



Substance use disorders and cooperative research on addictions: Spanish approach as a model

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ABSTRACT

Substance use disorders (SUD), also named addiction when it is severe, is a chronic brain disorder with serious impact on individual who suffer, the public health and with high burden of disease. They are multitude of mechanisms/factors involved in addiction: from individual characteristics of the person (from genetic to impacts of stress, sex, and age) to social and environmental situation (availability and accessibility of substances, cultural and legal aspects, socio-economical situation) and type of substance of use (pharmacological characteristics). Then, research on Addiction must include different, complementary, and translational perspectives. In this review, we explore the neurobiological, psychosocial, and epidemiological knowledge of substance addiction, and the main role played by pharmacology in the research in this field. In Spain, since 2002, collaborative networks have emerged for comprehensive research on addictions, with the creation of the Addictive Disorders Network (RTA), currently redefined as the Research Network for Primary Care in Addictions (RIAPAd) with the support of the Carlos III Health Institute (Instituto de Salud Carlos III). Basic (including neuropharmacology and behavioral pharmacology), clinical and epidemiological research groups stand out, combining efforts to address prevention, early detection and treatment through interdisciplinary cooperation and the subsequent dissemination of results.

1. Addiction: an introduction

Substance use disorders (SUD), also denominate addiction when it is severe, is a chronic brain disorder with serious consequences for individual and public health. The search for positive stimuli and avoidance of negative ones can be considered the starting point of any addictive disorder. Specific chemicals interacting with a discrete set of pharmacological targets located in motivational circuits modulate this search/avoidance behavior. Access to these highly reinforcing substances

combined with individual vulnerabilities, including genetic factors, sex or age, and sociocultural factors or interpersonal relationships, forms the basis of this phenomenon [1].

In substance use disorder the compulsive drug-seeking and drug-taking behavior persists despite serious negative consequences [2]. This condition is characterized by the loss of control when limiting consumption and the appearance of a negative emotional state when access to the drug is limited [3]. Research in the field of addiction requires a multidisciplinary approach that considers various factors,

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including physical, psychological, and behavioral dependence, which highlights the complexity of understanding the mechanisms underlying addiction.

Regarding neurobiological mechanisms, deregulation of the brain reward system is essential to understand the development of addiction [4]. Substances initially produce positive reinforcement action by acting on dopaminergic neurons of the ventral tegmental area, their projecting fields in the nucleus accumbens, the prefrontal cortex and the extended amygdala, as well as in the brain nuclei receiving inputs from the nucleus accumbens. These brain areas involve neurotransmitter as dopamine and endogenous opioids. Continuous consumption produces neuroadaptations observed in the withdrawal/negative affect stage (negative reinforcement) in areas as amygdala involving neurotransmitter as corticotrophin releasing factor, norepinephrine and dynorphin. Chronic changes in this system, especially the decreased function of the dopaminergic component of the reward system, lead to neuroadaptations in multitudes of neurotransmitters, such as the glutamatergic system, resulting in a modulation of neuroplasticity [1,5]. As a direct consequence of this deregulation, phenomena such as “craving” appear, defined as a very intense pathological desire to consume the substance. This desire is triggered by dysphoria and anhedonia during the withdrawal stage, combined with exposure to stimuli related to the substance in question. This drives people to seek it out, and ultimately culminates in compulsive consumption and subsequent intoxication [6]. This condition results from constant changes in the hedonic set point, the moment at which pleasure is achieved, and a dissociation between the desire for the drug and its pleasurable effect [2,4]. This dysregulation associated with reward also gives rise to the appearance of habits, which allows the addictive disorder to be conceived as chronic and recurrent [7].

Personal susceptibility plays a fundamental role in developing an addictive disorder [8]. From presence of psychiatric disorders, which carry a substantial increase in the risk of developing addiction (dual disorder) [9], to genetic factors that influence a variety of aspects, such as different comorbidities between various substances [10], that could explain why not everyone exposed to a given substance develops addiction, as well as the variability in recovery among addicts. Likewise, sociodemographic aspects, such as age or gender, influence the probabilities of develop and/or remission of substance use disorder, with younger developing addiction more than older, men being less likely to

remit than women, and ethnic-racial differences in the probability and time until remission, depending on the type of substance [11]. Gender issues are very relevant, since women usually demand less treatment, are more stigmatized, and display differential sensitivity for the toxic effect of drugs, as is the case for alcohol. Fig. 1 summarizes most relevant factors in substance use disorder.

The clinical criteria to define substance use disorder according to the classification of the American Psychiatry Association (The Diagnostic and Statistical Manual of Mental Disorders 5th ed, DSM-5) are found in Table 1 [6,8].

2. Epidemiology

According to the latest report from the United Nations (World Drug Report 2023), drug use, including alcohol and tobacco, continues to be a widespread problem worldwide, with more than significant impacts on public health and burden of disease. It causes important mortality and health loss in terms of high number of disability-adjusted life years (DALYs) and years lived with disability (YLDs).

Regarding alcohol, a legal substance in most countries in the world, it is estimated that 18.4 % of the world’s population experienced intense episodes of consumption in the last 30 days, contributing to 3 million deaths worldwide (which represents 5.3 % of the total), with particularly higher consumption in European regions.

On the other hand, tobacco continues to be a cause for concern, with 22.4 % of the world’s population using it during 2020, causing approximately 8 million deaths among direct users and exposed non-smokers.

Regarding illegal drugs, consumption has increased in the last 10 years (2011–2021) by 23 %, with a total of 296 million users who have tried a drug in the last 12 months in 2021.

The case of cannabis with an estimated consumption of 219 million users in 2021, observing a reduction in the gender gap in drug consumption, with regions such as North America with 42 % of female cannabis consumers, reflecting this trend. in the consumption of amphetamines and pharmaceutical products for non-medical use. However, men predominate in the consumption of cocaine (73 %) and opioids (75 %), the latter being the group of substances that contributes the most to serious harm, including fatal overdoses [12].

