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Psychiatric emergencies (part II): psychiatric disorders coexisting with organic diseases

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Abstract. – BACKGROUND: In this Part II psychiatric disorders coexisting with organic diseases are discussed.

"Comorbidity phenomenon" defines the not univocal interrelation between medical illnesses and psychiatric disorders, each other negatively influencing morbidity and mortality. Most severe psychiatric disorders, such as schizophrenia, bipolar disorder and depression, show increased prevalence of cardiovascular disease, related to poverty, use of psychotropic medication, and higher rate of preventable risk factors such as smoking, addiction, poor diet and lack of exercise.

Moreover, psychiatric and organic disorders can develop together in different conditions of toxic substance and prescription drug use or abuse, especially in the emergency setting population. Different combinations with mutual interaction of psychiatric disorders and substance use disorders are defined by the so called "dual diagnosis". The hypotheses that attempt to explain the psychiatric disorders and substance abuse relationship are examined: (1) common risk factors; (2) psychiatric disorders precipitated by substance use; (3) psychiatric disorders precipitating substance use (self-medication hypothesis); and (4) synergistic interaction. Diagnostic and therapeutic difficulty concerning the problem of dual diagnosis, and legal implications, are also discussed.

Substance induced psychiatric and organic symptoms can occur both in the intoxication and withdrawal state. Since ancient history, humans selected indigene psychotropic plants for recreational, medicinal, doping or spiritual purpose. After the isolation of active principles or their chemical synthesis, higher blood concentrations reached predispose to substance use, abuse and dependence. Abuse substances have specific molecular targets and very different acute mechanisms of action, mainly involving dopaminergic and serotoninergic systems, but finally converging on the brain's reward pathways, increasing dopamine in nucleus accumbens. The most common substances producing an addiction status may be assembled in depressants (alcohol, benzodiazepines, opiates), stimulants (cocaine, amphetamines, nicotine, caffeine, modafinil), hallucinogens (mescaline, LSD, ecstasy) and other substances (cannabis, dissociatives, inhalants). Anxiety disorders can occur in intoxication by stimulants, as well as in withdrawal syndrome, both by stimulants and sedatives. Substance induced mood disorders and psychotic symptoms are as much frequent conditions in ED, and the recognition of associated organic symptoms may allow to achieve diagnosis. Finally, psychiatric and organic symptoms may be caused by prescription and doping medications, either as a direct effect or after withdrawal. Adverse drug reactions can be divided in type A, dose dependent and predictable, including psychotropic drugs and hormones; and type B, dose independent and unpredictable, usually including non psychotropic drugs, more commonly included being cardiovascular, antibiotics, anti-inflammatory and antineoplastic medications.

Key Words:
Psychiatric emergencies, Anxiety disorders, Mood disorders, Psychosis, Comorbidity, Dual diagnosis, Substance abuse, Drug abuse, Substance addiction, Drug adverse reactions.

Abbreviations

ACE = angiotensin-converting enzyme
ADHD = attention deficit hyperactivity disorder
CNS = central nervous system
COPD = chronic obstructive pulmonary disease
CNS = central nervous system
ECG = electrocardiogram
ED = emergency department
EEG = electroencephalogram
GABA = gamma amino butyric acid
GHB = gamma hydroxybutyrate
GnRH = gonadotropin releasing hormone
GCS = Glasgow coma scale
HIV/AIDS = human immunodeficiency virus/acquired immune-deficiency syndrome
ICU = intensive care unit
IFN = interferon
LSD = lysergic acid

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MAOI = momoamino oxidase inhibitor
MDMA = 3,4-methylenedioxy-N-methylamphetamine
MR = magnetic resonance
NMDA = N-methyl-D-aspartate (receptor)
NRI = noradrenalin reuptake inhibitor
NSAID = non steroidal anti-inflammatory drug
PTSD = post-traumatic stress disorder
SNRI = selective serotonin/norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
THC = delta-9-tetrahydrocannabinol
VTA = ventral tegmental area

Introduction

The independent coexistence of psychiatric and organic disorders in the same patient results in the well known "*comorbidity phenomenon*". It defines the controversial interrelation between psychiatric disorders and organic diseases, each other negatively influencing morbidity and mortality. Indeed, concurrent or lifetime comorbidity phenomenon ranges from casual occurrence of psychiatric disorders and medical diseases, to the actual susceptibility of psychiatric patients to contract organic diseases, and vice versa.

Co-occurrence and mutual interaction of *psychiatric disorders* and/or *medical illness* and *substance* or *drug abuse* may also develop, causing diagnostic and therapeutic difficulty and significant legal implications[1]. Therefore, findings can vary depending on factors such as type of psychiatric and organic disorders and substance involved, making it necessary to differentiate whether clinical symptoms are primary, independent, or substance-induced, thus transient and treatable.

Co-morbidity of Psychiatric Disorders, Medical Diseases and Substance Abuse

Co-occurrence of Psychiatric Disorders and Medical Diseases

An alternative approach to "categorial" classification (DMS IV-TR and ICD-10) for definition of psychiatric disorders consists in the "dimensional" approach. This is based on the possibility that many psychiatric disorders present in a vague or episodic form, without satisfying the criteria for "categorical" disorders (so called subthreshold disorders). The dimensional approach allows to detect minor but clinically meaningful symptoms and adjust therapeutic approach, as integration of pharmacological and psycho-social approach, in proportion to its relevance[2].

The patient with *psychiatric disorder* who complains *medical illness* is disconcerted in relating his symptoms. Both the patient and the physician have great effort in diagnosing them as "real" or "unreal" symptoms. Most psychiatric disorders, such as schizophrenia, bipolar disorder and depression, are associated with undue medical morbidity and mortality. It represents a major health problem, with up to 30 year shorter lifetime compared with the general population, primarily due to premature cardiovascular disease. The causes of increased metabolic and cardiovascular disease in this population are strongly related to poverty and limited access to medical care, but also to the use of psychotropic medication. Moreover, the patients with severe mental illness have a higher rate of preventable risk factors such as smoking, addiction, poor diet and lack of exercise[3]. Anxiety and post-traumatic stress disorder (PTSD) seem to be interrelated with *heart diseases* in quite a similar way, contributing even more negatively to critical cardiologic events than depression. The prevalence rates of depressive disorders in various cardiologic conditions are significantly higher than the frequencies that can be expected in healthy general population[4]. A complex relationship is known even between psychiatric disorders and *respiratory illnesses*. Moreover, anxiety, depression and psychosis are considered significant causes of morbidity and mortality in patients suffering from COPD and asthma. Within *gastroenterological diseases*, mental illness and psychosomatic disorders have a main role either in therapy management or in patients quality of life, through the disease perception and its symptoms. Psychiatric patients are at high risk even for *hepatic* illnesses: because the diffuse substances abuse and addiction, they are more exposed to alcohol damage and infections by hepatic viruses and HIV. There is evidence that the association of *mellitus diabetes* and psychosis makes worse the prognosis both of psychiatric disorder and the metabolic disease. In the end, a mention deserves even *antipsychotics* because these drugs have a complex way of action and can manifest interactions with other drugs employed in different internal diseases and cause different side effects[5].

Otherwise, a patient with severe medical illness complaining psychiatric symptoms challenges in depicting their independent nature, or attributing a reactive significance (*somatopsychic disorders*), or recognizing the occurrence of drug side effects. Emergence anxiety, depression,

delirium and other acute psychotic manifestations affecting postoperative and ICU patients, cancer and HIV/AIDS patients, particularly elderly or adolescent patients, were discussed in Part I review.

Co-occurrence of Psychiatric Disorders and Substance Abuse: the "Dual Diagnosis"

Definition and Epidemiology

Concurrent or lifetime co-morbidity of *toxic substance abuse* (alcohol, heroin, cocaine etc.) and *psychiatric disorders* is high and subject of heated debate, without univocal conclusions on relative responsibilities ("what came first, the chicken or the egg?"), concerning the well-known "dual diagnosis" [6,7]. Indeed, this subset of pathologies present complex and particular features, due to the different combination of psychiatric problems, ranging from *casual coexistence* to *causal relationship*. Associations have also been found in the opposite direction, but retrospective and prospective studies both indicate that psychiatric disorders have a temporally primary age of onset in the majority of dual diagnosis cases. Although the full impact of primary psychiatric disorder is unknown, simulation studies have estimated that their early treatment or prevention might reduce up to 40% of cases of secondary substance dependence[8]. Effectively, in Western Countries the chances of lifetime developing a substance abuse is significantly higher among patients with a pre-existing primary psychiatric disorder, ranging from 21 and 72%, than in the general population without a psychiatric illness[6]. There is a statistically significant predominance of men, as well as a younger age. The substances most frequently used in dual diagnosis group are alcohol (78.1%), cannabis (62.5%), and cocaine (51.6%)[9]. On the other hand, a number of studies report a high prevalence of psychiatric disorders, namely mood and psychotic disorders, among heroin abusers (up to 90%), while anxiety, including PTSD, mood disorders and antisocial personality disorder prevail among cocaine abusers (about 50%). Finally, depression and anxiety disorders, namely panic, social anxiety and obsessive compulsive personality disorders, prevail among alcohol abusers (over 50%)[6,10,11]. Recent studies have confirmed causal relationship between major psychiatric disorders and concomitant substance abuse in 50-80% of forensic cases[1].

