RIAPAD
Atención Primaria en Adicciones

RED DE INVESTIGACIÓN EN ATENCIÓN PRIMARIA DE ADICCIONES

THE SPANISH NETWORK ON RESEARCH IN PRIMARY CARE

FOR ADDICTIONS

OUTCOMES 2023

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History

The Spanish Network on Research in Primary Care for Addictions (RIAPAd) stands as a pivotal national cooperative project committed to collaborative research in the field of addictive disorders, with a strong focus on health outcomes.

Comprising 18 distinguished research groups from 10 autonomous regions in Spain, RIAPAd is a dynamic consortium. This network brings together 9 clinical and epidemiological research teams from National Health Service (NHS) care centers and 9 basic research groups from leading academic institutions, alongside 3 clinical research associates. Coordinated by a steering committee and spearheaded by a national coordinator, RIAPAd's research initiatives are specifically targeted at enhancing health outcomes in primary care for addictive disorders.

RIAPAd represents the progression of a previous national network that has dedicated nearly two decades to cooperative and translational research in addiction. Currently, the network has recalibrated its focus to meet the emerging challenges of addiction diseases, with a direct focus on patients' needs. These challenges encompass a diverse range of issues, from substance-related addictions — including alcohol, benzodiazepines, and newly synthesized drugs originating from illicit labs within the EU — to the rise in behavioral addictions like gambling, internet, and video game usage. Additionally, innovative indicators for substance use, such as detection of drugs presence in wastewater or syringes, are being explored, opening a new era on epidemiological studies in drug use.

The COVID-19 pandemic has further underscored the necessity for adaptability in diagnostic approaches and treatment modalities. There is a growing need to expand the availability and accessibility of treatments, which includes the development of more e-health tools and long-lasting medications. Importantly, incorporating patient feedback is increasingly recognized as crucial for enhancing the efficacy of treatment protocols. RIAPAd is at the forefront of addressing these evolving demands, ensuring a responsive and effective approach to addiction research and care.

The Spanish Network on Research in Primary Care for Addictions (RIAPAd) aims to significantly influence health systems, the scientific community, key social stakeholders, and policy-makers focused on addiction diseases. This initiative is also directed towards the general public to furnish high-quality scientific information, thereby enhancing social problem-solving in a domain that necessitates the engagement of all societal actors, considering the relevance of scial stigma associated to drug abuse. A critical aspect of RIAPAd's mission is the dissemination of information, communication of breakthroughs, and the protection and utilization of research findings. Such efforts are pivotal in elevating national and EU standards in health and social services, particularly in ameliorating the quality of life for individuals grappling with drug abuse.

Dr. Torrens, the Coordinator of RIAPAd, plays a significant role internationally. As a member of the Informal Scientific Network of the World Health Organization & United Nations Office on Drugs and Crime, she contributed to the publication of the "International standards for the treatment of drug use disorders: revised edition incorporating field-testing results" (2020) (Available at: [WHO Publication] (https://apps.who.int/iris/handle/10665/331635)). Her involvement underscores RIAPAd's commitment to global standards in addiction treatment.

Furthermore, both Dr. Torrens and Dr. Rodriguez de Fonseca, as members of the Scientific Committee of the EMCDDA, are instrumental in:

a) Monitoring the state of drug problems, particularly through epidemiological indicators, and identifying emerging trends.

b) Reviewing solutions to drug-related issues, disseminating best practices among Member States, and facilitating information exchange.

c) Assessing risks of psychoactive substances and managing a rapid information system.

In alignment with these responsibilities, RIAPAd's milestones are poised to make a substantial impact on Health Systems and individuals affected by addictive disorders.

It is also noteworthy that numerous RIAPAd members are involved in significant roles in regional, national (Ministry of Health and Ministry of Economy and Competitiveness), and international organizations in the field of addiction. Notably, Dr. Torrens is an elected member of the Scientific EMCDDA and the Informal Scientific Network of UNODC and WHO for addiction. Additionally, Dr. Maldonado and Dr. Farré serve as consultants for WHO and UNODC, while Dr. Fonseca is a member of the Scientific Committee of EMCDDA. A substantial portion of the network members participate in the editorial boards of leading addiction journals. These affiliations highlight RIAPAd's extensive involvement and influence in shaping addiction research and policy at various levels.

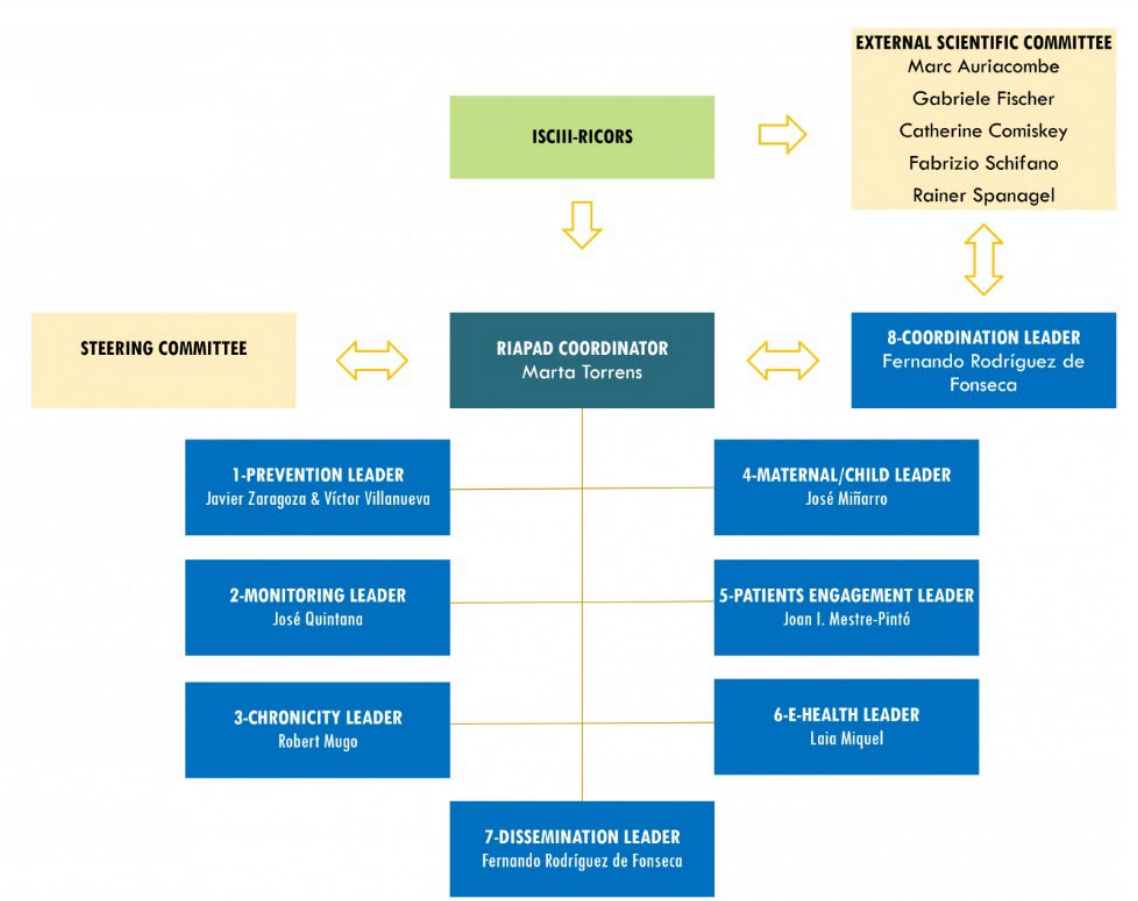
RIAPAd's General grant information

Dossier	RD21/0009
Dossier name	ATENCIÓN PRIMARIA, CRONICIDAD Y PROMOCIÓN DE LA SALUD
Thematic area	Primary care, chronocity and health promotion
RICORS Name	Red de Investigación en Atención Primaria de Adicciones (RIAPAd)
RICORS Leader	Marta Torrens Mèlich
Applicant Institution	Fundación Instituto Hospital del Mar de Investigaciones Médicas (FIMIM)
Work Institution	Instituto Hospital del Mar de Investigaciones Médicas (IMIM)
Period	2022-2024 (3 years)
Budget	2.274.250,30€

