Appendix 3: Health-related harms of emerging and established licit and illicit drugs commonly used in the UK

Source: Jones L, Bates G, Bellis M et al (2011) *A summary of the health harms of drugs*. London: Department of Health.

Amphetamines*
Acute adverse effects associated with the use of amphetamines

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Excitation syndrome • Abnormal heart rhythms (arrhythmias) associated with collapse/cardiac arrest leading to sudden death **Vascular accidents** • Increase in blood pressure (hypertension) • Stroke • Heart attack (myocardial infarction) • Cardiovascular shock	**Acute intoxication** • Agitation/aggression • Pupil dilation • Headache • Tremors and writhing movements of the body and limbs (dyskinesia) • Nausea, abdominal cramps • Dry mouth • Sweating • Anorectic effects, decreased appetite • Increase in body temperature (hyperthermia) • Increased breathing rate, blood pressure and heart rate (possible arrhythmia) • Dizziness, tremor, irritability and confusion • Hallucinations • Convulsions *Methamphetamine* **Acute intoxication** • More pronounced CNS stimulant effects and longer duration of effect than amphetamine sulphate **Lifestyle factors** • Use strongly associated with risky sexual practices	**Organic/neurological** • Toxic delirium with amnesia • As stimulant effects dissipate, users may experience drowsiness, reduced ability to concentrate and/or judgement and learning impairment **Personality/mood** • Low mood (dysphoria) • Anxiety, depression • Irritability, aggression **Acute paranoid psychosis** • Psychotic reaction similar to acute paranoid schizophrenia (vivid visual, auditory, or tactile hallucinations, paranoid ideation possibly resulting in aggressive behaviour) • May develop after single or repeated ingestion of amphetamines • People with underlying mental problems are at greatest risk

* Including amphetamine sulphate and methamphetamine.

Chronic adverse effects associated with the use of amphetamines

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
Excitation syndrome • Abnormal heart rhythms (arrhythmias) associated with collapse/cardiac arrest leading to sudden death **Cardiovascular complications** • Inflammation of the blood vessels (vasculitis) • Aortic dissection • Cardiovascular shock **Other complications** • Depression leading to suicide	**Cardiovascular complications** • Cumulative risk of cardiac and coronary artery disease • Abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension) • Inflammation of the blood vessels (vasculitis) • Bleeding into and along the wall of the aorta (aortic dissection) **Lifestyle factors** • Negative health effects from lack of food and sleep, such as lower resistance to disease	**Organic/ neurological** • Cognitive deficits associated with damage to the nervous system and brain (eg impairment of memory, learning and monitoring of complex goal-directed behaviour [executive function]) • Behaviour stereotypes – mechanical hyperactivities, repetitive actions, stereotype motor phenomena (eg teeth grinding)	**Dependence** • High abuse potential due to mood-elevating properties • Good evidence for an amphetamine dependence syndrome • Typically occurs after a period of sustained regular use **Withdrawal** • Rarely life threatening • Symptoms may include depression (increasing risk of suicide), seclusiveness, craving, fatigue/exhaustion, weakness, lack of energy and sleep disturbance • Psychotic symptoms may also be a feature of the methamphetamine withdrawal syndrome

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	Complications in pregnancy • Use in pregnancy has been associated with low birth weight, prematurity and increased fetal morbidity • Confounded by the impact of other situational, health and lifestyle factors, and polysubstance use	**Chronic paranoid psychosis** • Psychotic reaction similar to paranoid schizophrenia – hallucinations, paranoid ideation, possibly resulting in aggressive behaviour, potentially reversible • Incidence and severity of methamphetamine psychosis is related to the frequency of use and injection or smoking as the route of administration • Symptoms usually resolve with abstinence, but case reports suggest some methamphetamine users may experience prolonged or recurrent psychosis, even after stopping use	**Tolerance** • Users may become tolerant to the euphorigenic, anorectic, hyperthermic and cardiovascular effects

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
		Personality/mood • Irritability • Suspiciousness • Dysphoria • Anxiety • Paranoid psychosis • Depression • Restlessness • Delirium • Depersonalisation • Feelings of persecution • Lethargy *Methamphetamine* **Personality/mood** • User reports of physical aggression	