The global prevalence of substance consumption, both legal and

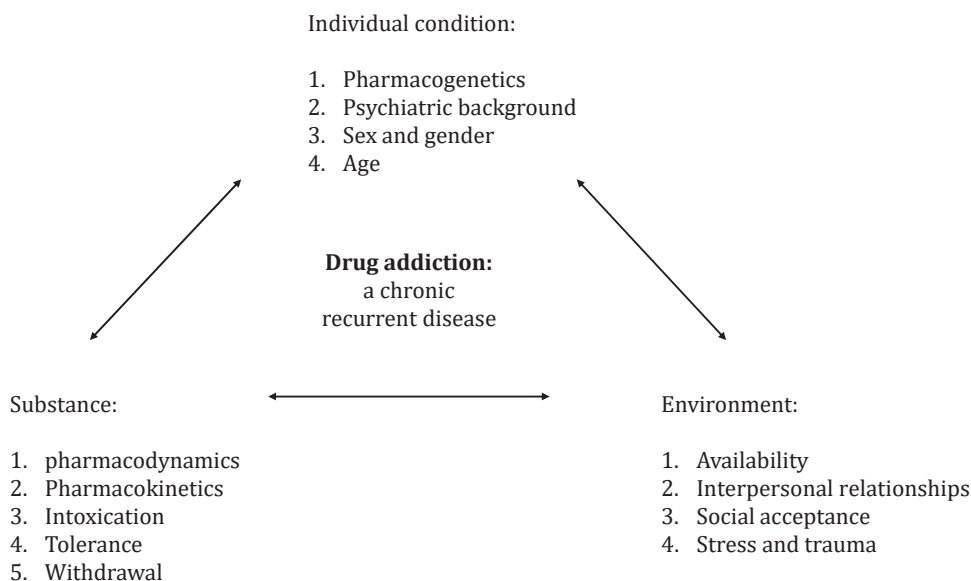


Fig. 1. Factors involved in development of substance use disorder

Table 1

DSM-5 diagnostic criteria for substance use disorder (includes categories of the criteria).

A. A problematic pattern of substance use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period:

Loss of control over the consumption of the substance

1. The individual may take the substance in larger amounts or over a longer period than was originally intended
2. The individual may express a persistent desire to cut down or regulate substance use and may report multiple unsuccessful efforts to decrease or discontinue use
3. The individual may spend a great deal of time obtaining the substance, using the substance, or recovering from its effects
4. Craving is manifested by an intense desire or urge for the drug that may occur at any time but is more likely when in an environment where the drug previously was obtained or used.

Social impairment

5. Recurrent substance use may result in a failure to fulfill major role obligations at work, school, or home
6. The individual may continue substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance
7. Important social, occupational, or recreational activities may be given up or reduced because of substance use.

Risky use of the substance

8. Recurrent substance use in situations in which it is physically hazardous
9. The individual may continue substance use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

Pharmacological criteria

10. Tolerance, as defined by either of the following:

- a. A need for markedly increased amounts of the substance to achieve intoxication or desired effect.
- b. A markedly diminished effect with continued use of the same amount of the substance.

11. Withdrawal, as manifested by either of the following:

- a. The characteristic withdrawal syndrome for the substance.
- b. The substance (or a closely related one) is used to relieve or avoid withdrawal symptoms.

Two or three symptoms indicate a mild substance use disorder; four or five symptoms indicate a moderate substance use disorder, and six or more symptoms indicate a severe substance use disorder. Tolerance and withdrawal criteria do not count toward the diagnosis if the patient is receiving appropriate medical treatment for pain, depression, or anxiety. Patients who follow these programs can be classified as SUD only if they have other symptoms of aberrant behavior demonstrating "compulsive search" for the substance.

illegal, reveals their extensive presence throughout the world. It is essential to recognize the addictive process as a chronic disorder, since it entails multiple implications that converge in a great risk that must be prevented. These implications range from clinical aspects, such as the transmission of diseases such as hepatitis C or HIV due to the use of injectable drugs or infections due to risky sexual practices due to impaired decision-making during consumption, to social aspects such as non-compliance with work obligations or domestic violence, drug use in physically dangerous situations, emergence of substance-related legal problems, and continued drug use despite recurrent interpersonal problems [2,12].

Finally, a new epidemiological concern arose from the emergence in the illegal market of new psychoactive substances (NPS), very potent and selective synthetic drugs designed to act at the main targets of traditional drugs, that include synthetic opioids (fentanyl, nitazenes), synthetic cannabinoids, cathinones, new hallucinogens, ketamine derivatives, new benzodiazepines etc. [13]. The importance of these phenomenon can be exemplified by either, the fentanyl crisis of the US or the intoxications generated by highly potent cannabinoid CB1 receptor agonists [14].

3. Role of pharmacology in drug addiction research

Pharmacology plays a key role in several aspects of addiction research by studying the effects of substances on the body, including mechanisms of action, pharmacokinetics, and pharmacodynamics. The pharmacological aspects that underlie addiction are of vital importance to find the most effective treatments. Some of the most important aspects are described below.

3.1. Molecular mechanisms and neurobiology

It is essential to investigate the molecular mechanisms involved in addiction, therefore, the interactions of substances and the central nervous system; this entails the study of the different signaling pathways and neurotransmitters involved. In this way, preclinical models are established for identification of specific pharmacological targets involved in the addictive process and to allow the development of new treatments and. Likewise, the impact of alterations in the different

neurotransmitter systems provides valuable information about the development of addiction. Furthermore, these mechanisms can explain the behavioral modifications observed in abuse and addiction in both experimental animals and humans. This knowledge is even more necessary to fight the emergence of NPS [15].