Etiopathogenetic Mechanisms

Several hypotheses have been advanced to explain the relationship between psychiatric disorders and substance abuse (dual diagnosis), exceeding the simple concept of the *independent coexistence*: (1) *common factors* (risk factors common to both disorders); (2) *secondary psychiatric disorder* (substance use precipitates psychiatric disorder); (3) *secondary substance use* (self-medication hypothesis); and (4) *bidirectional or synergistic interaction* (presence of either psychiatric disorder or substance use disorder can contribute to the development of the other)[7,12]. Firstly, individuals having a psychiatric disorder also may manifest biological vulnerability, caused by genetic and early stressful events. There is also evidence that social, economic, familial problems or traumatic life events can lead to both psychiatric disorders and substance abuse. Then, several evidences support a *causal link* between substance abuse, such as alcohol and cannabis, and later development of obsessive compulsive disorder and *psychosis*, respectively. Bipolar disorder and *anxiety disorder* also increased simultaneously with recent significant increase in cannabis use in Western Countries[13]. Moreover, patients complaining psychiatric symptoms could be incline to misuse or abuse substances in order to relieve their psychic (anxiety, depression) or somatic symptoms (insomnia, pain), and counter the negative side-effects of *antipsychotics adverse effects*, in line with the *self-medication* hypothesis[14]. Anxiety and unipolar mood disorders are associated with later onsets of substance use disorders. In particular, social anxiety disorder predicts onset of alcohol use disorders, and PTSD predicts the onset of all substance use disorders[13]. So, substances are not randomly chosen, but are specifically selected for their effects. Some studies show that nicotine administration can be effective for reducing motor side-effects of antipsychotics[15]. On the other hand, exposure to *psychiatric medication* is suggested to produce biochemical and anatomical alterations on CNS, potentially predisposing to toxic substance abuse.

Diagnostic and Therapeutic Concerns

Newly emerging psychiatric symptoms in the presence of substance abuse (or withdrawal) should be presumed to be "substance induced" until proven otherwise. Formally, in each case of co-morbidity, a psychiatric disorder should be di-

agnosed as independent only if its onset precedes the substance assumption, if it is not linked to its recent assumption (<1 month), if continues >1 month after its withdrawal. Although maybe its detection could be less complicated, it is usually easy to detect the abuse condition from history or from physical examination and toxicological tests.

Atypical antipsychotics are commonly used for concomitant schizophrenia and substance abuse. Whereas there is no difference between risperidone and olanzapine, clozapine appears to have a distinct advantage in reducing psychotic symptoms as well as substance abuse (including smoking). There is emerging evidence that quetiapine is beneficial in dually diagnosed patients, particularly using alcohol, cocaine and amphetamine. A combination of naltrexone and sertraline was found to be effective in patients with depressive disorder and alcohol dependence. Integrated intervention is the choice of treatment for patients with dual diagnosis[16].

Substance and Drug Induced Psychiatric and Organic Symptoms

General Concepts

Substance or drug abuse, or their withdrawal, can produce both *psychiatric* and *organic symptoms*, due to the damage on CNS, and gastroenteric, cardiovascular and endocrine systems other than the developing of deficiency states.

Historical Overview

Since the beginning of the world each society has selected natural substances that distorted the perception, mood or thought, for recreational, medical, military or spiritual purpose. In the Odyssey by Homer (Book IV), Helena "drugged the wine with an herb that banishes all care, sorrow, and ill humour." In popular comic books, Asterix's "magic potion" or Popeye's "spinach can" represent a masked version of doping usage. Australian and American aborigines used *nicotine* from their indigenous plants. Ethiopians and northern Africans were documented as having used an ephedrine-analogue from *Catha edulis*. Since Neolithic Era, people have cultivated and consumed *Cannabis sativa* and *Papaver somniferum* in Asian and European Countries, and *Erythroxylum coca* in the western Andes. *Mescaline*, alkaloid extracted from the *Peyote cactus*, was used for its psychedelic properties in religious ceremonies by Mexican natives. Finally, *alcoholic beverages* have been produced already in a remote past. The recipe for distilled wine dates about 1100 A.D., wine and alcoholic spirits being taken as an universal medicine. In an evolutionary theory, psychotropic plants evolved to emit allelochemical reactivity to deter threats from herbivores. These allelochemical responses evolved to imitate mammalian neurotransmitters. The fit of allelochemicals within the CNS indicates some coevolutionary activity between mammalian brains and psychotropic plants, meaning they interacted ecologically and therefore responded to one another evolutionarily.

These natural neurotransmitters analogues were not anciently so plentiful and potent to cause severe intoxication or to produce dependence. In modern era, isolation in pure form or chemical synthesis of active principles allowed their assumption in high doses, often intravenous, easily predisposing to abuse and addiction[17].

Frequently, toxic substance abuse is combined, and the physician must consider this occurrence because each substance may require specific treatment. Studies show up to 20% of alcohol-dependent individuals having problems of dependence and/or misuse of benzodiazepines. Alcohol is cross-tolerant with other sedative-hypnotics, increasing craving for benzodiazepines, but their combined assumption produces summarized life-threatening depressant effects (see below). Another common combination is represented by cocaine and heroin assumption (speedball), with the aim to enhance euphoric effects, to reduce withdrawal opiate symptoms, and to modulate irritability induced by cocaine. Benzodiazepines often are associated to methadone for increasing the excitement state. Alternatively, habitual cocaine and opiates users can assume benzodiazepines to mitigate anxiety symptoms, which occur during assumption or withdrawal, respectively. Experimental studies demonstrated that adaptation of the adenylate cyclase system following toluene repeated inhalation might be involved in the expression of behavioural sensitization to subsequent methamphetamine administration.

Main Psychiatric and Organic Symptoms Secondary to Substance and Drug Abuse

Anxiety disorders are common in intoxication by stimulants (cocaine, crack, amphetamines, ecstasy), and uncommon in intoxication by sedatives (opiates), except for alcohol. A paradoxical effect to benzodiazepines can occur, especially in elderly, producing anxiety manifestations. On the other hand, anxiety disorders commonly occur in withdrawal syndrome, both by sedatives (opiates, benzodiazepines) and by stimulants. The with-

drawal syndrome is due to: (1) substance withdrawn; (2) re-bound effect with hyperactivation of CNS; and 3) re-emergence of underlying anxiety disorder. Typical manifestation in any case are restlessness, psycho-motor agitation, craving till aggressive behaviours, generally associated to clear vegetative manifestations (insomnia, tachycardia, hypertension, sweating, nausea). In cases of suspected substance induced *mood disorders*, it is important to understand that many common organic symptoms of depression (e.g., fatigue, sleep changes, gastrointestinal problems) can arise as adverse effects of medications. Drugs with evidence of a link to depression include IFN-alpha, corticosteroids and digoxin. Likewise, many symptoms of mania (e.g., inattention, insomnia, excess motor movements) may occur as adverse drug reactions, such as antidepressants. The temporal relationship between use or withdrawal from the medication and the mood symptoms is crucial to formulate this diagnosis[18,19]. Substances with psychomimetic properties such as cocaine, amphetamines, hallucinogens and cannabis are widespread, and their use or abuse can provoke *psychotic reactions* resembling a primary psychotic disease, or disclose latent schizophrenia. The recent escalating use of methamphetamine throughout the world and its association with psychotic symptoms in regular users has fuelled concerns. Dependence upon and withdrawal from sedative hypnotics can be medically severe and, as with alcohol withdrawal, there is a risk of psychosis other than seizures if not managed properly[19,20]. Some studies suggest that only alcohol, antidepressants, benzodiazepines and cocaine are related to *aggressive behaviour*. Aggression as an adverse cannabis reaction is very rare and occurs in most cases in association with other drugs and in predisposed individuals.

Toxic Substances

Substances of abuse have specific molecular targets and very different acute mechanisms of action, but at the end they converge on the *brain's reward pathways*, increasing dopamine in *nucleus accumbens*, so producing a series of common functional effects after both acute and chronic administration (Table I)[21].

Depressants

The *alcohol* (ethanol) intake induces sedation and sleep. Low doses of alcohol produce comfortable sensation, with talkativeness and excitation, due to selective suppression of cerebral inhibitor systems. By high doses, sedative effects prevail with recent memory disorders (black out phenomenon) and potential development toward coma and death. The alcohol dependence syndrome ("alcoholism" in the past) presents a prevalence of 5-10% in West Countries, and is considered "the big simulator", for multiform individual clinical picture and its relation to blood levels. Anxiety symptoms may occur both in acute and chronic alcohol intoxication, associated to sadness and depressive signs of CNS. In withdrawal syndrome, anxiety symptoms are common (> 50% of cases), begin within 24 h from alcohol withdrawal, and combine with vegetative symptoms (insomnia, hypertension, tachycardia, sweating), tremor, restlessness, confusion state, visual hallucinations, seizures, till evolving toward the dramatic picture of "delirium tremens". This is a life-threatening condition if associated to infective, metabolic or traumatic comorbidities. Habitual consumers develop tolerance, and consequently physical dependence: to avoid withdrawal symptoms often they drink alcohol in the night and in the morning, to maintain high serum concentration[22].