RIAPAd's members and Institutions

PI Name	Work Institution	Region	Nº members
Marta Torrens Mèlich	Hospital del Mar	Cataluña	11
Fernando Rodriguez de Fonseca	Instituto de Investigación Biomédica de Málaga (IBIMA)	Andalucía	12
Roberto Muga Bustamante	Hospital Germans Trias i Pujol	Cataluña	9
José Miñarro López	Universidad de Valencia	Comunidad Valenciana	5
Pedro Grandes Moreno	Universidad del País Vasco	País Vasco	11
Gabriel Rubio Valladolid	Hospital 12 de octubre	Comunidad de Madrid	6
Jorge Manzanares Robles	Universidad Miguel Hernández	Comunidad Valenciana	5
Laia Miquel de Montagut	Hospital Clinic	Cataluña	18
Javier Costas Costas	Complejo Hospitalario Universitario de Santiago	Galicia	4
Jose Benito Quintana Alvarez	Universidad de Santiago de Compostela	Galicia	6
Gonzalo Herradon	Universidad San Pablo CEU	Comunidad de Madrid	9
Javier Zaragoza Casterad	Universidad Zaragoza	Aragón	12
Rafael Maldonado López	Universidad Pompeu Fabra	Cataluña	6
Emilio Ambrosio	Universidad Nacional de Educación a Distancia	Comunidad de Madrid	5
Guillermo Burillo Putze	Complejo Hospitalario Universitario de Canarias	Islas Canarias	4
Manuel Cuesta Zorita	Hospital Universitario de Navarra	Comunidad Foral de Navarra	5
Maribel Colado Megía	Universidad Complutense de Madrid	Comunidad de Madrid	11
Carlos Roncero	Complejo asistencial universitario de Salamanca	Castilla y Leon	4

RIAPAd's Chart



Objectives and workpakcages.

The RIAPAd Network's overarching goals encompass a multifaceted approach to addictive diseases, incorporating a gender perspective and applying translational methods. These objectives span seven critical areas:

1. Prevention: The focus here is on health promotion within educational environments and primary addiction treatment settings. This includes the training and education of health and social professionals in both substance use (such as tobacco and alcohol) and behavioral disorders (like gambling).

2. Monitoring: Emphasis is placed on utilizing diverse and innovative indicators for usage, enhancing diagnosis and comorbidity identification, and developing new treatments in response to the rapidly evolving landscape of addiction.

3. Chronicity: In tandem with monitoring, there is a concerted effort to better understand the chronicity and comorbidity associated with addiction diseases through advanced basic research.

4. Maternal and Child Health: This objective aims to improve the detection and understanding of addiction during pregnancy and childhood, and to develop translational models for addressing the consequences of perinatal and adolescent drug exposure.

5. Patient and Stakeholder Engagement: Implementation of patient-reported experiences (PROMs and PREMs) is key to enhancing patient involvement in treatment services, ensuring a patient-centric approach.

6. E-health Tools: The Network is committed to the development and utilization of E-health tools to streamline both the diagnosis and treatment processes in the realm of addiction.

7. Dissemination: A significant goal is to effectively communicate research activities to the broader society, policymakers, and health professionals. The aim is to improve the prevention, early detection, and management of individuals with addiction, thereby enhancing overall outcomes.

Collectively, these objectives reflect RIAPAd's commitment to advancing the field of addiction treatment and management through innovative, inclusive, and patient-focused strategies.

Specific objectives or work packages (WP), according to general objective are the following:

1. Prevention is focus mainly in tobacco and gambling in:
    - Health promotion in educational and primary addiction treatment settings (WP1).
    - Training/education of health and social professionals (WP2).
2. Monitoring addictive diseases aims to:
    - Indicators of drug use from different information sources, both clinical and non-clinical (WP3).
    - Diagnosis and comorbidities (physical and psychiatric) of addictive disorders (WP4).
    - Treatment development with new chemical entities or new targets for addiction and comorbidities (WP5).
3. Chronicity, this relevant objective has two specific objectives:
    - Characterizing chronicity & comorbidity in addiction (WP6).
    - Translational research in addiction chronicity (WP7).
4. Maternal and child health is focus on two specific objectives:
    - Implementing detection of addiction in pregnancy and childhood (WP8).
    - Translational models in perinatal and adolescent drug exposure (WP9).
5. Patients and stakeholders' engagement aims to:
    - Implementing PROMs (Patient-Reported Outcome Measure) and PREMs (Patient-Reported Experience Measures) (WP10).
6. E-health tools are implemented in primary addiction services to:
    - Diagnosis: implementation of DDSI e-health to increase diagnosis of psychiatric comorbidity (WP11).
    - Treatment: Canreduce e-health implementation to decrease cannabis use (WP12).
7. Dissemination aims to address information to:
    - Professionals of primary addiction settings, Hospital clinical settings, and scientific community (WP13).

- Patients associations, general society and stakeholders involved in addiction-associated problem management (WP13).

Work packages activities and outcomes

WP 1: Health promotion in educational and primary Addiction treatment settings

The primary goal of this Work Package (WP) is to design and test a model that evaluates the impact of intervention programs on various health determinants (drug use, internet gaming, and potentially gambling) in the school population. This model includes methods, tools, and procedures that can be used to assess a policy, program, or project according to its potential effects. Specifically, the general and specific objectives to be considered in the different phases of this project are:

Main Objective 1: Design, implement, and evaluate preventive education programs.

Specific Objectives:

a) Design a model that will include tools and indicators to evaluate the impact of programs within the Aragonese Network of Health Promoting Schools (HPS) (Primary and Secondary) from a comprehensive perspective[1].

b) Conduct a diagnosis of existing health promotion programs in the Aragonese Network of Health Promoting Schools, providing information on their efficiency/effectiveness and sustainability.

Deliverables:

- Prevention Program in Addictions in Health Promoting Schools
  Delivery Date: month 24
- Evaluation of the Prevention Program and development of the improvement plan
  Delivery Date: month 20
- Report of Results of Prevention Programs
  Delivery Date: month 36

[1]RIAPAD chose an autonomous community as a pilot element for the analysis of prevention in schools, given the regionalnature of educational and preventive plans.

Achievement Objectives:

1. Review of scientific evidence to identify effective prevention programs for substance abuse and gambling.

Deadline: month 12

Degree of Achievement: 80%

2. Harm reduction program related to substance use and gambling.

Deadline: month 18

Degree of Achievement: 70%

Justification:

Three systematic reviews on addiction prevention programs have been conducted, two of them related to school-based prevention programs.

The first of the systematic reviews has been published in the International Journal of Mental Health and Addiction under the title "Prevention Versus Pseudo-prevention: a Systematic Review of School Drug Prevention and its Indexing in Best Practice Portals". of School Drug Prevention and its Indexing in Best Practice Portals". The second of the reviews has been sent to the journal Adicciones with the title "Systematic Review on characteristics and effectiveness of school-based drug prevention programs in Spain". It is currently in the publication phase. The third and last of the articles on school-based prevention of problematic Internet use, gambling and video game addiction in Spain, is in the final revision period with the journal still to be determined.