Cannabis
Acute adverse effects associated with the use of cannabis

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
• No cases of fatal overdose have been reported • No confirmed cases of human deaths	**Acute intoxication** • Irritant effects of smoke on the respiratory system (coughing, sore throat and bronchospasm among people with asthma) • Facial flushing • Abdominal pain, nausea, vomiting • Can cause an increase in heart rate (tachycardia) and in some cases increased blood pressure (hypertension) • Difficulty in motor coordination and performance *Synthetic cannabinoids* • Not documented, limited evidence base	**Organic/neurological** • Perceptual distortion (hallucinations) • Amnesia/forgetfulness • Confusion of thought processes, impaired judgement **Personality/mood** The effects of cannabis upon mental state vary considerably between individuals; they are determined by dose, route of administration, expectations, concomitant use of other drugs, emotional state and psychiatric illness: • temporary psychological distress (especially naive users) • low mood (dysphoria) • anxiety • confusion • drowsiness • depression • panic attacks • agitation • symptoms indicative of a persistent and pervasive elevated (euphoric) or irritable mood (hypomanic symptoms)

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
		• short-lived and reversible psychotic reaction *Synthetic cannabinoids* **Organic/neurological** • Suggestion that overdose could include significant alterations in mental state with paranoia and perceptual distortions

Chronic adverse effects associated with the use of cannabis

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
Cancers • No conclusive evidence that cannabis causes cancer • Cannabis use may be an important risk factor for the development of respiratory cancers but the relationship is unclear[a] **Chronic respiratory disease**[a] • Chronic bronchitis • Lung damage • There are a number of reports in the literature of an association between cannabis use and bullous lung disease in relatively young users	**Cancers** • No conclusive evidence that cannabis causes cancer **Immune function** • Evidence for the effects of cannabis on human immune function is limited **Complications in pregnancy** • Like tobacco, cannabis use in pregnancy may be harmful to fetal development; studies show a consistent association between cannabis use in pregnancy and reduced birth weight – though less so than as a result of tobacco smoking during pregnancy	**Organic/ neurological** • No evidence of structural change in the brains of heavy long-term cannabis users • No severe or grossly debilitating impairment in cognitive function (subtle impairment in higher cognitive functions of memory, learning processes, attention and organisation and the integration of complex information – may or may not be reversible after abstinence)	**Dependence** • Good evidence for a cannabis dependence syndrome • Frequent, heavy users are at the greatest risk of dependence **Withdrawal** • Irritability • Anxious mood • Physical changes (tremor, perspiration and nausea) • Sleep disturbance **Tolerance** • Tolerance to psychoactive and physical effects is unlikely to occur unless there is sustained heavy exposure

[a] Studies of the harms associated with cannabis use are limited by confounding factors, as many users smoke tobacco as well as cannabis, or use tobacco as a vehicle for smoking cannabis resin. Although tobacco smoke and cannabis smoke are known to contain a similar range of mutagens and carcinogens, actual exposure to these compounds may differ between tobacco and cannabis users in terms of the frequency and duration of use, and because of factors such as the depth of inhalation.

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	• There are some reports that children born to women who have used cannabis in pregnancy may face mild developmental problems; however, the evidence is mixed and confounded by the other situational, health and lifestyle factors and polysubstance use in this population, eg cannabis users are more likely to use tobacco, alcohol and other illicit drugs during pregnancy **Reproductive disorders** • Use may inhibit reproductive functions and disrupt ovulation, sperm production and sperm function **Other complications** • Persistent sore throat	**Personality/mood** • Evidence that early initiation and regular, heavy cannabis use is associated with a small but significantly increased risk of psychotic symptoms and disorders in later life • Complex association between cannabis use and schizophrenia – some evidence that use may exacerbate psychotic symptoms and is linked with relapse but it is unknown whether this is a universal risk or due to differences in individual vulnerability • Insomnia, depression, aggression, anxiety	*Synthetic cannabinoids*

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
		• Inconsistent and mixed evidence for whether heavy, chronic cannabis use is associated with a persistent 'amotivational syndrome' characterised by social withdrawal and apathy	**Withdrawal** • Some evidence of a withdrawal syndrome among heavy users **Tolerance** • Suggestion that users may develop tolerance quickly

