




## Editorial

# The Genesis of a New Open-Access Journal Focused on the Latest Scientific Advances in Psychoactive Substances

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Psychoactive substances have been in use for millennia, and their use can be traced back to prehistory, where they were utilized for spiritual purposes in particular [1–3]. Changes in their legality and social acceptability have been described; an example is *Vin Mariani* (i.e., Mariani wine) [4,5]. This was a coca wine made from Bordeaux wine and coca leaves in the 1860s by Angelo Mariani. *Vin Mariani* went out of production after his death, and after more than 100 years of non-commercialization, in 2017, the wine was reintroduced to the market by Christophe Mariani, who, surprisingly, is not related to Angelo Mariani. This modern interpretation is made with Corsican white wine and decocainized Bolivian coca leaves. Psychoactive substances are full of surprises, and every day, they encourage an increasing number of researchers to determine a more scientific basis for their use. Some were considered forbidden for decades and had no recognized therapeutic potential. Nevertheless, currently, several pharmaceutical industries are exploring their benefits by taking advantage of the famous Renaissance physician, Paracelsus's (1493–1541), law of the threshold concept [6]: “what is there that is not poison? All things are poison and nothing is without poison. Solely the dose determines that a thing is not a poison”. By determining that a (lower) dose of a substance prevents adverse effects, Paracelsus laid the groundwork for the modern separation of the terms hazard and risk. Caffeine is by far the world's most widely consumed psychoactive, and it is legal and unregulated in nearly all jurisdictions. The complexity of psychoactives arises from the great diversity of disciplines (broadly characterized into chemical, biological, and physical sciences) that contribute to our scientific knowledge of them. Indeed, research into psychoactive substances requires a high degree of specialization, and in particular, a multidisciplinary background from pharmaceutical sciences and medicine.

The concept of psychoactives is prone to be subject to some misunderstanding, especially due to illicit and recreational uses that have popularized different colloquial terms for psychoactives, such as “soft drugs”, “hard” drugs, “uppers”, “downers”, “club drugs”, stupeficients, among others. Psychoactives, or psychotropics, are best terms to describe those compounds that act primarily on the central nervous system, where they alter brain function, resulting in temporary changes in perception, awareness, mood, consciousness, and behavior.

A common scientific classification divides psychoactive substances into several groups according to their clinical applications and their most relevant effects in the central nervous system at normal/classical doses. Nevertheless, superimposed effects typically occur, meaning that the confluence of more than one classification is needed to successfully classify them. Several psychoactive drugs have ongoing recognized therapeutic potential. These include