Despite to their large prescription to treat anxiety disorders and insomnia, *benzodiazepines* rarely constitute abuse substance, except for multi-substance abuse disorders. Pharmacological tolerance to their sedative action develop after several weeks of assumption, while the tolerance to anxiolytic and other effects is controversial. Benzodiazepines acute intoxication can precipitate respiratory function (apnoea), which is enhanced by alcohol and opiates co-assumption and by preexisting pulmonary disease. Other common adverse effects in acute and chronic intoxication consist in asthenia, loss of muscle coordination, anterograd amnesia, headache, emesis, diarrhoea, dimming of the eyesight, articular and chest pain. Rare paradoxical psychiatric manifestations may occur during benzodiazepine use or abuse, the so called "disinhibition reaction". So, anxiety, euphoria, irritability, hypomaniacal and aggressive behaviour, or depression and suicidal ideation, and hallucinations may coexist with talkativeness, tachycardia and sweating. Prolonged use of benzodiazepines may produce somnolence, memory impairment, and daytime drowsiness. Moreover it may cause falls resulting in hip fractures and may result in motor vehicle accidents. Not severe, but prolonged withdrawal syndrome generally occurs after benzodiazepine interruption in abusers, more than regular prescriptional users. The clinical pic-

Table I. Main classes of commonly abused substances, their main specific molecular targets, and some of their mechanism by which they activate the dopaminergic and serotonergic systems, leading to increase dopamine in nucleus accumbens.

Drug	Target	Mechanism
Depressants		
Alcohol, benzodiazepines and barbiturates	Multiple targets, including GABA and glutamate receptors	Facilitate GABAergic neurotransmission, which may disinhibit VTA dopamine neurons from GABA interneurons or may inhibit glutamate terminals that regulate dopamine release in nucleus accumbens.
Opiates(morphine, codeine and heroin)	μ-opioid receptor	Disinhibit neurons of the mesolimbic dopamine pathway by inhibiting GABA interneurons, that contain μ-opioid receptors in the ventral tegmental area, or directly activate nucleus accumbens neurons that contain μ-opioid receptor.
Stimulants		
Cocaine, amphetamine, methamphetamine or ecstasy	Dopamine transporter	Block dopamine transporter on the terminals of dopamine projecting neurons of the mesolimbic dopamine pathway (cocaine, crack), or release dopamine from the vesicles of dopamine terminals (amphetamine, methamphetamine).
Nicotine	Nicotinic receptors (predominantly $\alpha 4\beta 2$ subtype)	Directly activates neurons of the mesolimbic dopamine pathway by stimulating their nicotine receptors, and indirectly activates them by stimulating the nicotine receptors in glutamatergic terminals to ventral tegmental area dopamine neurons.
Caffeine	Adenosine receptors (predominantly A2A subtype)	Inhibits adenosine A2A receptors interaction with dopaminergic transmission in the striatal GABAergic neurons projecting to the ventral pallidum, so decreasing GABA release in the nucleus accumbens.
Eugeroics (modafinil, adrafinil, and ampakines)	Multiple targets, including orexin trasmission, $\alpha 1$-adrenergic and glutamate receptors	Induce wakefulness by its action in the anterior hypothalamus, activating orexin neurons, which project to the entire CNS. Facilitate excitatory glutamatergic signalling and also amplify midbrain noradrenergic signals, cortical serotonin release and extracellular levels of dopamine, including the nucleus accumbens.
Hallucinogens		
Mescaline, psilocybin, LSD, ecstasy	Serotonin receptors	Enhance glutamatergic transmission in the cerebral cortex, responsible for the higher-level cognitive, perceptual, and affective distortions produced by these drugs, acting on serotonin receptors. The coeruleo-cortical noradrenergic system and the cerebral cortex are among the regions where hallucinogens have prominent effects.
Other substances		
Cannabinoids (marijhuana, hashish)	Cannabinoid CB1 and CB2 receptors	Regulate dopaminergic signalling through CB1 and CB2 receptors in nucleus accumbens neurons and in GABA and glutamate terminals to nucleus accumbens
Club Drugs o dissociatives (ketamine, gamma-hydroxybutyrate o GHB)	NMDA receptors (by ketamine) GHB receptors (by gamma-hydroxybutyrate)	Ketamine binds to the NMDA receptor, blocking calcium flow and increasing dopamine release in prefrontal cortex and midbrain. NMDA blockade has also been linked to activation of serotonin systems. GHB receptors have the highest density in the hippocampus, cortex, and dopaminergic areas (striatum, olfactory tracts, and substantia nigra). GHB acts increasing central dopamine levels, which could be associated with the reinforcing effects of GHB.
Inhalants or volatile solvents (toluene, benzene, chloroform, xylene, acetone, alkyl nitrites, butane, benzene, nitrous oxide, chlorofluorocarbons, halothane)	Multiple targets, including GABA receptors (predominantly GABAA subtype) and NMDA receptors (predominantly NR1 and NR2B subtypes)	Their anxiolytic effects depend on their positive modulation of GABA receptors. Induce subjective psychedelic effects blocking NMDA receptors. Increase dopamine levels in the prefrontal cortex, striatum and VTA, so producing their rewarding effects.

ture of withdrawal syndrome resembles alcohol withdrawal one[23].

Opiates (morphine, codeine and heroin) produce *analgesia* acting on thalamus, *sedation* on reticular substance and *euphoria* on limbic system, often described as intense pleasure like orgasm, associated to transient heat sensation with rush, followed by a period of sedation. As other depressants, in heroin intoxication organic symptoms prevail on neuropsychiatric manifestations, with emesis, myosis, bradycardia, impairment of consciousness and breath, up to apnea and coma. Heroin consumers frequently present infections for the use of contaminated preparations and exchange of material per injection, with pneumonia, cutaneous abscesses, phlebitis, endocarditis and HIV infection. Opiates produce physical dependence with an acute withdrawal syndrome characterized by craving manifestations, hyperestesia and hyperalgesia, insomnia, depression, often preceded from anxiety symptoms and irritability. These behavioural and psychological symptoms are associated to organic manifestations, referable to the lost inhibition of locus ceruleous neurons, such as emesis, diarrhoea, mydriasis, sweating, horripilation, cramps, tachycardia, yawning, sometimes fever. Withdrawal syndrome may be precipitated from antagonists administration (naloxone or naltrexone) for overdose treatment[24].

Stimulants

Cocaine and its analogous (e.g. crack, in the form of free base, easy to inhale if previously warmed) show their pharmacological effects primarily on dopaminergic neurons in several areas of the brain, with inhibition of their re-uptake. The evidence indicates that frontal lobe dysfunction may be an important treatment target in cocaine use disorder. *Amphetamines* are similar to cocaine, but they act mainly as peripheral and central adrenergic agonist, by increasing presinaptic release of dopamine[25]. Acute and chronic intoxication by these stimulants produces anxiety symptoms, prevailing obsessive-compulsive disorder, panic attack and phobic disorders, depressive symptoms (anhedonia), and manifestations due to elevated mood, such as megalomania, anger and violent behaviour. Psychosis may also occur. Acute cocaine overdose is potentially lethal, such as suicidal behaviours, violent psychoses, strokes, seizures and encephalopathy. Also, cocaine's toxic effects on the cardiovascular (hypertensive crisis, myocardial infarction, tachyarrhythmia), muscular (tremor, abnormal involuntary movements), thermoregulatory (increased body temperature), and respiratory systems (tachypnea, bronchospasm), can present as or with acute neuropsychiatric symptoms. Indeed, the complex manifestations of cocaine can pose substantial problems in differential diagnoses and resuscitative treatment (Figure 1)[24,26]. Chronic cocaine use may be associated with deficits in neuro-cognition, hallucinations and paranoid delusions, irritability and violent behaviour. Tachycardia and hypertension prevail among the organic manifestations, with increasing risk for myocardial infarction, aortic dissection, cerebral ischemia, rabdomyolysis and seizures, other than increased traumatic injuries. Premature delivery is a common outcome in pregnant abusers[18]. Other organic adverse effects from chronic smoking of cocaine include hemoptysis, itching, fever, diffuse alveolar infiltrates without effusions, asthma, pulmonary and systemic eosinophilia, chest pain, sore throat, hoarse voice, and a flu-like syndrome. Moreover, cocaine does often cause bruxism, which can deteriorate tooth enamel and lead to gingivitis. Chronic intranasal usage can degrade the cartilage of the septum nasi, leading eventually to its complete disappearance. Finally, cocaine may also greatly increase this risk of developing connective tissue diseases (vasculitis). Cocaine and amphetamines withdrawal syndrome (crash) is frequent in heavy users, when dependence had begun. It is revealed by anxiety symptoms and depression, lethargy, asthenia and bradycardia. Urine titration of cocaine metabolites can detect its use up to 10 days after the last assumption[25].