As non-planned consequence of this collaborative effort, is the granting of a national research project to analyze the prevalence and consequences of problematic mobile phone use as a platform for gambling:"Estudio de la asociación juego patológico-uso anómalo del móvil en la población general española: determinantes sociales e individuales / *Study of the Association Between Pathological Gambling and Abnormal Mobile Phone Use in the Spanish General Population: Social and Individual Determinants*. Outcomes of this study will be delivered in the final report of the RIAPAd consortium.

Within the main objective number 1, but in its section B, a report on the evaluation of the sustainability of the intervention programs in the Health Promoting Schools (HPS) in Aragon has been carried out, with ISBN 978-84-09-54880-4.

Additionally, an expansion of the school preventive program "Sé tú mismo, sé tú misma" (Be yourself) is being developed, incorporating two additional sessions for 2nd year of secondary education (E.S.O.), aimed at preventing pathological gambling, problematic internet use, social networks, and video game addiction. An update of the guide and materials has been carried out, pending layout and subsequent submission to the Good Practice Portal.

Main Objective 2: Promote activities to prevent and reduce substance use and gaming-related harm in vulnerable groups.
Specific Objectives:
a) Increase the impact and sustainability of the intervention programs analyzed in the previous phase, generating and applying an improvement plan tailored to each center, which will include specific strategies in each of the evaluated dimensions.
b) Disseminate the protocols, results, conclusions, tools, and materials derived from the project at national and European levels, within the Health Promoting Schools Network, to help those responsible understand and possibly apply them.

Justification:
Progress has been made in adjusting and improving the design of the "REDEPS-Gestión" Platform, aimed at facilitating the comprehensive management and evaluation of Health Promoting Schools in Aragon. This platform allows educational centers to present their proposal, apply for accreditation, and base their Healthy School project on evidence. It also enables the responsible public administration to manage, monitor, and evaluate the proposed projects, with the aim of increasing the impact and sustainability of these actions. Versions 1 and 2 of the platform's user manual have been developed. Version 3 of the user manual has recently been developed, pending the inclusion of new items.
Regarding the assessment of behavior, and more specifically in the section on addictions, the selection of report models for both primary and secondary schools is

being carried out. This report gathers information from the group in relation to habits of consumption of psychoactive substances, addictive behaviors (internet use, video games). It gathers all the information self-reported by the pupils who make up the group, thus providing us with an estimate of their habits and behaviors that can serve as a reference for developing promotion and prevention strategies in the educational centre within the framework of Health Promoting Schools (HPS).

In turn, the article related to the main objective number 1 on the design of tools to evaluate the impact of the health programs of the Aragonese Network of Health Promoting Schools (HPS), is currently being revised in order to submit it to the Journal of Public Health and Surveillance under the title "Development of a web platform to facilitate the Health Promoting School 's implementation and evaluation: the Double Diamond Design Approach".

In relation to the objective of disseminating protocols, tools and results of the different studies, the following actions have been carried out:
- Communication EUSPR Congress Sarajevo. "REDEPS Platform as a prevention tool". Presentation 5th October.

- Communication Valencia Congress. "Diagnosis on Sedentary screen time, sleep, breakfast and tobacco". Presentation at the Congress Escola Activa y Salut Valencia from 9-11 November 2023.

- Round Table Valencia Congress. "(Re)Thinking the integration, development and sustainability of Health Promoting Schools". Presentation at the Congress Escola Activa y Salut Valencia 9-11 November 2023.

- Participation in the Scientific Committee of the Valencia Congress. Evaluation of the quality of HPS programs. Escola Activa y Salut Valencia Congress on 9-11 November 2023.

WP 2: Training/education of healthcare and social professionals

Specific Objectives:

a) Raise awareness among health and social care professionals about substance use, gaming disorders, and the harms associated with substance use and gambling.

b) Inform health and social care professionals about the available specialized care networks.

c) Develop training programs for health and socio-health professionals.

Deliverables:

- Specific awareness campaign about Schools and Health Professionals.
- Specific training aimed at improving knowledge about substance use and gambling prevention in health and socio-health professionals.

Achievement Objectives:

1. Implement the prevention program among professionals and in Health Promoting Schools.
2. Develop a specific awareness campaign to provide the population with tools for the prevention of gambling addiction and related harms.

Justification:

The actions to raise awareness among health and social professionals about substance use, gambling-related disorders and the harm associated with substance use and gambling were as follows:

- Communication UPNA (Public University of Navarra) Conference. "Lifestyles and addictions at school". 16 January 2023.

- A Training Day titled "Prevention of addictions and promotion of healthy lifestyles in the school population" was conducted.

Organization: HIASp research project (Health impact evaluation in school population, PID2019-105822RB-100), Consolidated Research Group S65 by the Government of Aragon Education Physical and Promotion of Physical Activity (EFYPAF) and Doctoral Program in Education.

Collaboration: Primary Care Addiction Research Network project (RIAPAd, RE21/0009/0015). Venue: Faculty of Education (Zaragoza), Classroom 1.5. March 2023.

- Communication Huelva Conference. "Prevention at local level of the consumption of tobacco-related products: electronic cigarettes and hookahs". 21 March 2023.

- Participation in the Scientific Committee of Ourense Congress. "Prevention, treatment and control of cannabis and its derivatives". 23-25 November 2023.

-Participation with several conferences, seminars and open debates in the Ourense Congress. "Prevention, treatment and control of cannabis and its derivatives". 23-25 November 2023. (See: https://congresocannabis2023.socidrogalcohol.org/programa)

- Interview at the International University of Valencia. Víctor Villanueva: "Tobacco, an analysis of the current panorama". Available at: https://www.universidadviu.com/es/actualidad/noticias/expertos-viu-dr-victor-jose-villanueva-tabaco-un-analisis-del-panorama-actual

- Interview at the International University of Valencia Víctor Villanueva: "Betting to lose: gambling addiction and teenagers". Available at: https://www.universidadviu.com/es/actualidad/noticias/expertos-viu-dr-victor-jose-villanueva-blasco-apostar-para-perder-adiccion-al-juego-y-adolescentes

A proposal has been made for an advanced course at the Menéndez Pelayo International University with the title: "Prevention of addictions in young people".
The course will be held at the Faculty of Human Sciences and Education in Huesca (University of Zaragoza) on 23 May 2024.
The objectives of the course will be the following:
a) Identify the scientific evidence of success in school preventive programs in addictions with and without substances.
b) Define the future challenges to be faced in the prevention of addictions in young people.
c) Justify the preventive role of sport in the problem of addiction.

d) Explain the strategies that are being implemented from a local corporation for the prevention of addictions.

The conference will consist of 3 presentations to discuss and then identify, through a round table, the main challenges in the prevention of addictions in the young population.

LECTURE 1: Current situation of school preventive programs for addictions with and without substance in Spain and future challenges. Dr. Víctor José Villanueva Blasco. Research Network in Primary Care of Addictions (RIAPAD).

LECTURE 2: Is sport an antidote to drug use and other addictions? Mr. Manuel Isorna. Research Network in Primary Care of Addictions (RIAPAD).

LECTURE 3: Addiction prevention plan at the local level. Mercedes Guiseris. Technical manager of the Youth and Children area of the Huesca City Council.

ROUND TABLE coordinated by Manuel Bueno. Technician of the Subdirectorate of Public Health of Huesca.