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general anesthetics (e.g., inhaled agents such as isoflurane, desflurane, sevoflurane, barbiturates, ketamine, and propofol); analgesics for pain relief (e.g., opioids such as morphine, codeine, oxycodone, hydrocodone, dihydromorphine, methadone, buprenorphine, pethidine (meperidine), tramadol, tapentadol, etc.); anticonvulsants or antiepileptic drugs, more recently known as antiseizure drugs (e.g., carbamazepine, oxcarbazepine, eslicarbazepine acetate, vigabatrin, tiagabine, topiramate, gabapentin, lamotrigine, phenytoin, etc.) used for the treatment of epileptic seizures; and antiparkinsonian drugs (e.g., levodopa, dopamine agonists such as bromocriptine, pergolide, pramipexole, and ropinirole, and monoamine oxidases (MAO)-B inhibitors such as selegiline and rasagiline) for the management and relief of symptoms of Parkinson's disease. Further examples include medications used to treat neuropsychiatric disorders, such as antidepressants (e.g., esketamine, sertraline, citalopram, fluoxetine, escitalopram, trazodone, venlafaxine, bupropion, duloxetine, paroxetine, amitriptyline, mirtazapine, etc.), which can also be used to treat major depressive and anxiety disorders and chronic pain conditions, and medications that can be used to help manage some substance use disorders, namely depressants such as anxiolytics, sedatives, and hypnotics (e.g., benzodiazepines such as alprazolam, bromazepam, diazepam, oxazepam, and lorazepam, Z-drugs such as zopiclone, zolpidem, and zaleplon, barbiturates such as phenobarbital, pentobarbital, and thiopental, gabapentinoids such as pregabalin and gabapentin, sodium oxybate, and opioids, etc.). These depressants are used to reduce arousal or stimulation in various areas of the brain and are the most common substances used in drug-facilitated sexual assault, as they may cause anterograde amnesia. Ethanol is by far the most studied depressant substance. Antipsychotics or neuroleptics, or "major tranquilizers" (e.g., risperidone, quetiapine, ziprasidone, clozapine, haloperidol, flupentixol, thiothixene, sertindole, chlorpromazine, aripiprazole, etc.), also have therapeutic potential, as they are primarily used to manage psychosis, including delusions, hallucinations, paranoia, or disordered thought, principally in individuals with schizophrenia but also in individuals with a range of other psychotic disorders. Stimulants (e.g., modafinil, lisdexamfetamine, methylphenidate, *d*-amphetamine, caffeine, cocaine, nicotine, arecoline, pseudoephedrine, 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"), etc.) also have therapeutic potential as they increase the activity in the central nervous system, which induces pleasurable and invigorating feelings and provides the effect of endurance, reducing the feeling of mental (alertness) and physical (motor activity) fatigue. They are used for the treatment of attention deficit hyperactivity disorder, narcolepsy, and obesity. Antihistamine drugs are used primarily for the treatment of allergies, but some, such as diphenhydramine and chlorpheniramine, have also been abused [7]. Curiously, several psychoactive substances are used in detoxification and rehabilitation programs related to substance use disorders, such as acamprosate or naltrexone in the treatment of alcoholism, or methadone or buprenorphine maintenance therapy in the case of opioid dependence [8,9]. Hallucinogens (e.g., lysergic acid diethylamide (LSD), mescaline, psilocybin, psilocin, MDMA, etc.) are a special group of psychoactive substances characterized by an overall capacity to induce mood alterations, such as intense euphoria or irritability, variations in a person's perception, mainly visual and auditory, and altered thought with overwhelming intellectual or spiritual insight, similar to what is experienced only through dreams or at times of religious exaltation. Based on the diverse effects of these drugs, in addition to the term hallucinogen (i.e., a drug that produces hallucinations, but this effect rarely occurs in typical doses) the preferred term that describes the nature of these drugs is psychedelic (i.e., "mind revealing" or "mind-manifesting"), as this term does not focus on one specific effect but on psychedelic experiences or "trips" [10]. Additionally, unlike most other psychoactive drugs, their use does not lead to addiction/dependence, nor are they usually consumed for prolonged periods of time [11–13]. The term entheogenic has also been increasingly used for this class (mostly in non-scientific forums) to highlight the ability of these substances to cause mystical and spiritual experiences [10]. All psychedelics have a commonality in the fact that they act as agonists (or partial agonists) of the serotonin 5-HT<sub>2A</sub> receptor, through which they exert effects in the central nervous system [10,14,15].

While most psychedelic drugs are illegal worldwide under the United Nations conventions, occasional exceptions in some countries exist for religious ceremonies [10].

Cannabis and its derivatives (e.g., marijuana, hashish, etc.) are the most illicit abused psychoactives worldwide and are generally treated as an independent category [16,17]. Despite the considered cannabis derivative, the main psychoactive substance present is always delta-9-tetrahydrocannabinol ( $\Delta^9$ -THC), which is generally considered to have depressant and sedative effects. Nevertheless, the cannabis plant is much more complex than  $\Delta^9$ -THC itself, as around 500 compounds (with at least 60 of them being cannabinoids) have already been described. Therefore, cannabis exerts mixed depressant, stimulant, and psychedelic effects, perhaps leaning more towards the latter. Moreover, cannabis is one of the most polemic recreational psychoactives, and there are several campaigns that aim to decriminalize or legalize its recreational use.