Nicotine is the main active substance in cigarette smoking. It may be considered the first cause of morbidity and mortality in Western Countries, other than the most common substance producing an addiction status. Deficit of attention, irritability, craving, anxiety symptoms and depressed mood prevail among withdrawal symptoms, being common behavioural and vegetative disturbances such as hostility, insomnia, bradycardia and appetite increase[27]. The universal appeal of *caffeine,* a xanthine derivative, assumed by beverages such as coffee, tea and cola, is related to its mild psychostimulant properties. Even though the primary action of caffeine may be to block adenosine receptors, this leads to very important secondary effects on many classes of neurotransmitters, including noradrenaline, dopamine, serotonin, acetylcholine, glutamate, and GABA. In a healthy person, caffeine pro-

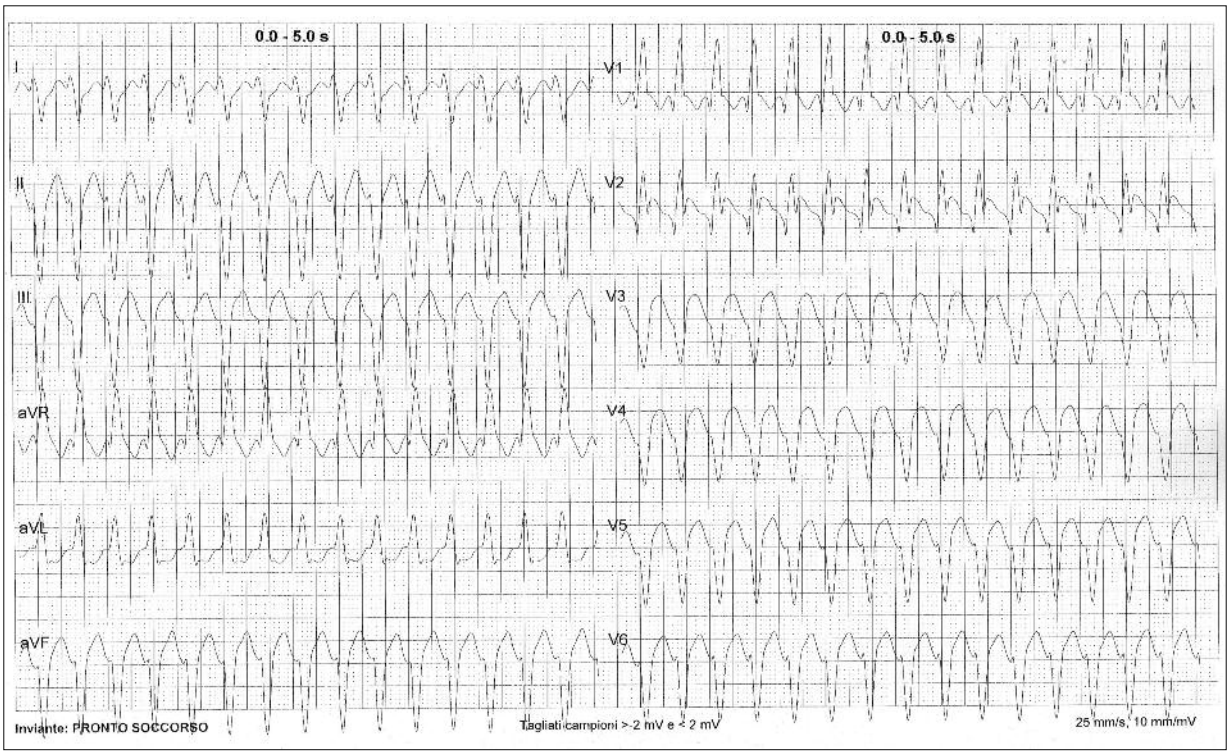

Figure 1. ECG showing a tachycardia with wide QRS complex (Ventricular Tachycardia). Tachyarrhythmias may represent a cardiovascular complication of cocaine and other stimulants overdose in ED.

motes cognitive arousal and fights fatigue, but these same activating properties can produce symptomatic distress in a small subset of the population, with 50% symptoms of nervousness, excitation, abdomen pain, dry mouth, tremor, nausea, and jitteriness. Susceptibility to this symptomatic distress is broadly determined by three factors: the dose consumed, individual vulnerability to caffeine, and pre-existing medical or psychiatric conditions (mood disorders in particular) that are aggravated by mild psychostimulant use. The caffeine excess produces persisting insomnia, nervousness, and mood fluctuations. Symptoms of ADHD may be altered by caffeine as well. Psychosis can be induced in normal individuals ingesting caffeine at toxic doses, and psychotic symptoms can also be worsened in schizophrenic patients using caffeine. Other symptoms affecting the cardiovascular system range from moderate increases in heart rate to more severe cardiac arrhythmia[28]. A number of drugs, including certain SSRIs, antipsychotics, antiarrhythmics, theophylline and quinolones, have been reported to be potent inhibitors of cytochrome P450, which participates in the metabolism of caffeine. This has important clinical implications, since the high potential for pharmacokinetic interactions. Withdrawal symptoms consist of dysphoric mood changes, fatigue, muscle pain, stiffness, lethargy, headache and nausea, with subjective psychological distress and significant impairment of psychomotor speed and cognitive performance tests[29].

Hallucinogens

Hallucinogens (or psychedelics) psilocybin, mescaline, lysergic acid (LSD), and 3,4-methylenedioxy-N-methylamphetamine (MDMA, commonly called ecstasy) produce perceptual disorders and visual hallucinations. Their psychic effects are referable to the affinity to the serotoninergic receptors mainly on raphe neurons, which tonically inhibit visual sensorial afferences. Recently, a serotonin receptor-mediated enhancement of *glutamatergic* transmission in the cerebral cortex has been proposed as responsible for the higher-level cognitive, perceptual, and affective distortions produced by these drugs. Panic attack with agoraphobia is the most common anxiety disturb in ED in abusers of LSD and ecstasy, who experience a “bad trip”, often occurring in adolescents assuming the substance by soaked

stamps or by pills supplied in discotheque. Mood disorders, such as empathy and euphoria, or depression, and prolonged psychotic reaction are also common[30]. Organic symptoms suggesting hallucinogens taking include mydriasis, tachycardia, hypertension, lacrimation, salivation (but dry mouth in ecstasy abuse), sweating and rush. Ecstasy can lead to acute, potentially lethal, toxicity (malignant hyperthermia and/or hepatitis), and neurotoxicity in the long-term, involving various neurobiological systems (serotonin, dopamine, noradrenalin), that may all interact[31].

Other Substances

Cannabis includes 61 cannabinoids having slow elimination (up to 30 days), the psychoactive agent being Delta-9-tetrahydrocannabinol (THC). Cannabis flowers (*marijuana*) and preparations derived from resinous extract (*hashish*) are consumed by smoking, vaporizing and oral ingestion, being estimated to be the most used illicit substance in USA. Their euphoric effects (high and mellowing out) differ from opiates and other stimulants. Cannabis abuse can produce severe anxiety symptoms, mainly as panic attacks, more frequent in occasional users, and hallucinations, till acute psychosis. Minor symptoms from smoking (bronchitis, sleep disturbances) may coexist. A causal role of acute cannabis intoxication in motor vehicle and other accidents has now been shown by the presence of measurable levels of THC in the blood of injured drivers in the absence of alcohol or other drugs. Chronic inflammatory and precancerous changes in the airways have been demonstrated in cannabis smokers. Several different studies indicate that the epidemiological link between cannabis use and schizophrenia probably represents a causal role of cannabis in precipitating the onset or relapse of schizophrenia. A weaker but significant link between cannabis and depression has been found in various cohort studies, but the nature of the link is not yet clear. A large body of evidence now demonstrates that cannabis dependence, both behavioural and physical, does occur in about 7-10% of regular users, and that early onset of use, and especially of weekly or daily use, is a strong predictor of future dependence[32]. After withdrawal in habitual users psychiatric and organic symptoms may occur within 48 hours: irritability and aggression, insomnia, restlessness, anxiety, electroencephalographic alterations and nausea and cramps are described; symptoms subside within 2 to 12 weeks[33]. There are various reports of *synthetic cannabinoids* adverse effects including tachycardia, hypertension, tachypnea, chest pain, heart palpitations, hallucinations, racing thoughts, and seizures. While reports suggest that toxic symptoms last no longer than 3-4 hours, with no residual adverse effects in many cases, there is concern about serious acute and long-term toxicities[34]. Coinciding with the increasing rates of cannabis abuse has been the recognition of a new clinical condition known as *cannabinoid hyperemesis syndrome*, characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and frequent hot bathing. Despite the well-established anti-emetic properties of marijuana, there is increasing evidence of its paradoxical effects on the gastrointestinal tract and CNS. Cyclic vomiting syndrome shares several similarities and the two conditions are often confused[35]. Finally, Raynaud's phenomenon, as well as arteritis due to cannabis consumption may be extremely severe and result in worrying situations for both clinicians and patients[36].

The U.S. Office of National Drug Control Policy identifies four specific "*club drugs*" (also known as "rave drugs" and "party drugs"): *ketamine, gamma hydroxybutyrate* (GHB), ecstasy, and flunitrazepam (Rohypnol). *Ketamine* is a derivative of phencyclidine used in human, both in trauma and emergency surgery, and veterinary medicine, for its anaesthetic and analgesic properties. It induces a state referred to as "dissociative anaesthesia" and is used as a recreational drug. In combination with psychiatric manifestations, such as acute delirium, short term neurological adverse effects are reported in 40% of patients, e.g. dizziness, diplopia, blurred vision, nystagmus, altered hearing[37]. Measurable changes in peripheral organ systems, including the cardiovascular, gastrointestinal, and respiratory systems, as referable to its effects on catecholaminergic transmission. Indeed, ketamine inhibits reuptake of catecholamines, resulting in hypertension and tachycardia, while stimulation of β_2 adrenergic receptors produces bronchodilation. Finally, inhibition of neuronal uptake and increased serotonergic activity are thought to underlie nausea and vomiting. Long term side effects include neurological abnormalities, with neurocognitive impairment, deficits in working and episodic memory, and urinary tract symptoms, which have been collectively referred as *ketamine-induced ulcerative cystitis*[38]. *Gamma-hydroxybutyric acid* (GHB) is a naturally occurring neurotransmitter in the brain, structurally related to the neurotransmitters gam-

ma-aminobutyric acid (GABA) and glutamic acid, acting on dopaminergic systems, with only common medical applications in the treatment of narcolepsy. Like alcohol, it is a CNS depressant, but at small doses can act as aphrodisiac and stimulant, inducing euphoria, disinhibition, and sociability. At higher doses, GHB may induce nausea, vomiting, gastrointestinal tract irritation, dizziness, depressed breathing, visual disturbances, drowsiness, agitation, amnesia, unconsciousness, and death. The effects of GHB can last from 1.5 to 3 hours, or even longer if large doses have been consumed[39]. GHB has also been associated with a withdrawal syndrome of insomnia, anxiety, muscular cramping, tremor, perspiration, and bowel and bladder incontinence, that usually resolves in 3-12 days. The withdrawal syndrome can be severe producing acute delirium and may require hospitalization in an ICU for management[40].