WP 3: Use indicators

Only two groups (RD21/0009/0012 Quintana and RD21/0009/0024 Burillo) of the four initial applicants were funded in the current call. Nonetheless, the proposed objectives have not been diminished, and synergies have been achieved that will lead to the development of an additional indicator (syringe residue analysis – SYDRES Project, see below).

The work associated with the analysis of wastewater (i.e. wastewater-based epidemiology, WBE) is developing as planned, through collaboration with the ESAR-Net network coordinated by J.B. Quintana. In this regard, more than 25 wastewater treatment plants are being analyzed annually across the country to assess the consumption of illicit substances of abuse, as well as alcohol and tobacco. A study on the impact of the COVID-19 lockdowns on substance use by WBE was concluded, already published in the STOTEN journal (IF: 10.754). Additionally, the development and pilot application of a methodology to estimate various cannabinoids (CBD, Δ9-THC, and Δ9-THC) and their metabolites in wastewater is underway. The analysis of benzodiazepine consumption at national level by this methodology is also planned. Furthermore, in 2023-2024, the evaluation of drug use in a prison is currently also undergoing. So far, in addition to the publication, the results have been presented at multiple conferences, contributing to 2 reports from the Spanish Observatory of Drugs and Addictions (OEDA) of the DGPNSD.

Regarding the emergency indicator, G. Burillo coordinates the REDurHe network, where the type of substances detected in emergency services nationwide, as well as gender and age conditions and the severity of associated clinical manifestations, have been studied. Special attention has been paid to cannabis use, as well as potential fentanyl and its derivatives. In addition, a study on possible chemical submissions associated with needle pricks has been developed. In total, 7 articles related to this indicator have been published. Possible funding sources are currently being evaluated to continue with the REDurHe network.

Finally, a new indicator related to the analysis of residues in syringes of drug users via parenteral self-administration is currently being developed. This is possible through the

award of a project funded by the DGPNSD for 2023-2024 (SYDRES: https://sydres.webnode.es/) led by R. Montes (RD21/0009/0012) with significant participation from the coordinating team (RD21/0009/0001). This indicator will allow access to populations that are more difficult to observe through other indicators, in addition to stratifying results by gender and conducting a study focused on Chemsex, as well as integrating Spain into the European ESCAPE network, coordinated by the EMCDDA.

WP3 is progressing adequately towards the achievement of the two milestones (M5 and M6) scheduled for month 30; and the two deliverables (D6 and D7) planned for month 36.

WP 4: Diagnosis and comorbidity

Objective: The evaluation of new diagnostic procedures for addictions and their associated comorbidities, focusing on new instruments, genetic vulnerability, the identification of biomarkers, and functional tests in addicted patients.

Justification:

The deliverables proposed in the program were: D8. Analysis of the efficacy and use of diagnostic procedures applicable to addictions and their comorbidities, depending on the healthcare resource used.

To undertake this task, two online meetings were held with interested groups to propose evaluation projects and detect patients with dual pathology, and to consider studies on the use of tools such as the dual screening interview, the PRISM interview, as well as to address the search for discriminative biomarkers of addiction severity, and their potential linkage to specific comorbidities. The RIAPAd consortium includes former members of the Addictive Disorders Network who contribute a cohort study (CohRTA) that has facilitated the initiation of these studies.

Specific work projects proposed include:

1. Study of psychotic symptoms in cocaine-using patients.
2. Studies on affective disorders in patients with alcohol and/or cocaine use disorder.
3. Biomarkers of psychiatric comorbidity in alcohol use disorder.
4. Biomarkers of psychiatric comorbidity in cocaine use disorder.
5. Biomarkers of psychotic disorder in the first episode, and their relationship with psychiatric comorbidity.
7. Translational research for identifying early biomarkers of cognitive impairment associated to alcohol and/or use is also under development.
6. Studies of polygenic risk estimates in addictions/psychiatric comorbidity in the CohRTA cohort.

Two specific EU4Health proposals for diagnosis and study of drug-associated co-morbidities have been led by RIAPAd members and submitted to the 2023 call:

- *DEMENTCOL*, an European consortium for developing of early biomarkers of cognitive impairment associated to the use of alcohol and drugs

- *HiPALc,* a MSCA doctoral network oriented to the interdisciplinary training of PhD students on the consequences of alcohol use disorders.

Doctoral Thesis:

Nerea Requena Ocaña

Protective factors and biomarkers of cognitive impairment in alcohol use disorder

Supervisors: Fernando Rodríguez de Fonseca and Pedro Araos

Complutense University of Madrid

WP 5: Development of treatments

The main goals of this WP5 are:

1. To explore new therapeutic targets (i.e. in depth analysis of CBD) and
2. To identify candidates already in development for both alcohol abuse and alcohol-induced fatty liver and depression (oleoyl ethanolamide and molecules modeled after it, and LPA1 receptor antagonists and GLP-1 receptor agonists).

To these aims, the following activities were carried out to advance in the achievement of milestone "M8 Promotion of new experimental therapeutic interventions," scheduled for month 30 and deliverable "D10 Report on new experimental approaches to addiction treatment," planned for month 36:

- The evaluation of the efficacy of cannabidiol (CBD) modulating anxiety and somatic signs of withdrawal in an animal model of spontaneous alcohol (DOI: 10.1111/adb.13150) and heroin (DOI: 10.1111/adb.13150) withdrawal.
- Efficacy of CBD in modulating behavioral and brain changes in an animal model of fetal alcohol syndrome (DOI: DOI: 10.1016/j.biopha.2021.111813; DOI: 10.1016/j.phrs.2023.106655).
- CBD exhibits early antidepressant actions in an animal model of depression (chronic mild stress) that closely relate to its ability to induce neuroadaptations in different brain regions of the mouse (DOI: 10.3389/fphar.2023.1171646). The use of genetic animal models revealed that the cannabinoid CB1 receptor is involved in the anxiolytic actions of CBD (DOI: 10.3390/ph15040473).
- Study on the correlation between some miRNAs and food addiction in mice (DOI: 10.1172/JCI156281) and cocaine addiction (DOI: 10.1111/adb.13201).
- Blockade of serotonergic 5HT6 receptors can prevent some of the alterations associated with early cannabis use in rodents (DOI: 10.15252/emmm.201910605). In contrast, blockade of enkephalin metabolism could be a new therapeutic strategy in opioid use disorders (DOI: 10.1111/bph.1565).
- Studies on erectile dysfunction (ED) induced by chronic intermittent alcohol exposure demonstrate that alcoholic mice exhibit erectile dysfunction in vitro and in vivo due to altered sGC redox state and suggest that sGC activators may be effective in alcoholism-associated ED (doi: 10.1111/bph.16087).