3.2. Pharmacokinetics and pharmacodynamics

The analysis of the absorption, distribution, metabolism, and excretion of drugs, that is, all the pharmacokinetic variables, is known to play a crucial role in the appearance of behavioral and neurobiological alterations in terms of addiction. Higher bioavailability, elevated blood concentrations and the rate of access to the CNS and the influence of the speed to cross the blood-brain barrier are relevant factors, which increases the abuse and addictive potential. Pharmacodynamics is also a pharmacological condition of drugs that influences drug abuse potential. Both efficacy and potency of drugs influence the rate of cellular and system activation, leading to differential acute responses and adaptive mechanisms after long-term use [16].

3.3. Neuroplasticity

The repeated consumption of substances with addictive potential causes neuroadaptive changes linked to alterations in the main neurotransmitter systems involved in addiction. Such as overstimulation of the dopaminergic pathway induces neuroplastic adaptations strongly involved in the neurological conditions caused by these substances, especially in phenomena of tolerance, physical dependence and relapses. In this sense, there is a clear increase in the potency/doses used, as we can deduct from the use of fentanyl (more potent than morphine), cannabis preparations up to 30 % of THC or synthetic cannabinoids with full agonism at the cannabinoid receptors, or cathinones with enhanced potency at monoamine transporters, might facilitate these neuroadaptations and the appearance of clinical complications [1,17].

3.4. Development of new pharmacological treatments

Pharmacology helps by detecting potential therapeutic targets, developing new medications based on modulators of the different

receptors of the neurotransmitters involved, such as the opioid partial agonist buprenorphine for the treatment of heroin/opioid agonist use. These treatments can intervene in phenomena of possible relapses, desires for consumption and promotion of recovery; the existence of clinical trials allows the evaluation of the effectiveness and safety of these new drugs [18].

3.5. Pharmacogenetics

Pharmacogenetics explains the genetic influence on the different individual responses to drugs, which responds to the possible factors that predispose people to develop an addiction, to be resistant or not present it, or even to personalize the most optimal therapies for each patient [19].

In summary, pharmacology offers biological and chemical insights into addiction that allow for the design of medications and interventions to treat the disorder. The interdisciplinary approach that this discipline provides, together with neuroscience and psychology, contribute to the global understanding of addiction and its possible treatment.

In Spain, there are several research groups involved in the study of the mechanisms of addiction. The vast majority are neuropharmacology/basic pharmacology groups and others from clinical pharmacology. In this review, we will include a brief description of some of the most relevant teams grouped in the Spanish addiction research program (Research Network in Primary Care of Addictions (RIAPAd)) and some more not included in RIAPAd.

4. Cooperative research on addictions in Spain

4.1. Addictive Disorders Network (RTA)

The concept of addictions has evolved considerably over time, going from being treated as a “moral deficiency, a vice or weakness, to being recognized today as a chronic recurring disorder with well-established neurobiological bases, considered as a brain disease [1].

Despite progress in understanding, research has always been complex due to the large number of mechanisms underlying the addictive disorder. This means that different aspects must be addressed, from preclinical and clinical pharmacological to epidemiological, sociological, pathophysiological, pharmacological, clinical and its prevention. Combining all these activities in a single project is a challenge. In 2002, the Ministry of Health of Spain, through the Carlos III Health Institute, raised the possibility of bringing together different research groups to comprehensively address different health problems, one of them the addictive disorders. To apply for these grants, it was a priority to cover different aspects of addiction, from epidemiology to preclinical and clinical research. The call was called Thematic Networks for Cooperative Research in Health (RETICS).

After this competitive RETICS call, in 2002, the first collaborative research network on substances of abuse was established: the so-called “Addictive Disorders Network (RTA)” This, originally, was made up of 22 research teams from 7 Autonomous Communities, covering three key aspects of drug addiction research: basic, clinical and epidemiological research. The coordinator of this Network was Prof. Fernando Rodríguez de Fonseca at the Malaga Research Institute (initially the Carlos Haya Hospital Foundation and later IBIMA). The main objectives of the RTA were the following:

- Generate a common space of research to integrate basic, clinical and epidemiological research with a clear translational aim.
- Prepare a map of cooperative research projects in the three mentioned areas: basic, clinical and epidemiological research.
- Establish a training structure through teletraining in drug addiction.
- Develop an informative system of the network’s activities, for the transmission of scientific progress in drug addiction to the population.

The initial consortium of this network had included basic (15), epidemiological (4) and clinical groups (3). Among the research groups, 6 linked to preclinical pharmacology of addictions in academic departments of pharmacology and another 6 dedicated to the neurobiology of addictions belonging to departments of psychoneurobiology. Among the clinical groups, one was dedicated to the clinical pharmacology of drugs of abuse [20].

This research network was renewed downwards in different stages for almost twenty years, three more times, spanning from 2003 to 2022 (RTA 2003–2005, RTA 2006–2011, RTA 2012–2015 AND RTA 2016–2022), facilitating interdisciplinary cooperation reflected in hundreds of scientific publications, several patents, and cooperative projects. As example of the outcomes of the network, groups belonging to the initial barely shared a 12 % of cooperative publications. This percentage grew to 20.4 % in 2006; 38.5 in 2012 and 40 % in 2019, remaining stable since. That increase in cooperation is reflected in the current mean of 50 cooperative publications per year in peer-reviewed journals, led by members of the network. Thus, more than 600 cooperative studies have been published since 2003 under the RTA framework. The cooperation extended towards coordinated projects, co-supervised doctoral thesis, participation as a network in major national (i.e. Sociodrogalcohol, Spanish Society for Neuroscience) or international meetings (i.e. Lisbon Addiction or Dual Pathology meetings). In addition, members from the different groups cooperate to create and support different master’s degree courses at Madrid, Barcelona and Valencia Universities. Importantly, and following ISCIII recommendations, since 2012 the network focused on alcohol and psychostimulant research, although cooperative studies on other illegal drugs and behavioral addictions continued.

