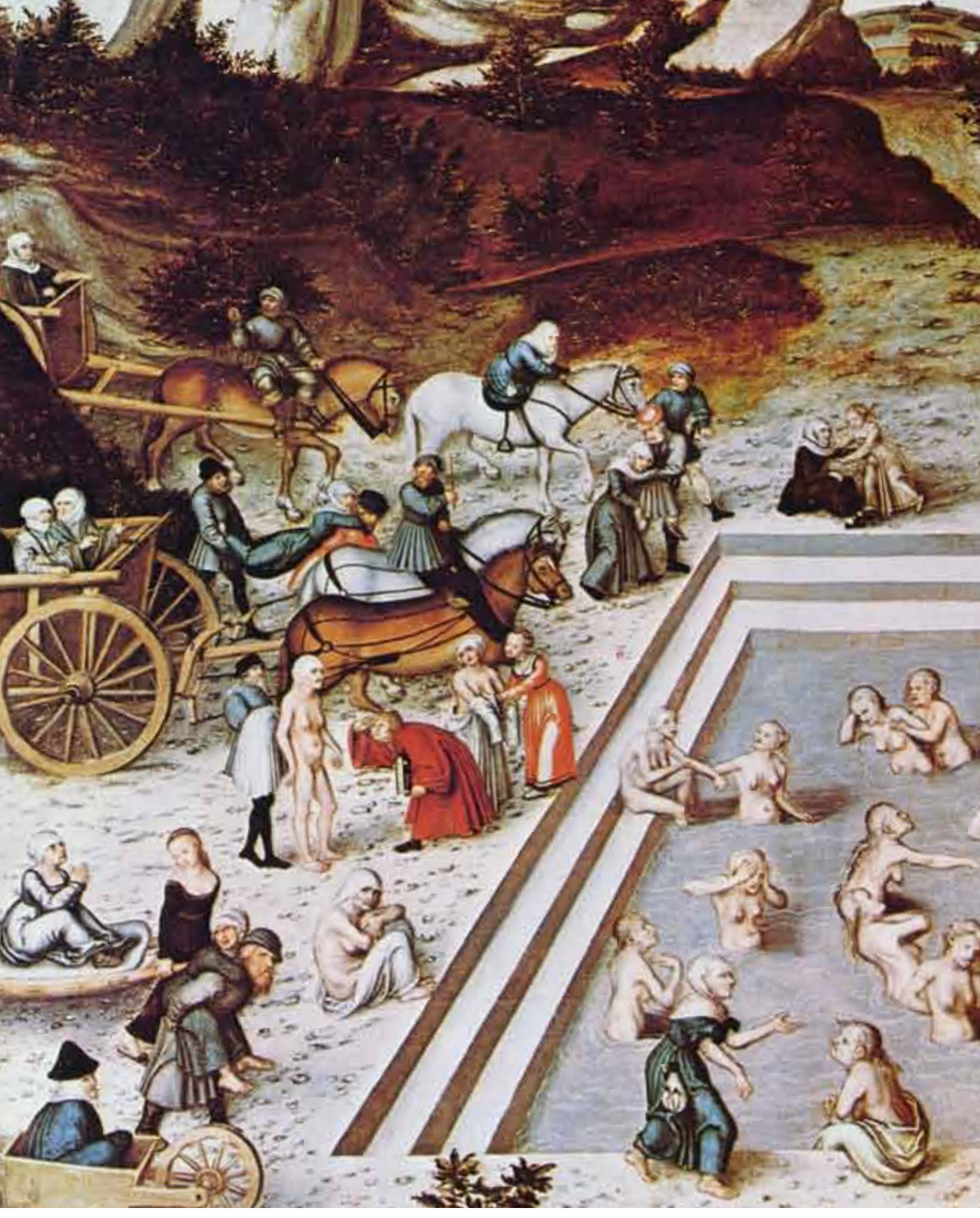

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