Cocaine*
Acute adverse effects associated with the use of cocaine

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Acute complications • Toxic reactions (eg cardiovascular complications) are not predictable from the route of administration, quantity taken, an individual's pattern of drug use, or blood concentrations of cocaine (or its metabolites) • Injection of cocaine powder or crack cocaine is associated with a greater risk of death than infrequent, intranasal use of cocaine powder alone; this appears to be linked to factors associated with injecting (such as more frequent use and higher levels of cocaine dependence) rather than the route of administration per se **Vascular complications** • Abnormal heart rhythms (arrhythmias) • Heart attack • Inflammation and injury to the intestines (mesenteric ischaemia) • Stroke	**Cardiovascular complications** • Increase in blood pressure • Accelerated heart rate • Abnormal heart rhythms (supraventricular/ventricular tachycardia, torsade de pointes) • Increased risk of heart attack, particularly in the first hour after use **Respiratory complications** • Chest pain • Shortness of breath • Rapid breathing **Neurological complications** • Stroke • Convulsions **Other complications** • Hyperthermia • Muscle spasms, tremor • Abdominal pain, nausea, vomiting • Insufficient blood flow (ischaemia) • Bleeding (haemorrhage) • Liver damage	**Personality/mood** • Sleep disturbance • Anxiety • Paranoia • Grandiosity • Transient psychotic reactions • Hallucinations (visual, auditory and tactile) after large doses • Aggression and possible violence (especially associated with crack cocaine use)

* Cocaine hydrochloride (eg cocaine powder) and cocaine base (eg crack cocaine and freebase cocaine).

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Allergic reaction from intravenous use of cocaine • Based on anecdotal citations – possibly caused by additives in street cocaine **Excited delirium syndrome** • Characterised by hyperthermia, delirium and agitation • Associated with cardiac/respiratory arrest and subsequent death	**Genitourinary** • Increased sexual appetite and desire	

Chronic adverse effects associated with the use of cocaine

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
Cardiovascular complications • Increased risk of cardiovascular disease through toxic effects on the cardiovascular system (including premature atherosclerosis, vasospasm and thrombus formation) • Heart attack • Heart failure • Abnormal heart rhythms (arrhythmias) • Aortic dissection • Inflammation and injury of the heart muscle (endocarditis, cardiomyopathy) • Sudden death	**Vascular complications** • Increased risk of cardiovascular disease through toxic effects on the cardiovascular system • Abnormally high blood pressure in the arteries of the lungs (pulmonary hypertension) • Inflammation and injury of blood vessels (vasculitis) **Neurological complications** • Stroke • Inflammation and injury of the blood vessels of the brain (cerebral vasculitis) **Renal complications** • Kidney failure – commonly associated with rhabdomyolysis	**Personality/mood** • Anxiety, depression • Obsessional rituals/ preoccupation, repetitive behaviours • Sleep disturbance (decrease in quantity and quality of sleep) • Irritability, restlessness • Auditory hallucinations • Paranoid delusions and psychosis • Hyperexcitability • Exhaustion • Aggression and possible violence (especially associated with crack cocaine use)	**Dependence** • Good evidence for a cocaine dependence syndrome • A minority of users may exhibit cocaine dependence soon after onset of cocaine use (in the first 1-2 years of use) – risk is greater among those who smoke crack cocaine and those who begin use at an earlier age **Withdrawal** Symptoms may be mild to moderate but the type and severity vary from person to person: • craving • exhaustion/lack of energy, fatigue • over-eating • depression • low (dysphoric) mood • unpleasant dreams

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
	Lifestyle factors • Anorectic effect – may contribute to malnutrition and weight loss • Chronic use diminishes sexual appetite and ability – reversible on stopping use **Localised effects** • Dental erosions • Perforation of the nasal septum • Chronic rhinitis • Loss of sense of smell • Nosebleeds **Complications in pregnancy** • Premature rupture of the membranes and placental abruption are associated with use during pregnancy	**Toxic syndrome** • Psychotic reaction similar to acute paranoid schizophrenia and psychoses with vivid auditory and tactile hallucinations, picking and excoriation of skin, delusions of infection from parasites, paranoid ideation **Neurological** • Studies have shown that chronic cocaine use may contribute to cognitive impairments in the group of processes involved in the learning, control and monitoring of complex goal-directed behaviour (executive function) • May include deficits in memory function and inhibitory control	• insomnia or hypersomnia, psychomotor retardation • agitation, irritability • anxiety, restlessness • aggression *Substance specific* **Withdrawal** • Craving – possibly of a greater magnitude for crack cocaine as compared to that for cocaine powder

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	• Effects of cocaine exposure may persist into childhood; suggestion that this may impact on behaviour problems, attention, language and cognition • Situational, health and lifestyle factors and polysubstance use in this population may also affect pregnancy outcomes		

Dissociative anaesthetics*
Acute adverse effects associated with the use of dissociative anaesthetics