- Modulating the kynurenine pathway by administration of Ro 61 -8048 in ethanol-dependent mice reduces ethanol consumption and preference in male and female mice via a mechanism involving a7nAChR. Modulating the kynurenine pathway is an effective strategy for treating ethanol dependence in both sexes (doi: 10.1111/bph.15825). However, does not modulate the analgesic effects produced by fentanyl in the hot plat test. In addition, mice treated with kynurenine and probenecid did not show hyperalgesia, while treatment with kynurenine and probenecid did not alter algesia in control animals.
- Ro 61 -8048 compound also mitigates addictive behavior in the acquisition of intravenous fentanyl self-administration behavior and notably reduces fentanyl consumption in dependent animals. However, the Modulation of NMDA or α7nAChR receptors is not involved in the decreased consumption produced by Ro 61-8048 in fentanyl-dependent animals.
- The role of galanin (1-15) in alcohol-seeking behavior and the involvement of the cortico-mesolimbic system, as well as the role of GAL (1-15) in environmentally induced alcohol relapse, have been studied. GAL (1-15) reduced alcohol-seeking behavior in the operant self-administration model in an FR1 protocol and at the breakpoint in a PR program. Galanin receptors are implicated (doi: 10.1016/j.biopha.2022.113508).
- A positive allosteric modulator of GLP-1R has been identified, presenting remarkable in vivo activity, reducing food intake and improving glucose handling in normal and diabetic rodents. Its behavior reinforces the interest of a small-molecule PAM of GLP-1R as a promising therapeutic approach for increasingly prevalent obesity-associated diabetes (doi: 10.1021/acs.jmedchem.1c01842).
- Pharmacological inhibition of Receptor Protein Tyrosine Phosphatase (RPTP) β/ζ with newly designed inhibitors as MY10 decreases ethanol consumption in adolescent mice and ethanol neurotoxic effects (doi: 10.1016/j.neuro.2022.11.008; doi: 10.1016/j.neuropharm.2023.109438). Intermittent access to ethanol during adolescence increased the number of PV+ cells in the female hippocampus and reduced Perineuronal nets (PNNs) intensity in different hippocampal regions, particularly in male mice. Inhibition of

RPTPβ/ζ with MY10 regulates ethanol-induced alterations of PNNs intensity, which correlates with the protection of hippocampal neurogenesis from ethanol neurotoxic effects.

- Patients with alcoholic liver fibrosis presented an increased NK cytotoxic phenotype and activated T cells concomitant with a decreased NK cytokine-secreting phenotype (doi.org/10.1007/s10238-023-01121-1). In addition, changes in the CD4 T cell subsets and the interactions occurring between these in patients with alcohol-related cirrhosis were analyzed, and the results have been presented in the National Congress of Internal Medicine (Valencia, 2023).
- The relative contributions of alcohol and thiamine-containing diet on various factors present in the pathophysiology of Wernicke Korsakoff syndrome (WKS) have been studied. The study reinforces the need for neuroprotective therapeutic approaches and preventive treatments for nutritional deficiency in WKS (doi: 10.3390/biomedicines10020260). It highlights the need for a complete and comprehensive cognitive evaluation in patients with Wernicke's encephalopathy (WE) (doi: 10.1111/pcn.13444). In the patient diagnosed with alcohol-induced WE, the TLR4/MyD88 pathway was up-regulated in cortex and cerebellum. In the animal model and the post-mortem human brain, there is a positive up-regulation of the proinflammatory TLR4/MyD88 pathway in alcohol consumption-related WE. Lipopolysaccharides could be a helpful risk biomarker to identify the early stages of this disease (doi: 10.3389/fphar.2022.866574).
- Studies examining the relationship between classical psychedelics and alcohol consumption have been reviewed over the past two decades. Psilocybin appears to show the most consistent data indicating that this compound could be a potential candidate for treating alcohol use disorders. More studies, including methodological quality parameters, are needed (doi: 10.1111/adb.13229).
- Study showing that cannabidiol decreases motivation for cocaine in a behavioral economics paradigm but does not prevent incubation of craving in mice (doi: 10.1016/j.biopha.2022.112708), and that the FAAH inhibitor URB597 reduces cocaine intake during conditioned punishment and mitigates cocaine seeking during withdrawal (doi: 10.1016/j.biopha.2023.115194.). Moreover, FAAH

inhibitor restores loss of LTP and social impairments induced by cocaine (doi: 10.1038/s41598-023-45476-7).

- Cannabidiol partially reverses emotional and molecular alterations induced by early-life stress in female mice (doi: 10.1016/j.pnpbp.2021.110508)
- Development of a model of post-partum depression in mice and evaluation of the effects of ketamine as antidepressant in comparison with allopregnanolone (doi: 10.1016/j.biopha.2022.113598.)

Collaborations

Throughout the project implementation period, several collaborations have been established between the clinical and preclinical groups that make up the network. Synergies with the clinical groups have been strengthened, especially between the group led by Dr. Rodríguez de Fonseca (RD21/0009/0003) and the groups of the Hospital del Mar (RD21/0009/0001) and Hospital 12 de octubre (RD21/0009/0007) and Hospital de Navarra (RD21/0009/0025) (Studies on chemokines and growth factors in Dual Psychosis, submitted for publication). Studies on drug development and interventions with microbiota have been carried out within the scope of collaborations between Dr. Rodríguez de Fonseca's group and groups from the University of Valencia, the UCM group (Dr. Colado) and groups from the screening network (Santiago, Madrid, Barcelona). Also, collaborative investigations between the groups of Dr. Pedro Grandes (RD21/0009/0006), Dr. Fernando Rodríguez de Fonseca (RD21/0009/0003) and Dr. Marta Rodríguez (RD21/0009/0005), have shown that Omega-3 fatty acids enhance cognition and behavior in adult brain after adolescent binge drinking through their impact on the endocannabinoid system. These Omega-3 effects also associate with reversion of the enzymatic imbalance involved in endocannabinoid-derived inflammation. Through RIAPAd and in view of the promising results with the MY10 compound developed by Dr. Gonzalo Herradón's group (RD21/0009/0013), a collaboration has been started with Dr. Jorge Manzanares' group (RD21/0009/0008) to identify the mechanisms by which treatment with MY10 significantly decreases alcohol consumption in adolescent males. Groups RD21/0009/0027 (Colado) and RD21/0009/0008 Manzanares are investigating the influence of the intestinal microbiota as a biomarker of the stage of alcohol consumption disorder, which would allow assessing the possibility of carrying out interventions based on microbiota

transplants. Dr. Gonzalo Herradón's group (RD21/0009/0013), has initiated a collaboration with Dr. Colado's group (RD21/0009/0027) to identify biomarkers and new therapeutic targets (neurotrophic factors and modulators of immune response) in the animal model of Wernicke Korsakoff syndrome (WKS). Finally, a collaborative project is being carried out between groups RD21/0009/0010 (PI: Miquel de Montagut, Laia) and RD21/0009/0003 (PI: Rodríguez de Fonseca, Fernando), to assess the potential usefulness of oleoylethanolamide (OEA) on alcohol consumption and relapse prevention. The main objective of this study is to observe the possible relationship between chocolate consumption, alcohol craving and OEA levels in patients with alcohol use disorder and those already in detoxification phases. Here, all the planned patients have been recruited and the relevant analyses have been carried out, and the results have been disseminated at various congresses and conferences.

PhD defense (between July and December)

Laia Alegre Zurano

Phytocannabinoids and endocannabinoids as modulators of cocaine reinforcement in mice. Excellent "Cum Laude", International Mention.

Supervisor: Olga Valverde

Master's thesis defense (between July and December)

Maria Llach Folcrà

Evaluating the Effects of Cannabidiol on Cocaine Abuse in a Conditioned Punishment Model with Mice.

Supervisor: Olga Valverde

Master of Neuroscience. UB-UPF

Asier Lazkano Zorroza

Changes in the brain endocannabinoid system caused by excessive alcohol consumption during adolescence.

Supervisors: Inmaculada Gerrikagoitia, Itziar Bonilla Del Río

Master in Neurosciences. UPV/EHU (RD21/0009/0006)

Alba García Guerra

Pharmacological modulation of perineuronal nets for the treatment of Alcohol Use Disorder: implication of Receptor Protein Tyrosine Phosphatase β/ζ.

Supervisor: Gonzalo Herradón

Máster Interuniversitario en descubrimiento de fármacos. USP-CEU, UCM, UAH.

Luisa Gutiérrez Esteve

Characterization of a progressive murine model of Parkinson's disease.