Inhalants (or *volatile solvents*) such as glues and adhesives (toluene, benzene, chloroform, etc.), cleaning agents (tetrachloroethylene, trichloroethane, xylene), solvents (acetone, ethyl acetate, alkyl nitrites), gases (butane, isopropane), aerosols (chlorofluorocarbons), gasoline (benzene, xylene), and anaesthetics (nitrous oxide, halothane, enflurane, desflurane, isoflurane, ethyl chloride), are very lipophilic molecules which when inhaled produce changes in mental status, prevalently analgesia and euphoric-oniroide status. Inhalant use disorders are among the least prevalent and dangerous substance use disorders, their lifetime prevalence being estimated in about 10% among teenagers, up to 50% of whom may develop dependence. Panic attack and generalized anxiety disorder represent the most common adverse psychiatric events associated to intoxication by inhalants, which generally produces a syndrome similar to alcohol intoxication, consisting of dizziness, slurred speech, euphoria, lethargy, slowed reflexes, slowed thinking and movement, incoordination, tremor, generalized muscle weakness, involuntary eye movement, blurred vision, stupor, coma and death. Inhalant intoxication also increases the risk for fatal injuries from motor vehicle or other accidents, and catastrophic medical emergencies such as ventricular arrhythmias, leading to "sudden sniffing death". Recreational inhalant users, as occupational exposures, may present memory, attention, and judgment deficits compared with controls. Recurrent inhalant intoxication can lead to neurological disorders, including Parkinsonism, impaired cognition due to degradation of brain cells (encephalopathy) or loss of brain cells (cerebral atrophy), and loss of muscle strength and coordination due to damage to the cerebellum (cerebellar ataxia). Moreover, inhalants can cause chronic medical problems affecting multiple organ systems, so causing liver, heart, and kidney toxicity, bone demineralization, bone marrow suppression, reduced immunity (T-cell response) and pulmonary dysfunction, injured alveolo-capillary membrane and predisposing with tuberculosis, bronchitis, asthma and sinusitis. *Poppers*, a slang term for various alkyl nitrites, can induce vertigo, headache, palpitation, hypotension and temporary changes in vision. Despite to the negative indications of DSM-IV, a recent study provides evidence for a lifetime inhalant-related withdrawal syndrome in approximately 20% of inhalant abusers and 50% of those with inhalant dependence. The most commonly reported withdrawal symptoms are hypersomnia, feeling tired, and nausea. Other neuropsychiatric symptoms are hallucinations and restlessness, which may coexist with vegetative and organic manifestations, such as headache, sweating, tachycardia, tremors muscular pain and fever[41].

Medicaments

Prescription medications are commonly responsible of psychiatric and organic symptoms. In primary health care approximately 2% of patients receiving pharmacotherapy develop side effects, hence in hospitalised patients clinically relevant side effects exceeds 10%. Additionally, it has been estimated that approximately 3-5% of all hospital admissions are related to adverse drug reactions[42,43]. Clinically relevant adverse drug reactions concern most frequently the gastrointestinal tract, the haematological systems, the skin, the cardiovascular system, other than the CNS. Factors predisposing for clinically relevant adverse drug reactions are female gender, elderly and polypharmacy, with meanly 6 drugs administered per day in inhospital patients in Internal Medicine[42]. Depending on the development mechanism, psychiatric as well organic side effects can be divided in two basic groups: *type A side effects*, characterized by the qualitatively standard, but quantitative augmented pharmacologic effects, dose dependent and predictable, including psychotropic drugs and hormones; *type B side effects*, unexpected considering the pharmacological features of the medication, and dose independent and unpredictable, usually including non psychotropic drugs (e.g. cardiovascular, antibiotics, anti-inflammatory and antineoplastics) (Table II)[43]. The psy-

chiatric symptoms are often dose related, e.g. type A side effects. Hence, age and slow speed of detoxification will increase the risk of patients developing sleep disturbances, anxiety, delirium, and hallucinations[43,44]. Several medications (e.g., barbiturates, vigabatrin, topiramate, flunarizine, corticosteroids, mefloquine, efavirenz, and IFN-alpha) do appear to cause *depression* in some patients and should be used with caution in patients at risk for depression. On the other hand, many other relationships are still controversial, such as the association of depression with sedatives, anti-hypertensive and oral contraceptives[45]. Sedative drugs are those most commonly associated with *psychomotor impairment*, and may include psychotherapeutic drugs, sedative antihistamines and narcotic analgesics. *Delirious states* are most often associated with drugs that possess central anticholinergic actions, including not only drugs clearly identified as anticholinergics, but also tricyclic antidepressants and anti-Parkinson drugs. Cimetidine, which is often used parenterally in seriously ill patients, is also a prominent cause. The association of *schizophrenic-like psychoses* with dopaminomimetic drugs tends to support the prevailing dopamine hypothesis of schizophrenia. Levodopa and bromocriptine are examples of such relationships. *Manic reactions* are clinically difficult to differentiate from schizophrenic-like psychoses and are often produced by similar drugs[46]. Psychiatric and organic symptoms can also occur when drugs to which a patient has developed some measure of tolerance are abruptly withdrawn, especially psychotropic drugs. Medicaments more commonly producing coexistent psychiatric and organic adverse reactions are listed in Table III. A systematic classification according to their usual therapeutic use is presented, to facilitate a prompt anamnestic recognition.

Psychotropic Agents

Psychoactive substances and medications are commonly classified into four categories: tranquilizers, depressants, stimulants and hallucinogens, including the novel class of psychostimulants eugeroics under which modafinil, adrafinil, and ampakine are categorized. However, the bounds of these categories are not precisely delineated; rather, they have several effects that overlap or combine into a new, different one (Figure 2)[47].

The evidence suggests that although illegal drug use is relatively rare among older adults compared with younger adults and adolescents, there is a growing problem of the misuse and abuse of prescription drugs. *Psychoactive medications* are used by at least 1 in 4 older adults, and such use is likely to grow as the population ages. It is estimated that up to 11% of older women misuse prescription drugs[49].

Sedatives-hypnotics, such as benzodiazepines and barbiturates, are reported to have a significant association with depression[45,50]. Nevertheless, toxic influence of *tricyclic antidepressants* (e.g., amitriptyline, imipramine, doxepin and trazodone) on CNS can result in confusion, memory disorder, anxiety, irritability and agitation which diagnostically should be differentiated from the increase of depressive symptoms or relapse of depressive disorder. Organic symptoms and signs of antidepressant toxicity, such as dry mouth, drowsiness, weight gain, level of consciousness by GCS, convulsions, and QT and QRS prolongation, can be very helpful in differential diagnosis, as well as determining their blood level[43]. Some patients that are more than six months on *selective serotonin reuptake inhibitors* (SSRIs) fluoxetine, fluvoxamine, paroxetine, sertraline, escitalopram, citalopram, or on *selective serotonin/norepinephrine reuptake in-*

Table II. Comparison of features type A and type B side effects of medications.

	Type A (augmented pharmacologic effects)	Type B (unexpected reactions)
Pharmacologic predictable	Yes	No
Dose dependent	Yes	No
Medication number dependent	Yes	No
Drug interactions dependent	Yes	No
Incidence	High	Low
Morbidity	High	Low
Mortality	Low	High
Treatment	Appropriation of medication dose	Discontinuation of medication

(From: Mihanovi M et al. Psychiatria Danubina, 2009)[43].

Table III. Most common *prescription* and *illicit medications* causing psychiatric and somatic symptoms, as direct effect or for their withdrawl. A systematic classification according to their usual therapeutic use is presented, to facilitate a prompt anamnestic recognition.