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
Acute complications • Death is more often a result of accidents due to loss of coordination/ control, disassociation and analgesia (eg jumping from heights, road traffic accidents, drowning) • Risk of respiratory depression *Ketamine* **Acute complications** • The evidence base is limited, but there is a low risk of mortality associated with the medicinal use of ketamine • Rare reports of overdose deaths from heart attack or respiratory problems • The majority of fatalities have been attributed to polysubstance use (multiple drug toxicity)	**Acute intoxication** • Increased heart rate and respiration • Loss of consciousness, coma • Muscle jerking, repetitive movements, outbursts (automatic behaviour) • Gastric/stomach pain • Many effects are polarised among users (ie reports of opposing responses in different individuals) *Ketamine* **Injury** • Increased risk of injury from jumping from heights, road traffic accidents and drowning; associated with loss of coordination/temporary paralysis and/or dissociative effects (eg depersonalisation, derealisation and reduced perception of pain)	**Organic/neurological** • Hallucinations, distorted sensory perception • Impaired attention, memory and learning • Altered body perception • Impairments of cognitive function and verbal fluency **Personality/mood** • Confusion • Depersonalisation • Derealisation • Panic attacks, agitation, paranoia • Delirium • Depression • Night terrors • Behavioural effects resembling certain symptoms of schizophrenia • Extreme loss of motor skills (catatonia)

* Ketamine and phencyclidine (PCP).

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
PCP **Acute complications** • Substantially more toxic than ketamine • Death as a result of hyperthermia, convulsions	*PCP* **Acute intoxication** • Increase in body temperature (hyperthermia) • Stroke • Respiratory arrest • Nausea, vomiting • Loss of coordination (ataxia) • Hypersalivation	*PCP* **Organic/neurological** • Toxic psychosis (catatonia or paranoia)

Chronic adverse effects associated with the use of dissociative anaesthetics

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
• Very low risk of mortality	*Ketamine* **Chronic complications** • Ketamine-induced ulcerative cystitis (marked thickening of the bladder wall and severe inflammation) has been described in clinical case reports; only following heavy use • Vague abdominal pains (gastritis) *PCP* **Chronic complications** • No human evidence to suggest long-term physical damage • Evidence from animal studies of congenital malformations and reproductive disorders	**Organic/ neurological** • Memory impairment • Prolonged hallucinations, flashbacks, persistent perceptual changes **Personality/mood** • Night terrors • Evidence of triggering depression, post-traumatic stress disorder, or mania in susceptible individuals • May aggravate psychotic symptomatology	*Ketamine* **Dependence** • There have been few published reports of ketamine dependence; however, cases have been noted among regular, heavy users **Withdrawal** • No evidence to suggest withdrawal symptoms or syndrome **Tolerance** • Evidence to support the rapid development of tolerance over regular repeated dosing *PCP* **Dependence** • Evidence to suggest a dependence syndrome for PCP

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
		Ketamine **Organic/ neurological** • Evidence from animal studies suggests that ketamine may accelerate nerve cell death in the brain – no evidence that such an effect occurs in humans • Some evidence of cognitive impairments among regular, heavy users *PCP* **Personality/mood** • Anorexia • Insomnia • Auditory hallucinations • Disorientation • Paranoid delusions	**Withdrawal** • Some evidence to suggest withdrawal syndrome • Craving • Increased appetite • Hypersomnia • Depression

Gamma-hydroxybutyrate and gamma-butyrolactone*
Acute adverse effects associated with the use of GHB, GBL or 1,4-BD

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Acute complications • Loss of consciousness – difficult to get dose right and solutions of GHB often vary in concentration • Deaths solely caused by GHB appear to be rare – fatalities appear to be mostly in combination with alcohol or other CNS depressants	**Acute intoxication** • Loss of consciousness • Coma • Respiratory and cardiac depression, bradycardia • Hypothermia • Nausea, vomiting • Seizures • Confusion • Involuntary muscle twitching or spasm (myoclonus, dystonia) • Breathing difficulties • Agitation	• Limited evidence for the psychological/psychiatric effects of GHB, GBL and 1,4-BD **Personality/mood** • Agitation • Combativeness

*Gamma-hydroxybutyrate (GHB), gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD).