In 2021, it was considered that aspects of primary care should be incorporated into these networks, trying to further advance towards the implementation of the scientific results obtained since 2002. To this end, the program entitled Cooperative Research Networks Oriented to Health Results (RICORS) was initiated as structures made up of a set of research groups with a common research objective, concrete and achievable. These multidisciplinary groups belong to a variable set of biomedical research centers, dependent on the different public administrations or the private sector and belonging to a minimum of ten Autonomous Communities.

4.2. Research Network in Primary Care of Addictions (RIAPAd)

The experience gained through the RTA since 2002, facilitated the design of a new network that adjusted to RICORS program condition. Thus, the RTA has evolved into the RICORS to become the Research Network in Primary Care of Addictions (RIAPAd), made up of 18 research groups from 10 Autonomous Communities and which maintains the bases that were established in the RTA, researching to improve the prevention and treatment of addictions (Table 2). There are 7 objectives that are broken down in the work plan established for 2022–2024:

- Prevention, through interventions in educational and primary addiction treatment settings, as well as with the training of health professionals through specialized master’s programs.
- Monitoring the evolution of addictive disorders, through early detection of changes in consumption patterns, the final characterization of clinical characteristics and the temporal evolution of addiction.
- Chronicity, exploring aspects of chronic comorbidity and follow-up through cohort studies.
- Maternal and child health in addictions, improving drug detection throughout the perinatal period.
- Patient participation, implementing the results reported by patients and their experiences.

Table 2
RIAPAd research groups and research fields.

Cluster	Institution	Research scope
Marta Torrens Olga Valverde Subgroup	Hospital del Mar Research Institute (IMIM). Pompeu Fabra University (UPF)	Clinical aspects of addictive disorders, dual pathology, new substances of abuse and gender differences in consumption Research on alcohol during prenatal and breastfeeding periods, cannabinoids and phytocannabinoids
Fernando Rodríguez de Fonseca	Biomedical Research Institute of Málaga (IBIMA)	Pathophysiology of addictive disorders, alcoholic hepatotoxicity
Roberto Muga Magí Farré Subgroup	Germans Trias i Pujol University Hospital and Germans Trias i Pujol Research Institute (HUGTiP-IGTP)	Medical complications of substance use disorders, with a focus on alcohol, cocaine, cannabis, opiates, and tobacco. Acute pharmacological effects and toxicity caused by new psychoactive substances, psychostimulants and acute effects of excessive alcohol consumption in young people
José Miñarro	University of Valencia (UV)	Neurobiological mechanisms of addictive behavior, with emphasis on relapse, effects of drug use during adolescence
Pedro Grandes	University of the Basque Country (UPV/EHU)	Effects of excessive alcohol consumption during adolescence, alteration of the endocannabinoid system
Gabriel Rubio	12 de Octubre University Hospital	Neurobiological and cognitive markers related to alcohol dependence.
Jorge Manzanares	Miguel Hernández University (UMH)	Role of the endocannabinoid system and its therapeutic potential, identification of genes and proteins related to neuropsychiatric disorders
Laija Miquel	Hospital Clinic Barcelona. August Pi i Sunyer Biomedical Research Institute (IDIBAPS)	Molecular mechanisms of addiction, socioeconomic costs, stigmatization associated with addictions
Javier Costas	Santiago de Compostela Health Research Institute (IDIS)	Identification of genetic predisposition factors, polygenic risk estimates
Jose Benito	University of Santiago de Compostela (USC)	Analysis of the presence of drugs and toxins in wastewater
Gonzalo Herradón	CEU San Pablo University	Study of PTN/PTPRZ1 as a regulator of neuroinflammation induced by alcohol consumption during adolescence.
Javier Zaragoza	University of Zaragoza (UNIZAR)	Analysis and evaluation of comprehensive programs to promote healthy habits in early childhood and primary schools
Rafael Maldonado	Pompeu Fabra University (UPF)	Study of the neurobiological substrate of drug addiction, pain, affective disorders and eating disorders, participation of endogenous opioid and cannabinoid systems in the pathophysiology of these disorders
Emilio Ambrosio	National University of Distance Education (UNED)	Study of the long-term effects of exposure to cannabinoids during adolescence, the psychobiological mechanisms involved in relapse to drug use
Guillermo Burillo-Putze	University of La Laguna (ULL)	Acute drug poisoning in hospital emergencies, with special emphasis on new psychoactive substances.
Manuel Cuesta	Navarra Biomedicine Research Center (Hospital	Phenotypic characterization of psychoses, research in dual pathology

Table 2 (continued)

Cluster	Institution	Research scope
María Isabel Colado	Universitario de Navarra, IdiSNa) Complutense University of Madrid (UCM)	Toxicology of MDMA, pre-exposure to ethanol in MDMA-induced changes, involvement of the kynurenine pathway in the effects of psychostimulants and alcohol
Carlos Roncero	Salamanca Biomedical Research Institute (IBSAL)	Sexual dysfunctions in patients who consume alcohol and cocaine; monitoring of psychotic symptoms in relation to the severity of addiction and violent behaviors in patients with substance use disorder

- E-health tools in the treatment of addictions for diagnosis and treatment.
- Dissemination of the results to professionals and the general population.

The objectives of RIAPAd are described below:

Prevention is the first objective set by the RIAPAd. In this regard, Javier Zaragoza and Victor J. Villanueva-Blasco, together with the Barcelona Public Health Agency work on interventions in educational and primary addiction treatment settings, health promotion in relation to problematic drug use,

The second objective, led by Jose Benito, focuses on the development of new drug use indicators, beyond the traditional methods used by the National Focal Points of the EU and reported to the EMCDDA, as central monitoring center in Europe. This is accomplished through techniques such as wastewater analysis or syringe content analysis. The groups of Guillermo Burillo and Bernardino Leon further contributed to this activity, oriented to better monitoring the presence of drugs in emergency rooms cases of intoxication. Members of the team are part of The European Drug Emergencies Network (Euro-DEN). The work is being focused not only on monitoring but also on age, gender and Clinical presentation of toxicity cases studied, with a special attention to fentanyl/cannabinoids intoxication.