Supervisors: Aní Gasparyan and Jorge Manzanares

Master in Neurosciences. UMH

Congresses

23ª Reunión Anual de la Sociedad Española de Investigación sobre Cannabinoides - First Joint Spanish-French Meeting on Cannabinoid Research, Bordeaux 23-25 November, 2023. (0006, Dr. Grandes)

- EFFECTS OF OMEGA-3 FATTY ACIDS ON THE ENDOCANNABINOID SYSTEM IMPAIRED IN THE HIPPOCAMPUS OF ADULT MALE MICE AFTER ADOLESCENT BINGE DRINKING

Serrano M. et al. (0006, Dr. Grandes)

- OMEGA-3 REVERSES THE IMBALANCE IN THE MACHINERY RESPONSIBLE FOR THE PRODUCTION OF ENDOCANNABINOID-DERIVED PROINFLAMMATORY MEDIATORS CAUSED BY BINGE DRINKING DURING ADOLESCENCE

Ocerin G. et al. (0006, Dr. Grandes)

WP 6: Characterization of chronicity and comorbidity in addiction

Performed activities for the consecution of hallmarks and deliverables of the WP6 expected for months 30 and 36 respectively:

Part of the work of this objective is based on the Multicentric Study CohRTA. This project collects data from patients that seek treatment of Alcohol Use Disorder (AUD) for the first time. The CohRTA database has well over 200 variables and gathers information about sociodemographic factors, the severity of the disorder, the pattern of alcohol use, other drug and tobacco use, blood biochemical analyses, organic and psychiatric comorbidities, treatment at discharge and the patient's own perception of their health status.

During the first and a half year, the CohRTA Study has kept recruiting patients, reaching 1,190 individuals on March of 2023. Here is a list of the CohRTA Study participating centres: Parc de Salut Mar (0001), Hospital Universitari Germans Trias i Pujol (0004), Hospital Clínic de Barcelona (0010), Hospital 12 de Octubre (0007), Hospital Universitari Son Espases, Hospital Universitari de Bellvitge, Hospital Regional Universitario de Málaga (0003), Hospital Universitario de Salamanca (0029) y el Hospital Universitario de Canarias.

During this first period of the Network, the design of variables that are to be analysed longitudinally in the CohRTA Study has been conducted and finalised. These variables will allow characterisation of the chronicity and comorbidity of the patients that seek AUD treatment for the first time. Longitudinal data collection has started in 3 centres (Hospital Universitari Germans Trias i Pujol, Hospital Universitari de Bellvitge y Hospital Psiquiátrico de Palma/Son Espases) and their experience will provide fine-tuning suggestions towards the definitive version of the Longitudinal CohRTA Variables.

February 2022. After a quality control of the CohRTA Study's database, an internal report was issued to the participating centres to show the results of data quality and aspects to improve.

An observational and multicentric study, with a random sample of patients being treated for Substance Use Disorder (SUD) or Mental Disorders (MD) in different autonomous communities in Spain has been conducted (n=1783). 67 health professionals filled an online questionnaire ad hoc, collecting sociodemographic variables and pharmacological treatment of SUD and MD diagnosed patients in order to study differences in prevalence, sociodemographic and clincal profile, pharmacological

treatment and gender perspective of co-occurrence of SUD and MD. Results showed a high MD prevalence in patients treated for SUD (71%) and in the diagnosed of MD by SUD (59%). These findings will contribute to adequate the therapeutic response with a better precision and efficacy.

Responses to the startle reflex to different stimuli have been evaluated in young adults with different types of child abuse in comparison with a control group depending on their alcohol use and the presence/absence of a parent with alcohol dependence. In 606 adolescents, divided in 5 groups: without child abuse, physical negligence, emotional negligence, emotional abuse, physical and sexual abuse; evaluating their alcohol use pattern and their familial history of alcoholism. The proportion of participants with at least one parent with alcohol dependence was bigger in all types of abuse, and the population with an excessive alcohol use or with dependence criteria was bigger in groups with physical negligence and sexual abuse. Child abuse modulates the emotional processing of alcohol-related stimuli during adolescence.

A case report was published of an individual with Wernicke's encephalopathy who maintained long-term cognitive decline but not inflammation, even though thiamine was supplemented. The importance of performing a complete and thorough cognitive evaluation is emphasized in these patients, since it can be associated with a severe and persistent cognitive decline that manifests in a wide range of specific cognitive domains, regardless of thiamine supplementation.

By March 2023, the contract with the company who hosted the online database of the CohRTA Study ended. This has hampered the recruitment of new clinical cases and the implementation of the Longitudinal CohRTA Variables. Advances in the implementation of the CohRTA database in REDCap have been made whilst new patients are being included to the study by collecting their information by hand or in an Excel that is ready to import to REDCap.

Publications

doi:10.3390/biology11050645

doi:10.1016/j.drugalcdep.2023.109822

doi:10.3389/fpsyt.2022.956120

doi:10.3390/jcm11020305

doi:10.1038/s41598-022-06010-3

doi:10.1111/pcn.13444

doi:10.1007/s11469-022-00989-6
doi:10.3390/brainsci12101346
doi:10.3390/brainsci12050588
doi:10.1080/15504263.2022.2053770
doi:10.20882/adicciones.1498
doi:10.3390/biomedicines10051137
doi:10.1016/j.ijregi.2022.05.007

WP 7: Translational research in the chronicity of addictions

Between March and May 2023, a recount of the available DNA samples of the CohRTA Study patients in the RIAPAd Biobank was performed. This will be key for the PNSD 2022I058 project.

Alcohol

The long-term effects of alcohol use upon CB1 receptors have been studied. Specifically, in the excitatory synapses of the medial perforant pathway using an adolescence binge drinking model. Results show that an enriched environment has a beneficial effect on the long-term cognitive impairment associated to adolescence binge drinking and that fatty acids (Omega-3) improved the observed loss of memory in adult mice after adolescence binge drinking.

Also, the Receptor Protein Tyrosine Phosphatase ß/ζ (RPTP ß/ζ; PTPRZ) has been studied. RPTP is a new pharmacological target with potential to become a therapeutic strategy in AUD and its associated psychiatric pathologies. MY10 significantly reduces alcohol consumption, only in male mice. Furthermore, this alcohol consumption provoked a significant decline of hippocampal neurogenesis also only in male mice, damage that was prevented by MY10 treatment.

Wernicke's encephalopathy (WE) is a neurologic disease caused by thiamine deficit (TD) and AUD is its primary risk factor. Patients with WE present with motor, cognitive and limiting emotional alterations, related with a selective cerebral vulnerability. Neuroinflammation has been proposed as one of the phenomena contributing to cerebral damage.

The PTN/PTPRZ1 axis as a regulator of induced neuroinflammation by alcohol consumption during adolescence. PNSD (Ref. PNSD2019I015).

Cocaine

Prepulse inhibition (PPI) of the startle response can identify rodents that are more sensitive to the effects of cocaine, thus suggesting that PPI could be a physiological biomarker to the effects of cocaine. Mice with low PPI presented with a higher vulnerability to cocaine effects and an increased susceptibility to develop a SUD.

Adverse social experiences during adolescence are associated with the appearance of mental diseases in adult age. Social defeat (SD) is a preclinical model used to study the consequences of social stress in the adult age. The increase in anxiety was more significant in resilient mice with an increased preference for cocaine and alcohol

consumption. Stress responses produced by SD are more complex and singular in adolescents versus adults.