Psychiatric drugs
Benzodiazepines
Barbiturates
Antipsychotics
Tryciclic antidepressants
SSRI/SNRI antidepressants
NRIs
Atomoxetine

Neurological drugs
MAOIs
Anticholinergic
L-dopa
Dopaminergic
Antiepileptics
H1-antihistaminics
Triptans
Melatonin

Cardiovascular drugs
Digoxin
Clonidine
Methyldopa
Beta-blockers
ACE-inhibitors
Angiotensin-II blockers
Calcium channel blockers
Diuretis
Statins

Respiratory drugs
Corticosteroids
Destrometorphan

Gastroenterologic drugs
Metoclopramide
Scopolamine
H2-histamine blockers
Pantoprazole

Hormones
L-thyroxine
Progestinics
GnRH agonists
Oral contraceptives
Finasteride
Anabolic-androgenic steroids

Dermatologic drugs
H1-antihistaminics
Isotretinoin

Analgesics and antinflammatory drugs
Opioid analgesics
NSAIDs
Corticosteroids

Antibiotics, antimalarials, antituberculosis and antiviral agents
Sulfonamides
Quinolones
Clarithromycin
Amoxicillin
Linezolid
Cephalexin
Metronidazole
Chloroquine
Mefloquine
Isoniazid
Ethionamide
Cycloserine
Terizidone
Oseltamivir
Efavirenz

Immunosoppressors and immunomodulators
Corticosteroids
Interferon-Alpha
Interleukin-2
Cyclosporine
Tacrolimus

Antineoplastics
Methotrexate
Vincristine
Ifosfamide
Cyclosporine
Fludarabine
Cytarabine
5-fluorouracil
Cisplatin
L-asparaginase
Paclitaxel
Doxorubicin
Cyclophosphamide

Doping agents
Psychostimulants
Modafinil
GHB
Anabolic-androgenic steroids
Beta2-agonists
Diuretics
Corticosteroids
Beta-blockers

hibitor (SNRIs) venlafaxine and duloxetine, can develop symptoms such as apathy, lack of motivation and emotional blunt presented as inability to cry, frequently associated to sexual dysfunctioning, sleepiness, and weight gain. These psychopathologic symptoms should be distinguished from the symptoms of primary depressive disorder, and clinical experience shows that these symptoms tend to reduce after discontinuation of SSRIs or after administration of dopamine agonists such as atypical antidepressant bupropion. SSRI citalopram, escitalopram, and fluoxetine are associated with hyponatraemia an increased risk of stroke. A fatal serotonin syndrome has been described, especially in combination with triptans, characterized by hyperthermia, mental status changes, restlessness, myoclonus, hyperreflexia, diaphoresis, or evidence of autonomic hyperactivity[43,51]. The frequency and severity of the discontinuation syndrome is linked with half-life of drug, paroxetine. Paroxetine and venlafaxine, whose half-lives are shorter, are mainly involved. Most of the discontinuation symptoms are physical (flu-like, symptoms, myalgia and abdominal discomfort) and misdiagnosis can also lead to unnecessary investigations or to inappropriate treatment. *Bupropion,* an atypical antidepressant also effective in smoking cessation, is structurally similar to diethylpropion, an appetite suppressant, showing poor selective noradrenergic effects. Its dopaminergic action is thought to play a role in the pathophysiology of acute delirium described during its therapeutic use. The most serious adverse effect of bupropion is seizure, which affects an estimated 1 in 1000 users, while more common side effects include dry mouth, insomnia, skin rash and pruritus[52].

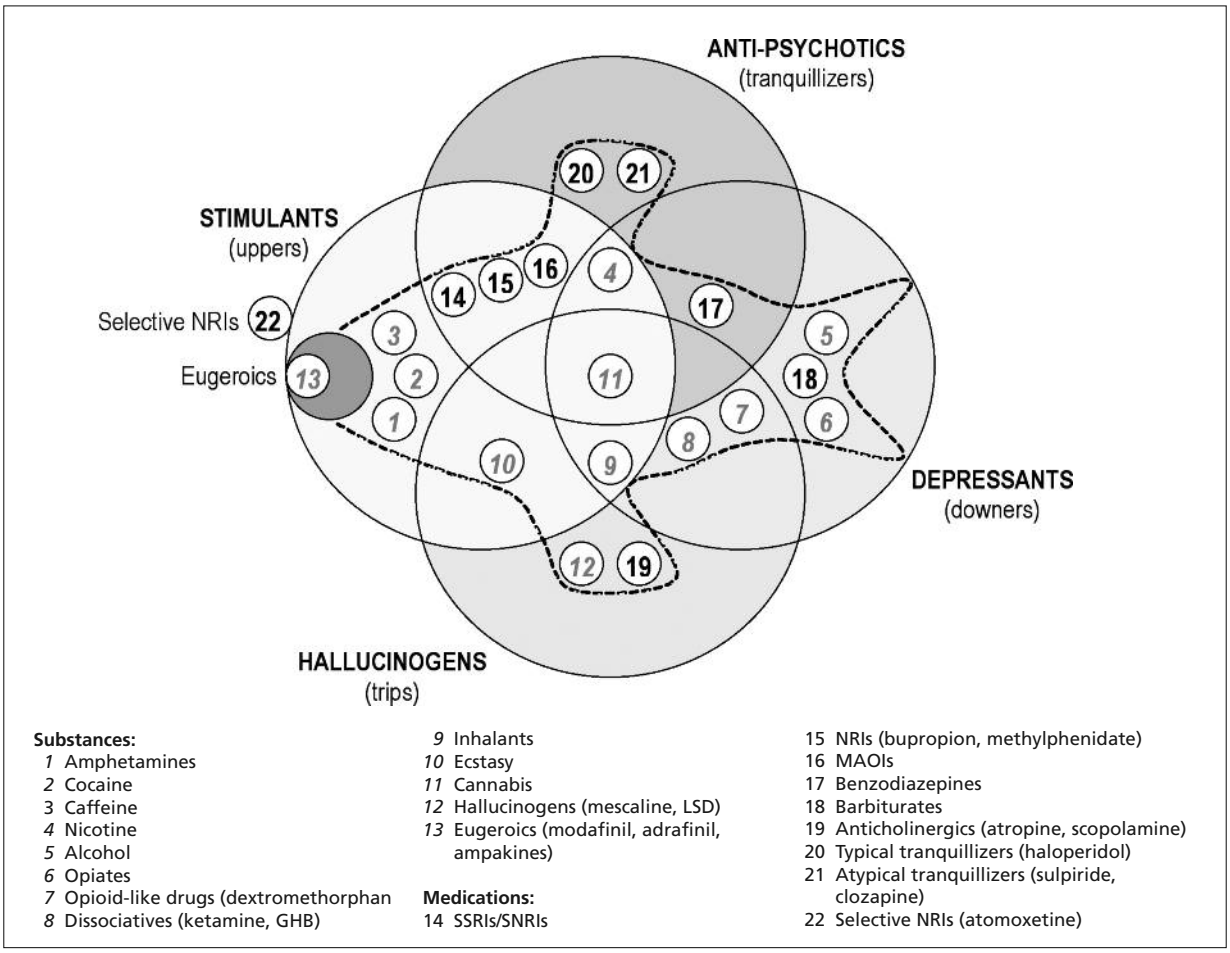

Figure 2. Classification of prescriptional and illicit psychoactive drugs, and their overlapping (modified from: Kim D. Environ Health Toxicol, 2012)[47]. The reference numbers arrange themselves in a "fish shape" crossing the 4 circles, an effective mnemonic device. Hence, fish represents a traditional source of vitamins, whose healing properties are told since in Bible, and a modern healthful food rich in omega-3 fatty acids. Its antidepressant properties, by a regular intake of cod liver oil, has been recently reported[48].

Methylphenidate, a derivative of amphetamine, is a stimulant effective for the treatment of attention-deficit/hyperactivity disorder (ADHD). Its use includes adverse cardiac effects, such as a modest rise in blood pressure and heart rate, appetite suppression, and negative emotional symptoms and psychotic episodes[53]. Atomoxetine is a *selective noradrenaline reuptake inhibitor* (NRI) that is not classified as a stimulant, and also indicated for use in patients with ADHD. It is particularly useful for patients at risk of substance abuse, as well as those who have co-morbid anxiety or tics. The mechanism of action of atomoxetine is unclear, but is thought to be related to its selective inhibition of presynaptic noradrenaline reuptake in the prefrontal cortex. Atomoxetine is generally associated with increases in both heart rate and blood pressure. Common adverse events included headache, abdominal pain, decreased appetite, vomiting, somnolence, and nausea, with a significantly higher incidence of suicidal ideation than placebo[54].

Anticholinergic drugs for treating neurological (Parkinson's disease), respiratory (asthma), gastroenterological (spastic manifestations) and urological (overactive bladder) diseases, and *tryciclic antidepressants* and *antipsychotics* such as chlorpromazine, clozapine and olanzapine with anticholinergic features, can induce delirium. Coexistence with confusion, disorientation, tactile and visual hallucinations together with typical antimuscarinic adverse reactions, such as the headache, blurred vision with mydriasis, tachycardia, dry mouth, constipation and urine retention, and information about taking anticholinergics indicate that it is most probably anticholinergic delirium[43].

Fever may develop in childhood, while cardiac arrhythmias constitute less common but potentially life-threatening adverse reactions, due to prolonged QTc interval. They occur only in the presence of multiple additional risk factors, such as age over 65 years, bradycardia, hypokalemia, hypomagnesemia, supratherapeutic or toxic serum concentration, or interference with drug metabolism. The ECG and electrolytes should be taken in account in ED patients taking psychotropic drugs, and pre-existing cardiovascular disease or simultaneous administration of other drugs delaying repolarization carefully investigated[55].

Finally, *serotonin syndrome* and *neuroleptic malignant syndrome* are uncommon but potentially life-threatening adverse reactions associated with psychotropic medications, often combined, in which neuropsychiatric and organic symptoms may co-occur. Both conditions present as mental status changes, autonomic nervous system disturbances, neurologic manifestations, and hyperthermia or hyperpirexia. However, the elevation in creatine kinase, liver function tests (lactate dehydrogenase, aspartate transaminase), and white blood cell count, coupled with a low serum iron level, distinguishes neuroleptic malignant syndrome, for which dantrolene is the effective evidence-based drug treatment, from serotonin syndrome, for which only supportive care is indicated, among patients taking neuroleptic and serotonin agonist medications simultaneously[56].