Dissociative drugs (e.g., phencyclidine (PCP) and ketamine) acquire such a designation as they produce dissociative anesthesia (i.e., a sense of dissociation from the body and the environment), a neologism firstly coined by Corrsen and Domino [18,19]. This means that the user remains conscious and appears to be awake (i.e., eyes may be open with the presence of nystagmus) but exhibit no apparent response to surgical pain; “the lights are on, but no one’s home” [20]. Users represent a “trance-like cataleptic state” characterized by profound and complete analgesia and total amnesia with the preservation of protective airway reflexes (i.e., intubation is unnecessary), spontaneous respirations, and cardiovascular stability (i.e., blood pressure and pulse rate do not decrease and may even increase slightly) [20–22].

Finally, inhalants are a special class, as this encompasses household and industrial chemicals, the volatile vapors, or pressurized gases of which can be concentrated and breathed in via the nose or mouth. Examples include butane, hexane, propane, alkyl nitrites (described by the slang term poppers), toluene, benzene, gasoline, acetone, nitrous oxide, etc. Some of them may also fall into other categories, such as nitrous oxide, which is also an analgesic [23,24].

Other psychoactives are probably more recognized by their illicit use, such as heroin and cocaine. Nevertheless, it should be remembered that even in these cases, licit therapeutic applications are also possible. In this biunivocal market, there are several examples of psychoactives that can be labeled with different designations such as 3,6-diacetylmorphine (i.e., heroin) and sodium oxybate (i.e.,  $\gamma$ -hydroxybutyric acid; GHB). Others (the list ever-growing) are currently being tested to complement the therapeutic arsenal, such as the treatment of depression with psilocybin (present in *Psilocybe cubensis*), mescaline (present in *Lophophora williamsii*), ibothenic acid and muscimol (both present in *Amanita muscaria*). Similarly, 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) has been demonstrated benefits in the treatment of depression, anxiety, and stress and it is widespread in nature such as in the Ayahuasca (i.e., an hallucinogenic botanical beverage), in the *Arundo donax* (i.e., perennial cane), in the Colorado River toad (*Incilius alvarius*), and in the Sonoran Desert toad (*Incilius alvarius*). In the case of toads and *Arundo donax*, bufotadine is also another psychoactive substance present with potential therapeutic interest [11,25–27]. Ibogaine (present in *Tabernanthe iboga*) was also evaluated for the treatment of drug dependence [28]. Ergine (also known as *d*-lysergic acid amide (LSA) and *d*-lysergamide) is an ergoline alkaloid that occurs in various species of vines in the Convolvulaceae family (e.g., *Argyria nervosa* and *Argyria nervosa*) and some species of fungi (e.g., *Claviceps purpurea*); this compound has been described to have therapeutic potential in the treatment of ethanol addiction and anxiety [29–31].

The literature also simply divides psychoactives into licit (e.g., nicotine, caffeine, ethanol, nasal decongestants, benzodiazepines, codeine, etc.) or illicit (or controlled) substances (e.g., heroin, cocaine, ecstasy, etc.), and into natural (e.g.,  $\Delta^9$ -THC, cocaine, psilocybin, mescaline), and synthetic ones (e.g., ecstasy, lysergic acid diethylamide, GHB). Another type of classification uses colloquial terms to group certain psychoactive drugs. Hard (e.g., heroin, cocaine, and methamphetamine) and soft (e.g., cannabis derivatives,

psilocybin, mescaline, and ibogaine) drugs are colloquial terms used based on the assumption that “soft” drugs are not as dangerous, having less potent, more controllable effects and being less likely to cause dependence than “hard” drugs. These terms should not be used, as the borderline between the categories is tenuous. Club drugs is also a common term applied to describe synthetic psychoactives used as a status symbol in nightclubs, bars, at parties, and electronic dance music concerts, such as ecstasy, GHB, nitric oxide, LSD, ketamine, benzylpiperazine, and flunitrazepam [32]. Finally, “uppers” is colloquially used to refer to stimulants and “downers” to refer to depressants.