Chronic adverse effects associated with the use of GHB, GBL or 1,4-BD

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
Withdrawal • Severe cases of withdrawal, including fatalities have been reported	• Not documented	• Not documented	**Dependence** • Evidence of a dependence syndrome associated with heavy, frequent use • No dependence syndrome has been observed at low doses of GHB **Withdrawal** • Examples in the literature of physical dependence evidenced by a withdrawal syndrome • Anxiety • Insomnia • Increased heart rate (tachycardia) • Hallucinations, delirium and psychosis • Sweating • Aches • Abdominal pain • Impotence • Severe depression • Reports of severe withdrawal symptoms (eg rapid onset of delirium) associated with unplanned detoxification

Khat and *Salvia divinorum*

Acute adverse effects associated with the use of khat and *Salvia divinorum*

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
• Not documented, limited evidence base	*Khat* **Acute complications** • Dry mouth • Hyperthermia • Sweating • Aching **Cardiovascular complications** • Transient facial and conjunctival congestion • Increased heart rate (tachycardia) • Raised blood pressure • Heart palpitations (extra-systoles) • Myocardial insufficiency and cerebral haemorrhage through stimulation of adrenergic pathways **Gastrointestinal complications** • Constipation **Genitourinary complications** • Increased libido	*Khat* **Personality/mood** • Insomnia • Transient confusional states *Salvia divinorum* **Organic/neurological** • Hallucinations • Giddiness/dizziness • Confusion/disorientation

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
	Salvia divinorum **Acute complications** • Some users report experiencing physical and mental tiredness • Flushed sensation • Tachycardia	

Chronic adverse effects associated with the use of khat and *Salvia divinorum*

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
• Not documented, limited evidence base	*Khat* **Cardiovascular complications** • Transient facial and conjunctival congestion • Increased heart rate and raised blood pressure • Heart palpitations (extra-systoles) • Myocardial insufficiency and cerebral haemorrhage through stimulation of adrenergic pathways **Gastrointestinal complications** • Brown staining of the teeth, periodontal disease • Inflammation of the mouth and digestive system • Anorectic effect and delayed intestinal absorption; may contribute to malnutrition	*Khat* **Personality/mood** • Anxiety • 'Mood swings' (lability of mood) • Nightmares • Irritability, aggressive behaviour • Psychotic phenomena • Khat psychosis cases have been reported in the literature; individuals had recorded family histories of psychotic disorders **Organic/ neurological** • Cognitive dysfunction including disturbed perceptual-visual memory function *Salvia divinorum* • Not documented	*Khat* **Dependence** • Limited evidence for a khat dependence syndrome • Elements of ICD-10 stimulant dependence have been described among users including: compulsive consumption; tolerance; borderline withdrawal syndrome of tiredness, fine tremors and nightmares; craving and the urge to seek out khat are well known *Salvia divinorum* **Dependence** • Limited evidence base but one survey found little evidence of dependence among users

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	• Constipation – may lead to laxative abuse • Liver cirrhosis **Respiratory complications** • Increased prevalence of respiratory diseases including tuberculosis may be related to secondary malnutrition and heavy tobacco smoking **Reproductive disorders** • Limited evidence suggests that khat chewing during pregnancy may have an impact on fetal growth and development; low mean birth weights have been reported in some studies • No published evidence that khat causes teratogenic effects in humans		

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	• Limited evidence base for effects on male reproductive health but suggestion that use may be associated with decreased fertility *Salvia divinorum* • Not documented		

MDMA and related substances*

Acute adverse effects associated with the use of MDMA and related substances

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Overheating/heat stroke (hyperthermia) • Major acute symptom of MDMA-related toxicity that can lead to death • Associated with serotonin syndrome, and complications including rhabdomyolysis, abnormal blood clotting (disseminated intravascular coagulation), kidney failure and liver failure **Swelling of the brain (cerebral oedema)** • Caused by low sodium levels (hyponatraemia) secondary to water intoxication • Propensity for women to be disproportionately affected	**Acute intoxication** • Elevated blood pressure and increased heart rate (palpitations) • Nausea, vomiting • Fatigue, dizziness and/or vertigo • Overheating, dehydration • Headache • Dry mouth and throat • Loss of appetite • Difficulty with bodily coordination, muscle aches or tightness • Agitation/aggression • Convulsions	**Personality/mood** • Anxiety, panic attacks • Confusion • Depressive symptomatology • Insomnia • Restlessness • Fatigue • Anorexia • Paranoia • Visual and auditory hallucinations are rare – tend to be associated with high doses • Suggestions that use may have mild and transient effects on cognition after acute administration • Individual or unpredictable psychotic episodes may occur • Incorrect interpretation of emotions and other social cues

* 3,4-Methylenedioxymethamphetamine (MDMA; ecstasy) and related analogues, including 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyethylamphetamine (MDEA), methylbenzodioxolylbutanamine (MBDB), 3-methoxy-4,5-methylenedioxyamphetamine (MMDA), 4-methylthioamphetamine (4-MTA).