Psychostimulants

Methamphetamine consumption is associated with cognitive decline and its effect varies depending on the starting age of consumption. A human study found that the ones starting in adolescence had higher antisocial beliefs as well as a deficient emotional recognition compared to the ones that started in the adult life. In a study with mice, methamphetamine exposition during adolescence decreased social exploration conduct, and they did not observe any effects on aggressive behaviours. Methamphetamine can affect social cognition in a differential manner depending on the starting age of consumption.

Scientific production

Granted project: "Differences in genetic susceptibility to AUD by sex/gender: treatment implications and prognosis" (PNSD 2022I058). This project brings Personalised Medicine closer to the clinical practice in addictions and will genotype samples of the CohRTA Study and other RIAPAd collections. It intends to (1) identify genetic evidences of predominant distinctive pathways towards AUD in men (externalising) and women (internalising); and (2) to detect interactions between genotype (by Poligenic Risk Scores, PRS) and sex/genre in predicting AUD's severity, polydrug use and psychiatric comorbidity. Up until now, PRS models have been generated for genetic factors of predisposition towards externalising and internalising behaviours in order to obtain genetic evidence of the different predominance of said behaviours and the effects of the genetic factors by sex (a higher effect is expected in women). If this were to be confirmed, genomic biomarkers for women stratification would be generated, and could be implemented as indicators for an early or a more intense intervention depending on severe AUD susceptibility.

Publications

doi:10.3390/ijms24119387

doi:10.3389/fnut.2023.1068343

doi:10.3389/fncel.2023.1068472

doi:10.1111/febs.15907

doi:10.1007/s00418-022-02139-4.

doi:10.1523/JNEUROSCI.2514-21.2022

doi:10.3389/fnana.2022.1004702
doi:10.1016/j.bbr.2021.113545
doi:10.1016/j.pnpbp.2022.110591
doi:10.1016/j.drugalcdep.2021.109183
doi:10.1017/S0033291723000326
doi:10.1016/j.neuropharm.2023.109438
doi:10.3390/biomedicines10050947
doi:10.3390/ijms24021183.
doi:10.1002/eat.23917.
doi:10.1002/npr2.12289.
doi:10.3389/fphar.2022.866574

Achieved results and impact

Thanks to the work of the groups collaborating in this objective, both the expected results and the impact indicators are being met. Here is a list containing some results that are worth underscoring, extracted from the different publications related with the Work Packages 6 and 7:

1. Alterations in the immune system of AUD patients with early stages of alcohol-related liver disease were found. These alterations were characterised by T-Cell lymphopenia and an inflammatory status with a great cytotoxic response (expansion of NK and CD3-CD8+ cells). Such alterations might be an answer to the persistent and inadequate activation of the immune system. (10.3390/jcm11020305)
2. Almost 1 in 4 middle-aged patients that start AUD treatment had serum folate deficiency and 1 in 10 in tissue deposits. These factors could promote megaloblastic anaemia. Macrocytosis seems to be a strong predictor of erythrocyte and serum folate deficiency. Moreover, metabolic syndrome's (MetS) prevalence is lower than the one reported in the available literature. This could be due to the observed proportion of *heavy drinkers* without a clinical history of cardiovascular disease, suggesting that most of these cases are premorbid for MetS. Patients with a renal function eGFR <60mL/min were 5 times more likely to meet MetS' criteria. MetS can increase the risk of renal

disease via chronic inflammation and oxidative stress. (10.1038/s41598-022-06010-3)

3. Hypomagnesemia's prevalence in the serum of patients that seek AUD treatment for the first time (CohRTA Study) was found to be lower than in patients with AUD that are hospitalised by major complications. In this study, hypomagnesemia was the most common cause of electrolyte disequilibrium, even over hypocalcemia, hyponatremia and hypokalaemia. In addition, hypomagnesemia was more prone to occur in patients with hyponatremia or hypokalaemia. This suggests that, when a person with AUD starts treatment, a monitorisation of electrolytes is needed to detect dyselectrolytemia's risk. Advanced Liver Fibrosis and impaired renal glomerular filtration rate were associated with hypomagnesemia, suggesting that both comorbidities should be evaluated when serum Mg deficiency is detected. These results suggest that patients with excessive alcohol consumption, liver fibrosis, and kidney dysfunction should be tested for hypomagnesemia. (10.1016/j.drugalcdep.2023.109822)
4. An analytical method for quantifying 4-chloromethcathinone (clephedrone), N-ethyl Pentedrone, and N-ethyl Hexedrone in human oral fluid and sweat was developed and validated. These matrices are an alternative for both clinical and toxicological requests when blood or urine are unavailable, allowing for the detection of a recend drug assumption and the gathering of information in a simple, speedy and non-invasive manner. (10.3390/ijms24119387)
5. Urinalysis was performed in patients with Opioid Use Disorder (OUD) by high-sensitivity gas chromatography-mass spectrometry (GC-MS) and ultra-high-performance liquid chromatography-high –resolution mass spectrometry (UHPLC-HRMS) in a cross-sectional study with 301 samples. Several types of synthetic cannabinoids were detected in patients with OUD, besides the fact that cannabis was detected in 18.6% of the samples. These findings suggest that cannabis use is prevalent among patients with OUD and may be substituted by cannabinoid-like new psychoactive substances (NPS) to avoid detection in clinical tests, given that neither the instruments nor the protocols for NPS detection are prepared for clinical practice. (10.3389/fpsyt.2022.956120). In another study that used the same methods,

the presence of any type of NPS was detected in 27.3% of the analysed urine samples of patients with an OUD diagnosis attending a treatment centre. Stimulant-type NPS were the most frequently detected, which goes in line with worldwide NPS identifications. (10.3390/biology11050645)

These results provide new knowledge and ideas or complement other studies; pose the ground for new reflections that should be taken into account for future research in the topic of Substance Use Disorders, and rise considerations that suggest some clinical practices should be revised.

Accomplished synergies

The Badalona Germans Trias i Pujol/IGTP group (RD21/0009/0004) has established the following collaborations since the start of the RIAPAd:

Dr. Laura Orio (Maribel Colado's Group, UCM (RD21/0009/0025) for the assessment of cytokines in samples from Badalona's AUD patients being treated.

Dr. Emilio Ambrosio (RD21/0009/0020) for the assessment of Peth (phosphatidyl ethanol) by chromatography/spectrometry in patients with AUD from Badalona.

Dr. Laia Miquel (Hospital Clínic/IDIBAPS's Group) (RD21/0009/0010) for the CohRTA Study's longitudinal follow-up.

Dr. Gabriel Rubio (12 de Octubre's Group) (RD21/0009/0007) for the CohRTA Study's longitudinal follow-up.

Dr. Torrens (Hospital del Mar's Group) (RD21/0009/0001) for the CohRTA Study's longitudinal follow-up.

Dr. Jorge Manzanares (Alicante's Group, UMH) (RD21/0009/0008) for the CohRTA Study's sample selection of the stored samples in the BioBank.

Dr. Gonzalo Herradón (San Pablo-CEU's group) (RD21/0009/0014) for a study regarding pleiotrophin in samples of patients with AUD.

Dr. Javier Costas (Instituto de Investigación Sanitaria de Santiago de Compostela's Group, Complexo Hospitalario Universitario de Santiago) (RD21/0009/0011) to conduct an assessment regarding genetic susceptibility towards AUD of the CohRTA Study's patients.

Images and graphics

Table 1. Characteristics of 834 men and 356 women requesting a first treatment for AUD in the CohRTA Study.