In addition to the drug monitoring this objective is complemented by completing clinical phenotyping through the use of new biomarkers, as well as the promoting of new therapies, including preclinical research. The development of treatments is directed by Rafael Maldonado, trying to propose new treatments based on alternative pharmacological targets and the support of biomarkers that might help to achieve a better patient stratification and to identify treatment response.

Addiction is a transversal disorder that demands attention at every physiological system in the body, so medical comorbidities stand in this cooperative project as a center pillar of the cooperative research. The third objective, led by Roberto Muga addresses this objective by promoting the study of new aspects of chronic comorbidity in humans and its biological correlation with preclinical study models, such as liver disease or cognitive impairment associated with alcohol use disorders, depression due to cocaine use or polygenic risk assessment associated to these comorbidities. In this regard, the participation of clinical groups such as Manuel J. Cuesta from Navarra, Joaquin Costas from Galicia, Carlos Roncero from Salamanca or Gabriel Rubio from Madrid, Marta Torrens and Laija Miquel from Barcelona, provides patients, and support cohort studies that allowed to achieve this specific aim. On the other side, excellent preclinical research groups such as those from José Miñarro in Valencia, Pedro Grandes in Basque Country, María Isabel Colado and Gonzalo Herradón in Madrid or Jorge Manzanares in Alicante contributed with late-state-of-the art models of drug-associated comorbidities.

Bernardino Barceló from Mallorca Hospital was proposed to lead the fourth objective, which aims to understand maternal and child health in addictions, through the detection of drug use in pregnancy, and the development of perinatal and adolescent drug exposure models to understand the impact in late stages of life. This objective was partially funded, focusing its activity mainly in the development of preclinical models of maternal-infant impact of drugs. In this sense, the groups of Olga Valverde from Barcelona, Jose Miñarro from Valencia, Jorge Manzanares in Alicante and Fernando Rodríguez de Fonseca in Malaga have coordinately worked on the impact of alcohol, stress and adverse events along pregnancy/lactation on the appearance of chronic disorders in the adulthood using murine models. Patient participation is essential, this objective is developed by the network leader, Marta Torrens. This objective includes collecting the results and experiences reported by patients (PROMs and PREMs), with the participation of clinical groups from Madrid, the Balearic Islands, Canary Islands, Badajoz, Navarra, Málaga and Castellón, taking advantage of the Primary Care network.

Gabriel Rubio leads the sixth objective, which seeks to improve diagnosis through e-health tools, such as improving diagnosis through the implementation of dual diagnosis screening interviews (DDSI) in primary clinical settings, identifying psychiatric comorbidity among individuals with disorders due to substance use.

Fernando Rodríguez de Fonseca is responsible for dissemination to professionals, the Scientific Community, patients and society in general, this being the last of the objectives. To achieve this, a wide variety of channels are used, such as publication in high-impact journals and good practice guides aimed at primary care and hospital environments, in the case of professionals and the Scientific Community. The presentation of results in forums and meetings, the RIAPad website and society-oriented events such as Open Sessions at Scientific Meetings, such as SOCIDROGALCOHOL, are the channels used for patient associations and society in general, although specific patient associations-oriented meetings (i.e. in alcohol, opioid analgesics use, etc.) have been organized to fully transfer RIAPad's findings to the society [21].

At the recent meeting of the External Scientific Committee of the RIAPad, which took place on February 7 and 8, 2024, the results and degree of achievement of each of the objectives in the middle of the duration were presented. The most representative milestones include more than 70 cooperative publications in peer review journals in 2 years, more than 115 cooperative communications at scientific conferences and more than 90 cooperative communicative actions at scientific conferences [22].

The main research groups that make up the RIAPad are described below.

As leader of the Network, Prof **Marta Torrens**, Coordinator of the Addiction Research Group (GRAd) at the Hospital del Mar Research Institute and member of Scientific Committee of the European Monitoring Center for Drug and Drug Dependence. The Addiction Research Group is a multidisciplinary team made up of health professionals (psychiatrist, infectious specialist, psychologists, nurses...). The main objective of the GRAd is the study of addictions from different perspectives in order to improve both prevention and treatment. Research lines include:

1. Clinical and therapeutic aspects of addictive disorders, with evaluations of new therapeutic approaches and studies on treatments for opiate, cocaine and alcohol dependence.
2. Dual pathology, psychiatric comorbidity in addictive disorders and its clinical and social implications.
3. New substances of abuse, mainly in the field of detection, potential for abuse and neurotoxicity.
4. Gender differences in substance use.

This group includes a subgroup led by Prof. **Olga Valverde** responsible for the Behavioral Neurobiology Research Group (GReNeC-

Neurobio) at the Pompeu Fabra University in Barcelona. This team studies the neurobiological substrates of psychiatric disorders, with the following lines of research: alcohol research in the prenatal period and breastfeeding, cannabinoids and phytocannabinoids, Alzheimer's disease and depression and maternal separation as a model of depression. In addition, a subgroup led by Gabriela Barbaglia of the Public Health Agency of Barcelona take care for epidemiological aspects [23,24].

Prof. **Fernando Rodríguez de Fonseca** is Coordinator of Innovation at IBIMA, principal investigator at the Neuropsychopharmacology group of the Institute, and member of the scientific committee of the European Monitoring Center for Drug and Drug Dependence since 2006. Its multidisciplinary group addresses the investigation of the biological bases of behavioral alterations and the pathophysiology of prevalent diseases associated with addictive disorders, such as anxiety and depression syndromes, as well as alcoholic and non-alcoholic hepatotoxicity, neurodegenerative diseases such as ischemia, Alzheimer's and Parkinson's, and metabolic programming in development and growth. His research includes the development of new pharmacological therapies, evaluation of foods for medical purposes, and toxicokinetic and toxicodynamic studies [25].