Neurological Drugs

Notselective monoamine oxidase inhibitors (MAOIs) phenelzine, tranylcypromine, isocarboxazid, and selective inhibitors for MAO-B selegiline and rasagiline, are clinically used to treat Parkinson's disease by blocking the degradation of neuroactive catecholamines. In depression, their usage is now limited to refractory cases, because of their negative side effects. Inhibition of other enzymes, such as the drug-metabolizing cytochromes P450 with food and drug interactions, is responsible of tyramine-induced hypertensive crisis (e.g., the "cheese reaction"). Therapy with new MAOIs appears to be associated with a low incidence of cognitive and behavioural adverse events. Nervousness may occur, but a potentially lethal serotonin syndrome has been reported. Vegetative and organic symptoms more commonly associated in MAOIs toxicity are sleep disorders, dizziness, muscle pain, paresthesias, edema, orthostatic hypotension, dry mouth, diarrhoea, sexual dysfunctions, difficulty urinating, and hepatotoxicity[57].

Changes in transmitter balance and receptor excitability are the main causes of the type A toxic side-effects of *L-dopa*. Confusion and acute psychosis may occur with peripheral gastroenteric (nausea) and cardiac symptoms (hypotension), other than with more usual dyskinesic manifestations, while a malign neuroleptic syndrome is described after its withdrawal. Secondary psychosis was recognized in 1.3% of patients treated with therapeutic dosages of the *dopamine agonist drugs* bromocriptine, cabergoline and lisuride, also used for treating functioning pituitary tumours. Symptoms included auditory hallucinations, delusional ideas, and appreciable changes in mood[58].

A significant increase in suicidal attempts results in patients taking *antiepileptic drugs*, particularly when the individuals had a preexisting history of depression[59]. Several data reveal evidence for both positive and negative effects on anxiety, aggression, sleep, depression and psychosis in patients with epilepsy. Topiramate, vigabatrin, levetiracetam, tiagabine and zonisamide have been associated primarily with adverse psychotropic effects, especially depression, that may be often under-diagnosed, and psychosis[45]. *Gabapentin* withdrawal can occur at doses ranging from 400-8000 mg/day for as little as 3 weeks. Patients can experience restlessness, disorientation, confusion, agitation, anxiety, confusion, headache and light sensitivity[60].

Cinnarizine and *flunarizine* are piperazine derivatives with H1-antihistamine properties and calcium channel blocking activity. They are effective in the prophylaxis of migraine, occlusive peripheral vascular disease, vertigo of central and peripheral origin, and as an adjuvant in the therapy of epilepsy. Several reports have described extrapyramidal reactions and depression associated with their use[61]. *Triptans* (sumatriptan, zolmitriptan, rizatriptan, naratriptan, almotriptan, eletriptan and frovatriptan) are effective in the treatment for acute attacks of migraine, showing associated adverse events similar to placebo. They include dizziness, somnolence, asthenia, and chest tightness[62]. However, alert should be warned about the potential life-threatening risk of serotonin syndrome when triptans are used in combination with selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/norepinephrine reuptake inhibitors (SNRIs).

The interest on *melatonin* for the prevention and treatment of jet lag and insomnia has increased a lot in the last decade. This is mainly due to its safety and its lack of serious adverse

reactions. Indeed, neuropsychiatric adverse reactions were prevalently described, including confusion due to melatonin overdose, fragmented sleep, a psychotic episode, optic neuropathy, nistagmus, seizures and headache. Autoimmune hepatitis and skin eruptions also occurred[63].

Cardiovascular Drugs

A number of psychiatric effects, including mood syndromes, psychosis, and cognitive disturbances, have been reported in patients taking *digoxin, clonidine, methyldopa, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II blockers, calcium channel blockers* and *diuretics*. In particular, digitalis toxicity has been shown to cause hallucinations, mania, euphoria, and depression, in combination with visual changes, gastroenteric (anorexia, emesis, abdominal pain) and cardiovascular (arrhythmias) problems. Thiazide diuretics, which minimally cross the blood-brain barrier, can result in neuropsychiatric complications, ranging from sedation to psychosis, due to their effects on electrolytes (primarily sodium and calcium). Some antiarrhythmic drugs have been associated with delirium in single case reports. Amiodarone is associated with thyroid abnormalities in 15% of patients, and untreated thyroid dysregulation can lead to a variety of mood, cognitive, and psychotic symptoms. In contrast, direct neuropsychiatric effects of amiodarone are uncommon. Methyldopa, clonidine, and propranolol are associated with higher rates of fatigue, sedation and sleep disturbances than placebo, related to their antiadrenergic actions[50,64]. Recent interest has been focused on a potential risk of psychiatric adverse reactions associated with *statins*. Special attention is currently being paid to the potential statin-induced sleep disorders (insomnia, somnolence), the most other frequently reported psychiatric events being agitation, confusion and hallucination[65].

Respiratory Drugs

The cumulative data indicate that psychiatric complications of *corticosteroids* are not rare, ranging from 6% (for severe reactions, including psychosis, other than mania and depression) to 23% for moderate reactions (anxiety and insomnia). Euphoria and hypomania were the most common psychiatric symptoms reported during short courses of steroids, while during long-term treatment, depressive symptoms were the most common[50,66]. Hence, inhaled glucocorticoids and montelukast resulted the most frequently suspected drugs responsible for serious psychiatric adverse reactions in paediatric population, other than central simpaticomimetic drugs[67]. *Montelukast* is a potent leukotriene-receptor antagonist used in the treatment of asthma and allergic rhinitis. Psychiatric disorders reported include nightmares, unspecified anxiety, aggressiveness, sleep disorders, irritability, hallucination, hyperactivity, and personality disorder[68]. Cough suppressant *destrometorphan*, a typical morphine-like opioid, is frequently prescribed and bought over the counter. It has been shown to cause neurological side effects, including hyperexcitability, increased muscle tone, and ataxia, other than several neuropsychotoxic effects, such as maniac episodes and dissociative symptoms, and potential abuse. Massive ingestions of the drug may be associated with untoward effects, including tachycardia, hypertension, and respiratory depression. Supra-therapeutic destromethorphan doses combined with a therapeutic amount of a SSRI may induce a serotonin syndrome[69].

Gastroenterologic Drugs

Although prokinetic cholinergic agent *metoclopramide* is well-known for its side effects related to dopamine blockade, its action at serotonin receptors may also be clinically significant in the genesis of neuropsychiatric side effects, especially related to mood and behaviour. Anxiety, agitation, depression, suicidal but also homicidal ideation may follow brief exposure to metoclopramide in occasional cases[70,71]. Anecdotal reports exist on psychosis accompanied by delusional beliefs, personality changes and disorientation during Helicobacter pylori eradication treatment with amoxicillin, clarithromycin and *pantoprazole*[72]. *H2-histamine antagonists* (cimetidine, ranitidine and famotidine) are known to cause secondary mania[73].

Hormones

Neuropsychiatric and somatic side effects significantly occur during treatment with supraphysiological doses of *thyroid hormones*, comparable to hyperthyroid patients (see Part III).

Discordant results are reported about the increased odds ratios for depression in patients treated with *progestogens*. However, there is no evidence of any association between levonorgestrel and depression, despite of its increased occurrence among medroxyprogesterone acetate users[74]. Depressive symptoms have been reported during *gonadotropin-releasing-hormone*

(GnRH) agonists administration, but not conclusive data exist. The association between the use of *oral contraceptives* and depression is not clear. Depression is not considered a common side effect of hormone-based contraceptives, but negative mood symptoms remain one of the major reasons for discontinuation of combined oral contraceptive pills[75].

Variable but significant percentage of patients receiving *finasteride* seem to develop moderate to severe depression during the course of their treatment[76]. The adverse side of *anabolic-androgenic steroids*, synthetic drugs derived from *testosterone*, included sexual dysfunction, alterations of the cardiovascular system, liver toxicity, psychiatric and behavioural disorders. Possibly irreversible neuropsychiatric toxicity include dependence syndrome, mood disorders, and progression to other forms of substance abuse. Occasionally, anabolic-androgenic steroids abuse may be linked to certain social and psychological traits of the user, like low self-esteem, low self-confidence, suffered hostility, childhood conduct disorder, and tendency to high-risk behaviour. Use of anabolic-androgenic steroids in combination with alcohol largely increases the risk of violence and aggression. Both humans and animals exhibit a well-documented withdrawal syndrome, mediated by neuroendocrine particularly opioidergic mechanisms, and cortical neurotransmitter systems[77].

Dermatologic Drugs

First *H1-histamine blockers* (diphenhydramine, promethazine), commonly having sedative effect, can also induce stimulant effects on CNS. Restlessness and insomnia may occur at usual therapeutic dosage. Convulsion may develop in children due to overdosage. Their anticholinergic and dopaminergic features may be related to the development of delirium and acute psychosis[70]. Since the introduction of *isotretinoin* (a retinoid receptor agonist) to the market, many adverse psychiatric effects, including depression, anxiety and suicide attempts were reported, with controversial results[50,78].

Analgesics and Antinflammatory Drugs

Potential adverse psychosocial effects, particularly for clinical depression and behavioural deactivation were detected among patients using chronic *opioid* therapy for chronic non-cancer pain. *Tramadol* is an analgesic medication with partial mu agonist activity, also affecting release of serotonin and inhibition of reuptake of noradrenaline. Its toxicity appears to be due to monoamine uptake inhibition rather than its opioid effects[79]. Like tramadol, *fentanyl*, frequently used for analgesia during emergency procedures, is implicated in precipitating serotonin syndrome after intravenous administration, especially in patients chronically taking SSRIs[80].