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Other complications • Fatal cases of liver damage are rare • A small number of case reports have linked the use of ecstasy with cerebrovascular accidents (eg stroke) • A few fatalities have been reported in the literature associated with the use of 'counterfeit ecstasy' containing paramethoxymethamphetamine (PMMA) and/or paramethoxyamphetamine (PMA) • Many MDMA-related fatalities are attributable to polysubstance use (multiple drug toxicity)	**Other complications** • May inhibit orgasm in men and women, and male erection • Examples of acute liver injury reported in the literature – may be secondary to hyperthermia or caused by direct drug toxicity • Associated with risk taking in general, and sexual risk taking in particular • Teeth grinding and clenching (bruxism)/teeth problems	*4-Methylthioamphetamine (4-MTA)* **Personality/mood** • 4-Methylthioamphetamine (4-MTA) has a greater propensity to cause visual hallucinations than MDMA

Chronic adverse effects associated with the use of MDMA and related substances

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
• Not documented, limited evidence base	**Immune function** • Emerging evidence that MDMA may have immunosuppressive properties – users report increased susceptibility to minor ailments including colds, flu and sore throats **Other complications** • Possible liver damage	**Organic/ neurological** • Unclear whether long-term use is associated with memory and learning (cognitive) impairment • Growing evidence that chronic, heavy use is most strongly associated with subtle cognitive effects • Unclear whether deficits reflect the use of MDMA or the combination of MDMA and other substances **Personality/mood** • Repeated use may have long-lasting effects on mood and personality characteristics, such as depression and anxiety, but evidence is inconsistent	**Dependence** • Evidence for a dependence syndrome is limited • In cases of dependence, the psychological aspects of dependence appear to predominate **Withdrawal** • Features of a withdrawal syndrome are not clearly defined and are mainly based on user reports **Tolerance** • Tolerance potential, but evidence is based on self-report

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
		Animal studies • An excess of serotonin in the CNS (serotonergic toxicity) has been demonstrated in experimental animal studies of MDMA • Inconsistent effects in humans – may result in increased risk of depression or other mental illness later in life but the equivalence is uncertain	

Nitrites*
Acute adverse effects associated with the use of nitrites

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Acute complications • Death may be caused by a lack of oxygen (hypoxia) resulting in severe injury to red blood cells and reduction in the supply of oxygen to vital organs • Users may lose consciousness and die through choking on own vomit • 'Sudden sniffing death syndrome' fatality caused by abnormal heart rhythms (cardiac arrhythmia) • Some cases of death have been reported from direct oral consumption of nitrites	**Acute intoxication** • Nausea • Headache • Loss of consciousness, sedation, anaesthesia • Loss of coordination (ataxia), weakness (less common) **Lifestyle factors** • Associated with high-risk sexual practices **Cardiovascular complications** • Profound hypotension (low blood pressure) • Rebound tachycardia • Flushed skin followed by vasoconstriction **Other complications** • Rash around the nose and mouth and contact dermatitis • Irritation of the nose and throat • Increased ocular pressure, blurred vision	**Personality/mood** • Disorientation • Distorted perceptions • Delirium

* Amyl nitrite, butyl nitrite and isobutyl nitrite.

Chronic adverse effects associated with the use of nitrites

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
Carcinogenic properties • Use produces nitrosamine which is carcinogenic – however it is still to be determined whether this is formed in sufficient quantities to make the risk clinically significant **Lifestyle factors** • Some evidence that, by facilitating unsafe sexual practices, use indirectly increases susceptibility to Kaposi's sarcoma in people who are HIV positive **Immune function** • Limited evidence that immunologic function may be suppressed – use of nitrites has been associated with facilitating the transmission of HIV	**Chronic medical problems** • Rash and irritation around the nose, mouth or other exposed areas • Sinusitis **Blood-related (haematological) complications** • Anaemia • Difficulty circulating oxygen through the blood stream (methaemoglobin-aemia)	**Organic/ neurological** There is some evidence to suggest impairment to: • cognition • movement • vision • hearing	**Dependence** • No evidence for a dependence syndrome **Withdrawal** • No withdrawal syndrome documented **Tolerance** • Evidence to suggest chronic, regular users may develop tolerance