Prof. **Roberto Muga**, head of the Addictions Unit of the Internal Medicine Service of the Germans Trias i Pujol University Hospital, leads a research group based on the complications of alcohol and other substance abuse. The clinical research group focuses on the diagnosis and treatment of medical complications of substance use disorders (SUDs). Its main objective is to expand knowledge about SUDs and their complications, with special attention to alcohol, cocaine, cannabis, opiates, and tobacco. He is coordinator of the multicenter project CohRTA, a scientific structure in which information is collected over time from patients with alcohol use disorder who request treatment for the first time, promoted within the framework of the Network [26].

The group includes a clinical pharmacology research subgroup led by Prof. **Magí Farré**. The members of the group are mainly doctors from the Germans Trias i Pujol Hospital. The primary objective of the group is to study the acute pharmacological effects and toxicity caused by substances of abuse in humans, including the evaluation of the potential for abuse and the consequences of chronic use in substance use disorders and addiction. Research lines include the evaluation of the acute effects of new psychoactive substances (synthetic cathinones such as methylone, pyrovalerone derivatives and others), and classic psychostimulants (MDMA, amphetamines and cocaine), as well as the study of the acute effects of excessive alcohol consumption in young people and its combination with other substances (cannabis, energy drinks), and the evaluation of the effects of natural and synthetic cannabinoids, including cannabis and its components, and their therapeutic use (medical cannabis). Finally, they study pharmacogenomics and substance use, including drugs of abuse and medications, and the influence of genetic polymorphisms on drug effects and pharmacokinetics [26].

Prof. **José Miñarro** leads with Prof. Marta Rodríguez-Arias the Psychobiology of Drug Addiction group at the University of Valencia (School of Psychology), focused on studying the neurobiological mechanisms of addictive behavior, with emphasis on relapse, this being one of the fundamental processes to understand addictive behavior as a disease chronic and recurrent. They also investigate the effects of early life events such as social defeat on drug consumption during adolescence, for which the group has developed a model of polydrug use that more realistically approximates the consumption carried out by adolescents, as well as the awareness mechanisms related to addiction. Its objective is to contribute to the knowledge of these mechanisms to improve the prevention and treatment of addiction. His lines of research include the involvement of the glutamatergic and GABAergic systems in relapse, the role of stress, the neurotoxicity of MDMA, relapse prevention through social factors, and the effects of polyabuse in adolescents [27].

Prof. **Pedro Grandes** directs the Laboratory of Ultrastructural and Functional Neuroanatomy of the Synapse at the University of the Basque

Country in the Faculty of Medicine and Nursing of the University of the Basque Country. The group studies the molecular and functional organization of classical neurotransmitter systems and lipid transmitters in synapses of the prefrontal cortex of the mammalian brain. They study the effects of excessive alcohol consumption during adolescence on the adult brain, as well as the alteration of the endocannabinoid system. They seek treatments that can mitigate these disorders, including pharmacological, nutritional, or environmental interventions. His lines of research focus on the study of the endogenous cannabinoid system in brain function, the effects of drugs of abuse on the brain and behavior, and the mechanisms of action of alcohol on the endocannabinoid system [28].

Prof. **Gabriel Rubio** leads the Addictions and Comorbidity research group in the Psychiatry Service of the 12 de Octubre Hospital in Madrid. The group has clinical and basic researchers, focusing on studying neurobiological and cognitive markers related to alcohol dependence. Its objectives include identifying markers of vulnerability for the development of alcohol dependence, understanding the psychophysiological processes related to relapses, exploring treatment techniques based on updating-reconsolidation-extinction of associative memories, investigating neurobiological changes in animal models of consumption of alcohol, identify targets for the development of treatments and search for biomarkers for the diagnosis, treatment and prevention of the consequences of alcohol consumption [29].

Prof. **Jorge Manzanares** leads the Translational Neuropsychopharmacology group at the Miguel Hernández University in Alicante. His research focuses on identifying genes and proteins related to neuropsychiatric and neurological disorders, searching for new therapeutic targets to improve the pharmacological approach to these diseases. They have investigated the role of the endocannabinoid system and its therapeutic potential, using cannabinoid compounds such as cannabidiol, and evaluating their behavioral and neurochemical effects in models of early and adult exposure to drugs [30].

Prof. **Laia Miquel** is member of the Addictions Unit of the Hospital Clínic of Barcelona and the Institut Clínic de Neurociències. Her research group addresses everything from the molecular mechanisms of addiction to the socioeconomic costs and stigmatization associated with addictions. They have developed standardized measures such as the Standard Drink Unit and the Standard Joint Unit to study the health risks of consumption. Her lines of research include alcoholism and other addictions, cannabis use disorders, addiction prevention, training of addiction professionals, public health, and digital health in addictions [31].

Prof. **Javier Costas** leads the psychiatric genetics group at the Santiago de Compostela Health Research Institute (IDIS). His research focuses on identifying genetic factors associated with mental disorders, such as schizophrenia and drug use disorders, with the goal of improving the diagnosis, prognosis and treatment of patients. His lines of research include the identification of genetic predisposition factors, estimates of polygenic risk, associations with clinical characteristics, identification of functionally related genes, study of rare genetic variants, interaction between genetic and environmental factors, shared genetic susceptibility between mental disorders and their implication in comorbidity, and the hierarchical structure of psychopathology [32].

Prof. **José Benito Quintana** is a researcher at IAQBUS - Institute for Research in Chemical and Biological Analysis, of the Department of Analytical Chemistry of the University of Santiago de Compostela. The group investigates the presence of drugs and toxins in wastewater. His research focuses on using wastewater as a rapid and objective indicator of the consumption of substances of abuse, as well as detecting the presence of drugs in consumer materials such as syringes [33].