Nonsteroidal anti-inflammatory drugs (NSAIDs), another group of drugs extensively used in the treatment of pain, especially in the elderly, can induce or exacerbate anxiety disorders, depression, bipolar disorder and schizophrenia. These adverse effects may be more severe and frequent than thought previously, but are generally transient and disappeared on withdrawal of the drugs[81]. The anaesthetic agent *ketamine*, is also a potent analgesic and can be used in sub-anaesthetic doses to relieve acute pain, especially in traumatic patient. However, its psychotropic properties must be taken into account (see also before).

Antibiotics, Antimalarials, Antituberculous and Antiviral Agents

Antibiotics are implicated in about 20% of all ED visits for drug-related adverse events, most visits being for allergic reactions. Since their introduction in the 1930s, numerous (primarily anecdotal) reports described *antibiotics* induced psychiatric side effects, ranging from anxiety and panic to major depression, psychosis and delirium. Psychiatric toxicity may result from various mechanisms of action, including antagonism of gamma-aminobutyric acid or pyridoxine, adverse interactions with alcohol, or inhibition of protein synthesis, *sulfonamides* and *quinolones* being mainly involved[82]. Ciprofloxacin, ofloxacin and pefloxacin are the *quinolones* with more neurological and psychiatric adverse reactions reported in the literature. Dizziness, headache, tremors, insomnia, confusional state, mania, hallucinations, and delirium being the most frequently reported psychiatric adverse events (0.9-11% of patients). These events may affect not only susceptible patients, such as elderly patients and in those using theophylline or NSAIDS, but also healthy patients[83].

Reversible psychiatric illness was the most common comorbidity during macrolide antibiotic *clarithromycin*, yet medication with neuroleptics or benzodiazepine being required in the acute phase. Sometimes clarithromycin-induced delirium was related to non-convulsive status epilepticus, so an EEG is suggested to differentiate patients with psy-

chiatric illness from those with encephalopathy or epilepsy[84]. Some authors suggest to add "*antibiomania*", also called Hoigne's syndrome, as part of the differential diagnosis when altered post-anaesthesia behaviour or psychiatric symptoms (delusions, paranoia, and hallucinations) are observed, especially when *amoxicillin* and *clarithromycin* are administered[85]. *Linezolid*, a synthetic antibiotic used to treat resistant gram-positive bacteria, can inhibit MAO, so predisposing patients who are concomitantly taking serotonin agonists to serotonin syndrome. Although *cephalosporin* are generally safe, neurotoxic effects have been reported in some subjects, with developing symptoms of delirium during treatment[86].

Metronidazole has good cellular penetration and is believed to penetrate the CNS easily. It can produce peripheral neuropathies and encephalopathy with overall cerebellar dysfunction, similar to acute Wernicke encephalopathy, especially at dosages exceeding 2 g/day for prolonged periods. MR imaging shows characteristic lesion features and distributions. The mechanisms of metronidazole neurotoxicity may differ for white and gray matter lesions, presumably reflecting differences in degrees of edema, whether vasogenic or cytotoxic in nature[87].

The antimalarials *chloroquine* may achieve high concentrations in the brain having the same pathologic activity as the quinolones in acting as N-methyl-d-aspartate agonists and gamma-aminobutyric acid antagonists, producing serious psychiatric symptoms as a rare occurrence during standard treatment, with symptoms of depersonalization and anxiety[88]. No severe but common and mainly neuropsychiatric adverse drug reactions are described also during long-term antimalarial chemoprophylaxis with *mefloquine*. Anxiety, irritability, dizziness may frequently coexists with digestive disorders anorexia, diarrhoea and nausea[89].

The neuropsychiatric complications of *antituberculous agents* are known for a long time, incriminating usually *isoniazid*, which appears to increase the concentrations of gamma-aminobutyric acid in neural tissues. Aggressiveness, insomnia and memory problems may be noted, sometimes necessitating anxiolytics prescription. Hallucinations were also reported, especially in patients having a history of alcoholism. Peripheral neuritis, optic neuritis, diplopia, irritability, anxiety, depression, hallucinations, convulsions, and psychosis have been reported to occur in 1-2% of the patients treated with *ethionamide*. Adverse reactions to *cycloserine* and *terizidone* are mainly dose-related and especially occur when concomitantly administered with other neurotoxic drugs, such as isoniazid and ethionamide. Neurological (headache, vertigo, dysarthria, somnolence, convulsion, mental confusion, and memory deficit) and psychiatric adverse effects (psychotic states with catatonic, paranoid, and depressive reactions, with a risk of suicide), are noted in up to 50% of patients[90]. *Cycloserine* is a second-line antituberculous agent, whose main side effects consist in CNS manifestations, e.g. headache, irritability, depression, psychosis and convulsions. These psychotropic responses are related to its action as a partial agonist of the neuronal NMDA receptor for glutamate.

Neuropsychiatric adverse events, such as abnormal behaviour, delusions, perceptual disturbances, and delirium in children taking *oseltamivir* during the influenza season are reported, although the available data seem do not suggest a statistical significance[91]. Neuropsychiatric side effects have been reported in individuals treated with *efavirenz*, commonly used in highly active antiretroviral combination therapy in the treatment of HIV infection. There are early complications, such as acute psychosis resembling reactions to LSD intake, as well as generally disappearing nightmares, occurring for several days after the start of therapy. Late complications are depressive episodes that must be carefully differentiated from pre-existing psychiatric disease and virus-induced brain damage[92].

Immunosoppressors and Immunomodulators

Cytokines such as *IFN-alpha* and *interleukin-2* are often used in the treatment of certain cancers (melanoma) and chronic diseases (hepatitis C infection and multiple sclerosis). Depression, anxiety, psychosis, suicidal ideation, hypomanic mood and cognitive impairment are reported in patients who receive those medications. Dose-dependent psychic disorders are noticed for about 30% of patients treated with *IFN-alpha*. Depression is the most frequently found psychiatric pathology, its relatively high proportion in this population (20-45%) raising important questions about IFN tolerability/toxicity. Anxiety states are not much described, and adaptation disorders are more concerned with the announcement of the diagnosis and its seriousness than with the toxicity of the IFN-alpha molecule[93].

Severe symptoms affect up to 5% of patients receiving the immunosuppressant *cyclosporine* and *tacrolimus,* and include psychoses and hallucinations. Calcineurin inhibition by cyclosporine and tacrolimus alters sympathetic outflow, which may play a role in the mediation of neurotoxic effects[94].

Antineoplastics

Chemotherapeutic drugs for cancer treatment are, of necessity, cytotoxic. Recently the term "chemo-fog" was proposed to describe potential deleterious adverse effects on cognitive function due to excessive cytokine release by the cytotoxic agents[95]. The so-called "chemobrain" is a complex phenomenon, and various factors other than chemotherapy may affect cognitive function, including the impact of surgery and anaesthesia, hormonal therapy, menopause, supportive care medications, genetic predisposition, comorbid medical conditions, or possibly paraneoplastic phenomenon[96]. CNS toxicity of chemotherapeutic drugs can manifest in many ways, including encephalopathy syndromes and confusional states, alterations in cognition and consciousness, cerebellar dysfunction, seizures, headache, cerebrovascular complications and stroke, visual loss, spinal cord damage and psychiatric symptoms including dissociative symptoms and psychosis. For many drugs, the toxicity is related to route of administration and cumulative dose, and can vary from brief, transient episodes to more severe, chronic sequelae. However, the neurotoxicity can be idiosyncratic and unpredictable in some cases. The most common chemotherapeutic agents that might cause CNS toxicity manifested as encephalopathy of various severities include *methotrexate*, *vincristine*, *ifosfamide*, *cyclosporine*, *fludarabine*, *cytarabine*, *5-fluorouracil*, *cisplatin* and *L-asparaginase*[97]. Studies indicate that also *doxorubicin* and *cyclophosphamide* are significantly associated with psychiatric disorders, including generalized anxiety disorder, panic disorder, PTSD, adjustment disorders, major depressive disorder and dysthymic disorder, in patients with first breast cancer recurrence[98]. There have been occasional instances of CNS toxicity after *paclitaxel* treatment though the syndrome is not well described.

Doping Agents

Athletes use substances to produce pleasure, relieve pain and stress, improve socialization, recover from injury, and enhance performance. "Brain doping" refers to the illicit use of a subcategory of prescription drugs, whose *psychostimulants* (e.g., amphetamines, methylphenidate) and *modafinil* show significant effects on concentration, attentiveness, and vigilance in healthy subjects[99]. *Modafinil* is a waking drug commercialized in 2003 for sleep apnea and narcolepsy patients, but its use as a lifestyle drug is increasing, namely as a non-prescription medicine for students, hard-working professionals, athletes and soldiers. Thus modafinil may induce wakefulness by its action in the anterior hypothalamus, by activating orexin neurons. Orexin is a family of wakefulness-promoting and sleep-inhibiting peptides, involved in inducing narcolepsy. The disruption of circadian rhythm and sleep control may influence the neuroimmune circuits, inducing stress responses and impairing immune functions. Modafinil increases resting heart rate and blood pressure, inducing sympathomedullary activation[47]. *GHB* has also achieved popularity as a recreational drug and a nutritional supplement marketed to bodybuilders[37]. The problem of *anabolic-androgenic steroid* abuse has recently generated widespread public and media attention (see Hormones section). Different classes of doping substances, namely *stimulants, narcotics, cannabinoids, beta2-agonists, diuretics, glucocorticosteroids, beta-blockers* and others, may cause psychiatric adverse reactions and a wide range of cardiac arrhythmias (focal or re-entry type, supraventricular and/or ventricular), through a direct or indirect arrhythmogenic effect, that can even be lethal and which are frequently sport activity related[100].

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