Novel psychoactive substances*
Acute adverse effects associated with the use of novel psychoactive substances

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Acute complications • Substituted cathinones (primarily mephedrone) have been implicated in deaths in England and Scotland – however, with a limited evidence base, the exact role of cathinones in causing or contributing to death is still to be determined • One case of fatal overdose has been reported in the international literature relating to the use of 2C series phenethylamines • One case of fatal overdose has been reported in the international literature relating to the use of tryptamine derivatives	**Acute intoxication** • Few clinical data are available for novel psychoactive substances, most data regarding harms are self-reported • Chest pain is a common feature of acute intoxication *Substituted cathinones and piperazines* **Acute intoxication** Consistent with sympathomimetic toxicity: • agitation • palpitations • seizure • vomiting • sweating • headache • reduced appetite • severe vasoconstriction of the extremities, leading to bluing of the fingers or hands (cathinone users)	*Substituted cathinones and piperazines* **Personality/mood** Consistent with sympathomimetic toxicity: • mood swings • anxiety • strange thoughts • irritability, confusion *Substituted cathinones* **Organic/neurological** • High doses may be associated with hallucinations and psychosis *2C series phenethylamines* **Organic/neurological** • One case of acute intoxication associated with psychosis has been reported in the international literature *Tryptamine derivatives* **Organic/neurological** • Hallucinations

* Substituted cathinones, piperazines, 2C series phenethylamines and tryptamine derivatives.

Physical		Psychological/psychiatric
Morbidity	**Mortality**	
	2C series phenethylamines **Neurological complications** • One case of damage to the blood vessels in the brain associated with persistent neurologic deficits has been reported in the international literature *Tryptamine derivatives* • Not documented, limited evidence base	

Chronic adverse effects associated with the use of novel psychoactive substances

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
• Not documented	• Not documented	• Not documented	*Substituted cathinones and piperazines* **Dependence** • Suggestion that they are similar to amphetamine in terms of abuse and dependence potential **Tolerance** • Some evidence to suggest that substituted cathinone users may develop tolerance quickly

Opioid drugs*
Acute adverse effects associated with the use of illicit opioids and abuse of prescription opioids

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Overdose • Respiratory depression and drop in blood pressure resulting in respiratory arrest • Illicit opioid use is associated with the majority of illicit drug-related deaths in the UK, primarily from overdose **Common correlates of overdose fatality** • Long history of opioid dependence • High level of opioid dependence • Recent abstinence (eg prison, detoxification release) • Polydrug use (particularly with alcohol and benzodiazepines) • Being male • Increasing age (most fatalities occur among those in their 30s) • Social isolation • Neurocognitive deficits	**Common features of acute intoxication** • Nausea, vomiting • Depressed nervous system activity • Constipation • Drowsiness, decreased consciousness • Sedation, mental confusion **Infrequent features of acute intoxication** • Sweating • Facial flushing • Itching (pruritus) • Dry mouth • Hallucinations • Dysphoria • Difficulty in passing urine (urinary retention) **Rare features of acute intoxication** • Complications associated with non-fatal overdose eg hypoxia causing brain damage	• No acute psychological adverse effects • Cause little psychomotor or cognitive impairment in tolerant users

* Including illicit (ie heroin) and prescription (eg methadone, buprenorphine, tramadol, dihydrocodeine and oxycodone) opioids.

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
• While drug treatment generally provides a protective effect, there is a significantly enhanced risk in the first 2 weeks of methadone treatment, following detoxification treatment and on cessation of naltrexone treatment • Recent abstinence on release from prison	• Disease of the white matter of the brain (leukoencephalopathy) resulting from inhalation of heroin vapours, which does not seem to occur with injection; there are sporadic reports of cases in the literature *Prescription drugs* **Serotonin syndrome** • A few cases of tramadol use associated with serotonin syndrome, a potentially life threatening condition, have been reported in the literature	

Chronic adverse effects associated with the use of illicit opioids and abuse of prescription opioids