The worldwide *status quo* on psychoactives abuse has also been changing dramatically in recent years with the emergence of new psychoactive substances (NPS). Such new heterogeneous group divides psychoactives into categories of synthetic stimulants (e.g., cathinones, aminoindanes, phenethylamines, piperazines, and tryptamines), synthetic cannabinoids, synthetic hallucinogens (e.g., tryptamines, lysergamines, and phenethylamines), and synthetic depressants (which include synthetic opioids and synthetic benzodiazepines) [33,34]. These substances are also known as either designer or synthetic drugs, or by the more popular (but misleading) colloquial term of “legal highs” [34]. It is noteworthy that although NPS are not controlled by international conventions (the 1961 United Nations Single Convention on Narcotic Drugs or the 1971 United Nations Convention on Psychotropic Substances), they may pose a threat to public health that is comparable to the substances included in these conventions [35,36]. A designer drug is a structural or functional analog of a controlled substance that has been designed to mimic the pharmacological effects of the original drug, while avoiding classification as an illegal substance and/or detection in standard drug tests.

With this brief introductory overview to psychoactive substances, it is evident that there is a world of opportunities to research in this field and therefore to contribute to the development of humanity. *Psychoactives* (ISSN: 2813-1851) [37] is a new international, peer-reviewed, open-access journal related to the latest advancements in psychoactive substances, either in living beings or in the deceased, both from the clinical and forensic perspective, and aims to provide comprehensive and systematic knowledge on their biological risks and potential medicinal benefits. It aims to cover the chemical, biological, medical, environmental, social, recreative and political aspects of psychoactive drugs, emphasizing their putative therapeutic effects as might be the case of some psychedelics. We believe that only by bringing together experts from across all of these multidisciplinary fields, it will be possible to contribute to developments in this field due to the several different qualities of the members that belong to this huge group. Thus, we will publish original articles, reviews, short communications, letters to the editor, case reports, technical notes, protocols, editorials, guidelines, and commentaries, with no restriction on the length of the papers. Our aim is also to encourage scientists to dedicate their efforts to research into the pharmacological, chemical, and toxicological effects of psychoactives, not only concerning principal/classical psychoactives, but also researching on NPS. In a broad spectrum, we aim to cover physicochemical characteristics, structure versus activity relationships, pharmacokinetics, pharmacodynamics, pharmacogenetics, especially concerning polymorphisms in gene-encoding enzymes involved in metabolism (e.g., CYP450 isoforms), and other factors that may justify the interindividual variability in the psychological and physiological effects, drug–drug interactions, and toxicity of psychoactives.

The Editorial Board of *Psychoactives* invites high-quality contributions in the field and wishes all future contributors and readers the best for this new scientific project.

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### Short Biography of the Author



**Prof. Dr. Ricardo Jorge Dinis-Oliveira, PhD, European PhD, DSc** is a toxicologist, pharmacologist, and forensic sciences expert who develops his activity in cutting-edge topics of health and life sciences in the areas concerning the toxicology and pharmacology of psychoactive substances, pesticides, and drugs in their preclinical, clinical, and forensic aspects. He has supervised several Integrated Master's dissertations, Master's Dissertations, and PhD theses. He is a member of the Editorial Board and Ambassador of several international scientific journals. He is the author of more than 170 articles published (representing more than 4700 citations) in international indexed journals, with peer review, and the author of about 36 book chapters, 4 books, and 4 national and 3 international patents. He is the author of Guidelines in Forensic Sciences for Clinical and Forensic Toxicological samples collection with international scope, and has received recognition for his Pedagogical Excellence in Higher Education. He regularly presents oral communications/conferences and in the form of posters in scientific meetings, which globally number around 250, and he organizes, on a regular basis, several scientific events, namely congresses, conference circles, lectures, workshops, or seminars. He is an Associate Professor with Habilitation (Aggregation) at the University Institute of Health Sciences and of the Faculty of Medicine of University of Porto. He is the Director of the Research Unit TOXRUN—Toxicology Research Unit of IUCS—and an integrated researcher at UCIBIO-REQUIMTE—Applied Molecular Biosciences Unit/Associated Laboratory for Green Chemistry, Clean Technologies, and Processes. In 2021, he entered the World's Top 2% Scientist's list, which ranks the most highly cited scientists. He is the founder and current President of the Portuguese Association of Forensic Sciences (APCF) and was vice-president of the Portuguese Society for the Study of Abuse and Neglect (SPECAN). He is the Director of Medical Writing at MTG Research and Development Lab and he is the Scientific Consultant of Albert Labs Advisory Board. His current H index is approximately 31, depending on the calculation platform.