Prof. **Gonzalo Herradón** is director of the Neuropharmacology of addictions and degenerative disorders research group at the San Pablo CEU University in Madrid. Prof. Luis Fernando Alguacil is also a member of this group. The Neuropharmacology of Addictions and Degenerative Disorders (NEUROFAN) group carries out all phases of identification of

new biomarkers and therapeutic targets in diseases of the central nervous system. In the field of addictions, his main line of research is the study of PTN/PTPRZ1 as a regulator of neuroinflammation induced by alcohol consumption during adolescence [34].

Prof. **Javier Zaragoza** is a member of the research group in Physical Education and Promotion of Physical Activity (EFYPAF) at the University of Zaragoza in Huesca. His lines of research focus on the analysis and evaluation of comprehensive programs to promote healthy habits in early childhood and primary schools. In addition, he investigates the use of computer tools to evaluate school programs to promote healthy behaviors in schoolchildren in Aragon with the help of Prof. Victor J. Villanueva-Blasco from the International University of Valencia [35].

Prof. **Rafael Maldonado** is the leader of the neuropharmacology research group (NeuroPhar) of the Pompeu Fabra University attached to the IMIM. NeuroPhar studies the neurobiological substrate of drug addiction, pain, affective disorders and eating disorders, for which they investigate the participation of endogenous opioid and cannabinoid systems in the pathophysiology of these disorders. They have various lines of research focused on identifying new therapeutic targets in the central nervous system, focusing on the neurochemical and neuroanatomical bases of addiction induced by opioids, cannabinoids, nicotine, and psychostimulants. They use classical pharmacological approaches and genetically modified mouse models to address physical aspects of drug dependence and motivational components that lead to substance abuse [36]. Lately, his groups have developed advanced models for other addictive disorders such as food addiction, expanding the pharmacological research to this new and demanding emerging problem.

Prof. **Emilio Ambrosio** leads the psychobiology of addictions research group at the National University of Distance Education (UNED). His lines of research include the study of the long-term effects of exposure to cannabinoids during adolescence, the psychobiological mechanisms involved in relapse to drug use, genetic differences related to vulnerability to consumption and relapse of opiates and psychostimulants, the psychobiological bases of impulsive behavior with emphasis on the endocannabinoid system, and animal models of dual pathology [37].

Prof. **Guillermo Burillo-Putze** is leader of the Research Group: Emergencies and Clinical Toxicology: acute pathologies and care processes (GRUCATOX) at the University of La Laguna. A clinical group studies acute drug poisoning in hospital emergencies. The main lines of research deal with this type of poisoning and its treatment with special emphasis on drugs of abuse and new psychoactive substances [38].

Prof. **Manuel J. Cuesta** is the principal investigator of the psychosis research group at Navarrabiomed (biomedical research center of Navarra) and Hospital Universitario de Navarra (Psychiatry, IdiSNa). Its main objective is to delve into the phenotypic characterization of psychoses, developing alternative phenotypes that can be used in neurobiological studies. In addition, he investigates the initial phases of psychoses and the comorbid risk factors associated with the high mortality rate of these diseases. He especially focuses on advancing research in dual pathology, with special attention to first psychotic episodes [39].

Prof. **María Isabel Colado** leads the Neurobiology of Amphetamines and Ethanol Research Group, at the Faculty of Medicine of the Complutense University of Madrid. It is a multidisciplinary research group whose main objective is to provide policy makers with solid evidence for the development of tools that help reduce and prevent drug use from a public and social health perspective. His lines of research include the pharmacotoxicology and neurotoxicity of MDMA and other amphetamines, the effect of pre-exposure to ethanol on the changes induced by MDMA, the involvement of the kynurenine pathway in the effects of psychostimulants and alcohol, the neurobiological changes induced by intensive ethanol consumption in rodents and the identification of biomarkers for the diagnosis, treatment and prevention of the consequences of the consumption of these drugs in humans [40].

Prof. **Carlos Roncero** works in the Psychiatry Service of the Salamanca University Care Complex (CAUSA) and is principal investigator

of the Addictions and Dual Pathology group of the Salamanca Biomedical Research Institute (IBSAL). His lines of work include the study of sexual dysfunctions in patients who consume alcohol and patients who consume alcohol and cocaine; the monitoring of psychotic symptoms in relation to the severity of addiction and the appearance of violent behaviors in patients with substance use disorder [41].

5. Other Spanish pharmacology research groups not included in RIAPAd

In addition to the groups associated with RIAPAd, there are other groups prominent in addiction pharmacology research. At the University of the Basque Country, two research groups in Pharmacology stand out, led by Joseba Pineda and Javier Meana, the last one member of the network CIBER de Salud Mental (CIBERSAM) [42].

In Barcelona, it is worth mentioning the Pharmacology group of the School of Pharmacy of the University of Barcelona, directed by Jordi Camarasa [43] and Elena Escubedo [44]. Again, in Barcelona, the Clinical Pharmacology group of the Hospital de la Santa Creu i Sant Pau, led by Rosa María Antonijoan [45], continues part of the research on psychodysleptics started by Manel Barbanj (RIP). Prof. Francisco Ciruela [46], directs the Neuropharmacology and Pain research group at the School of Medicine of the University of Barcelona, on the Bellvitge campus (IDIBELL).

In Madrid, pharmacology groups from the School of Medicine of the Complutense University stand out, led by Juan Carlos Leza [47] belonging to the CIBER de Salud Mental (CIBERSAM). Other researcher in the same Department is Ignacio Lizasoain [48]. Additionally, at the same faculty, the cannabinoid research group, led by José Javier Fernández Ruiz [49], follows the line of José Antonio Ramos.

On the other hand, Prof. Fernando Berrendero coordinates the Neurobiology of Addictive and Anxiety Disorders research group at the Francisco de Vitoria University in Madrid, within the Institute of Biosanitary Research of the institution [50].