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
Overdose • Increased mortality risk from overdose and route-specific hazards **Suicide** • Suicide rate higher than in the general population; associated with situational, health and lifestyle factors	**Chronic complications** • Non-injected opioids carry little risk of chronic adverse health effects • Chronic constipation • Dry mouth • Menstrual irregularity • Malnutrition, anorexia; associated with situational, health and lifestyle factors • Tooth decay • Decreased sexual desire and performance **Respiratory complications** • Respiratory diseases (asthma, chronic obstructive pulmonary disease)	**Personality/mood** • Depressive disorder is common among those who are dependent on opioid drugs but it is difficult to attribute causality • Instability of mood • Lethargy • Opioid drugs are not causally linked to chronic psychiatric disorder	**Dependence** • Characterised by profound psychological and physical dependence • Develops after repeated administration over a period of time, which varies according to the quantity, frequency and route of administration – factors of individual vulnerability and the context of drug use also play a role **Withdrawal** • Rarely life threatening • Dependent on opioid used, dose, route of administration, the interval between doses, duration of use, and users' physical and psychological health

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	Hormones and immune function • Modest suppression of hormone levels • Suppression of immune system; social deprivation and malnutrition may also be factors **Complications in pregnancy** • Intra-uterine growth of the fetus may be inhibited • Neonates exposed to illicit opioid drugs may have low birth weight compared to non-exposed children, be born prematurely, and experience respiratory depression and withdrawal symptoms – these symptoms may contribute to the increased risk of perinatal mortality associated with use of illicit opioid drugs in pregnancy		• Symptoms include watery eyes, nasal discharge, yawning, sweating, sleep disturbance, dilated pupils, anorexia, gooseflesh, restlessness, irritability, tremor, sneezing, weakness, depression, nausea, vomiting, abdominal cramps, muscle spasms and diarrhoea **Tolerance** • Characterised by shortened duration and decreased intensity of the drug's depressant effects; there is marked elevation in the average lethal dose

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	Morbidity		
	• Evidence for a direct effect of illicit opioids is confounded by other situational, health and lifestyle factors (eg use of other drugs, mother's nutritional status, lifestyle, infections and exposure to trauma) that may be at least as decisive for the outcome of the pregnancy • Suggestion that a deprived social environment may also contribute to problems with neurological development		

Serotonergic hallucinogens*
Acute adverse effects associated with the use of serotonergic hallucinogens

Physical		Psychological/psychiatric
Mortality	**Morbidity**	
Acute complications • Risk of injury and accidental death owing to perceptual distortions and impaired decision making *LSD* **Acute complications** • One case of fatal overdose has been reported in the literature; associated with a high dose of LSD *Psilocybin* **Acute complications** • Fatal poisoning owing to mistaken identity of mushrooms	**Violence and injuries** • Self-harm, accidents or violence while intoxicated *LSD* **Common effects** • Adrenergic 'fight or flight' effects • Tachycardia • Flushing • Dry mouth • Sweating • Exhaustion, tiredness, weakness **Rare effects** • Ataxia • Convulsions • Hyperpyrexia *Psilocybin* **Acute intoxication** • Nausea, vomiting, stomach pains – commonly owing to mistaken identity of mushrooms • Dizziness *DMT* **Acute intoxication** • Nausea and vomiting	**Personality/mood** • Dysphoria • Unpleasant distortions in shapes and colours • Frightening illusions, delusions; 'true hallucinations' in psychiatric terms (ie indicative of psychiatric morbidity) are very rare • Anxiety, panic, depression • Dizziness, disorientation • Impaired concentration • Frequent mood changes (emotional lability) • Recall of psychologically troubling memories • Depersonalisation and derealisation at high doses • Short-lived psychotic episode (hallucinations, paranoia) • Precipitates relapses in schizophrenia

* Lysergic acid diethylamide (LSD), psilocybin, mescaline and *N*,*N*-dimethyltryptamine (DMT).

Chronic adverse effects associated with the use of serotonergic hallucinogens

Physical		Psychological /psychiatric	Dependence/ withdrawal/ tolerance
Mortality	**Morbidity**		
• Limited evidence base	• No known physical dangers associated with long-term LSD use	**Personality/mood**[a] • Persistence of low-level hallucinations, known as hallucinogen persisting perception disorder – rare • Brief flashbacks or recollection of previous hallucinatory experience may occur days or months after use • Depression • Feelings of isolation • Delirium **Psychosis** • It is uncertain whether this is a drug-induced condition or unmasking of a latent mental illness	**Dependence** • Evidence suggests that few users of hallucinogens experience signs or symptoms of dependence **Withdrawal** • A withdrawal syndrome has not been identified **Tolerance** • Tolerance develops rapidly to behavioural effects, and sensitivity returns after a comparable drug-free interval; tolerance to cardiovascular effects is less pronounced • Cross-tolerance between serotonergic hallucinogens

[a] Post-exposure.