Finally, Prof. María Julia Garcia Fuster coordinates the Neuropharmacology Laboratory (UNICS-IdISP) of the University of the Balearic Islands [51].

6. Funding for research in addictions in Spain. The National Drugs Plan

The main sources of public funding for drug research projects in Spain come from the Spanish government through the Ministry of Science, Innovation and Universities and the Ministry of Health.

The Ministry of Science annually calls for competitive grants for research projects through the National Research Agency, which includes grants for projects and the training of research personnel (<https://www.aei.gob.es/>). These projects are generally of basic science and designed for preclinical research groups. There is no specific line of addictions. In addition, other research grants become through the Carlos III Health Institute under the name of Strategic Action for Health (AES) (<https://www.isciii.es/QueHacemos/Financiacion/Paginas/default.aspx>).

There are grants for research projects, which are designed for clinical groups or those preclinical that demonstrate a translational component. Again, they are aid not specifically directed to addictions. These grants include research groups such as RIAPAd.

The only state agency that offers specific research grants for addictions is the Ministry of Health through research projects from the National Plan on Drugs (PNSD), which also serves as the National Focal Point for the EMCDDA. The PNSD's mission is the design, establishment, execution and evaluation of the policies that, regarding addictions, are developed by the Public Administrations and social entities in Spain. Its objective and vision are to promote a significant reduction in the health and social impact of addictions, with special emphasis on prevention, and on supporting the social incorporation of people affected by them. The Government Delegation for the PNSD annually calls for aid for the

development of research projects on addictions, carried out by public or private non-profit entities (<https://pnsd.sanidad.gob.es/profesionales/investigacion/home.htm>.) In the last call in 2023, these aids had a duration of two years. A total of 86 grants were requested, of which 14 were granted, with an amount of 1,059,790 euros. The topic of the aid was basic pharmacological aspects (5 projects), clinical aspects (4), social aspects (3) and epidemiological aspects (1).

In addition, researchers you can apply for European regional financing (always very reduced) in the Horizon Europe program and even funds from the National Institute on Drug Abuse (NIDA) or the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

7. Addiction scientific societies and Journals on addictions in Spain

In Spain, there are several scientific societies dedicated exclusively to addictions, as well as associated journals.

Preclinical and clinical researchers in the field of Pharmacology of addictions usually present their results in general Pharmacology societies (Spanish Society of Pharmacology [<https://www.socesfar.es/>] and its equivalents in Europe or worldwide) and/or or Clinical Pharmacology (Spanish Society of Clinical Pharmacology [<https://se-fc.org/>] or its equivalents in Europe or worldwide), or also in those representatives of neurosciences, psychiatry, or internal medicine.

The most important society exclusively for addictive disorders is the Spanish Scientific Society for Studies on alcohol, alcoholism and other drug addictions (Socidrogalcohol) (<https://socidrogalcohol.org/>); a multidisciplinary society that brings together mainly clinical and less basic professionals. Founded in 1969, it is national in scope, with various Autonomous Delegations. Include professionals with different academic qualifications. Socidrogalcohol offers training programs including a program of continuous learning, prevention, treatment, course design, lines of research at the national, regional and local level, expanding its cooperation and collaboration at an international level. The publication of manuals and clinical practice guidelines is relevant. The society annually organizes a congress in a Spanish city on a rotating basis, which for some years has been open to international presentations. The 2024 meeting will be held in Valencia and is the 51st national and 6th International (<https://jornadas2024.socidrogalcohol.org/>). At the congress, works on basic and clinical pharmacology are presented and a session is reserved for RIAPAd news.

The society has a scientific journal named Adicciones (Addictions) (<https://www.adicciones.es/index.php/adicciones>) that appeared in 1989. The vast majority of published works are clinical and epidemiological. Its impact factor in the JCR 2022 was 3.00 and it is in Q2 of the Substance Abuse category of the Science Citation Index Expanded (SCIE). It is free and open access.

Another society dedicated to addictions is the Spanish Association for the Study of Drug Dependence (AESED) (<https://www.aesed.com/es/aesed>), created in 1987 in the field of alcoholism and other drug addictions. It is a Scientific Association made up of professionals from different disciplines and academic qualifications in the field of addictions, mental health, education and other related socio-health fields. Clinical-socio-epidemiological research predominates. Its activity takes the form of training professionals through courses. The AESED publishes a magazine called *Revista Española de Drogodependencias*, which was founded in 1975 (<https://www.aesed.com/es/magazine>). It mainly publishes clinical works and is free and open access.

There is also a society dedicated to comorbid psychiatric pathology (dual disorders), the Spanish Society of Dual Pathology (SEPD) (<https://patologiadual.es/>). This society was established in 2005 and is made up of more than 2000 multidisciplinary professionals who carry out their work in the clinical, teaching and/or research field of "Dual Pathology". The society sponsors training with publications, courses, conferences and conferences. The congresses are open to international participation, the most recent will be held in Mallorca in 2024 (26th

Congress of the Spanish Society of Dual Pathology-SEPD and 8th World Congress of the World Association of Dual Disorders-WADD (<https://patologia-dual.com/>).

In summary, addiction is a global problem with a multitude of complexities for its study. In Spain, several research groups study the pharmacological aspects of drug abuse and addiction. In this brief review, we include the general elements of the most important structure for addiction research in Spain (RIAPAD) as well as relevant groups of basic and clinical pharmacologists dedicated to this field.

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CRedit authorship contribution statement

Magi Farre: Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization. **Fernando Rodríguez de Fonseca:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Rafael Maldonado:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization. **Joan Mestre-Pinto:** Writing – review & editing, Methodology, Formal analysis. **Jose Cardenas-Quesada:** Writing – original draft, Methodology. **Marta Torrens:** Writing – review & editing, Writing – original draft, Resources, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

None.

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