Variables	Men N=834 n (%)	Women N=356 n (%)
Age at first alcohol use Median (IQR)(n=1,143)	15 (13-17)	16 (14-18)
Age at starting regular alcohol consumption Median (IQR)(n=1,176)	20 (17-27)	27 (20-37)
DSM-5 criteria Median (IQR)(n=1,168)	8 (7-10)	8 (6-10)
AUD family history (n=1,144)		
No	321 (40.1)	108 (30.3)
Yes	461 (55.3)	229 (64.3)
Unknown	18 (2.3)	7 (2.0)
Number of alcohol intoxications (lifetime) (n=1,078)		
None	535 (71.4)	230 (69.9)
1-5	189 (25.2)	88 (26.7)
>5	25 (3.0)	11 (3.3)
Tobacco Smokers (n=889)	588 (94.2)	256 (96.6)
Detection of drugs in urine		
Amphetamines (n=948)	8 (1.2)	1 (0.4)
Cannabis (n=949)	119 (17.8)	38 (13.5)
Cocaine (n=949)	54 (8.1)	10 (3.5)

Observations

Here is a list of some worth-mentioning publications, from the Badalona's group, regarding SUD's. They do not include the expedient number of the RICORS/RIAPAd but are tightly related to objective 3 "Chronicity": 10.3390/biomedicines10051137, 10.3390/biomedicines10050947 and 10.1159/000524011.

Other publications from the Badalona's Group that include the expedient number of the RICORS/RIAPAd (14/06/2023):

1. Poyatos L, Pérez-Mañá C, Hladun O, Núñez-Montero M, de la Rosa G, Martín S, et al. Pharmacological effects of methylone and MDMA in humans. Front Pharmacol. 2023 Feb 17;14:1122861. doi: 10.3389/fphar.2023.1122861.
2. Mas M, García-Vicente JA, Estrada-Gelonch A, Pérez-Mañá C, Papaseit E, Torrens M, et al. Antidepressant Drugs and COVID-19: A Review of Basic and Clinical Evidence. J Clin Med. 2022 Jul 12;11(14):4038. doi: 10.3390/jcm11144038.
3. Poyatos L, Torres A, Papaseit E, Pérez-Mañá C, Hladun O, Núñez-Montero M, et al. Abuse Potential of Cathinones in Humans: A Systematic Review. J Clin Med. 2022 Feb 15;11(4):1004. doi: 10.3390/jcm11041004.
4. Domínguez-Domínguez L, Rava M, Bisbal O, Lopez-Cortés L, Portilla J, Podzamczer, et al. Low CD4/CD8 ratio is associated with increased morbidity and mortality in late and non-late presenters: results from a multicentre cohort study, 2004-2018. BMC Infect Dis. 2022 Apr 15;22(1):379. doi: 10.1186/s12879-022-07352-z.

Other book chapters:

1. Muga R, Muñoz A. Conceptos básicos en epidemiología. Farreras Rozman Medicina Interna. 20ª Ed. En prensa.

Other participations in Scientific Conferences:

1. Sanvisens A, Torrens M, Bolao F, Fuster D, Fonseca F, Zuluaga P, Hernández-Rubio A, Abellí-Deulofeu E, Muga R. EPD118 -Changes in survival of HIV-positive Heroin Use Disorder patients admitted to treatment in Barcelona, Spain: a 30-year multicenter observational study. The 24th International AIDS Conference. Montreal, Canada. 29 July – 2 August 2022.
2. Sanvisens A, Torrens M, Bolao F, Fuster D, Fonseca F, Zuluaga P, Farré M, García-Marchena N, Abellí-Deulofeu E, Muga R. Temporal trend in the survival

of injecting and noninjecting heroin-dependent patients admitted to treatment in Barcelona, Spain: a 30-year cohort study. Lisbon Addictions 2022. 23-25 November 2022.

- **Activities:**

The research of the Badalona's group is disclosed in professional forums (either national or international) and has been published scientific journals. The investigation's results are also disseminated through social media (@hugtipadd on Twitter) and on the group's own webpage (https://adiccioneshospitalgermanstrias.com/) in order to share them with society.

Associations of affected patients and NGO's find themselves represented in the Badalona's group research lines. That is because the group maintains a close collaboration with entities such as Alcoholics Anonymous (AA), *Associació Alcohòlics Rehabilitats de Sta. Coloma de Gramanet*, *Associació d'Intervenció Comunitària en Drogues* (ASAUPA'M-Badalona), *Proyecto Hombre* and the *Associació Catalana de Pacients Hepàtics* (ASSCAT).

WP 8: Implement addiction detection in pregnancy and childhood.

WP8 was to be led by Dr. Barceló, who, following the initial evaluation in the RICORS call, was excluded from the grant despite the allegations made. The main objective of WP8 was the determination of drugs of abuse and medications in different matrices, including maternal hair, meconium, neonatal hair, neonatal urine, umbilical cord blood, or placenta. The samples were to be analyzed in collaboration with the RIAPAd group led by Dr. Quintana (RD21/0009/0012). The deliverables, D16 Comparative analysis of self-report versus drug detection in mother and child matrices (blood, urine, meconium, hair) and D17 Description of the prevalence of drug use throughout pregnancy and correlation with clinical outcomes after birth, will not be able to be carried out due to the exclusion of Dr. Barceló's group.

During the 24 months that have passed, various avenues of collaboration with other groups outside RIAPAd have been explored, but none have materialized.

WP 9: Translational models in perinatal and adolescent drug exposure

WP9, is led by Dr. Miñarro (0005) and Dr. Valverde (0001).

Other collaborators are the RIAPAd teams led by:

- 0001. Dr. Torrens
- 0003. Dr. Rodríguez de Fonseca
- 0004. Dr. Muga
- 0006. Dr. Grandes
- 0008. Dr. Manzanares
- 0013. Dr. Herradón
- 0020. Dr. Ambrosio
- 0027. Dr. Colado

The main lines of research carried out by these teams include the study of

A) Vulnerability to drug consumption in adulthood,

B) Emergence of symptoms resembling psychiatric disorders in adulthood,

C) Development of cognitive impairment in adulthood. Data obtained from various studies clearly indicate that early drug exposure is a crucial factor in the development of comorbidity,

D) Alterations induced by perinatal alcohol exposure

Summary

Several preclinical experiments have been conducted with rodents, observing how social defeat stress during adolescence leads to long-term increases in cocaine and alcohol consumption. These experiments also involved proteomic analysis and the role of the endocannabinoid system in vulnerability to cocaine and alcohol addiction induced by adolescent social defeat stress (adolescent stress/bullying model). Potential therapeutic strategies for addressing increased alcohol and cocaine consumption include a ketogenic diet and oleoylethanolamide (OEA). Furthermore, it was observed that OEA decreases the expression of TLR4 receptors caused by social stress. Another approach involves the consumption of polyunsaturated Omega-3 fatty acids to reverse the cognitive deficits observed in adults due to binge drinking during adolescence. Various aspects such as learning, memory, motor performance, and anxiety were evaluated. Results indicate that Omega-3 improves memory loss in adult mice and

produces a long-term potentiation of cannabinoid-dependent excitatory synaptic transmission (eCB-LTP). To know the potential addictive properties of high-fat diets (HFD) that could lead to the development of obesity we have used two HFD that contained no sugar (SOLF, Saturated OiL-enriched Food, and UOLF, Unsaturated OiL-enriched Food) in an operant self- administration model in Skinner boxes following a three criteria protocol: 1) food-seeking behavior, 2) motivation to obtain a reward and 3) compulsive-like behavior. Young C57BL/6J male and female mice, were subjected to a reinforcement program of increasing fixed ratio (FR1, FR3, FR5, and FR10), followed by a progressive ratio session aimed at finding the breaking point and finally, a cue-induced reinstatement session following the extinction of the food seeking behavior. Our results showed, on one hand, that both SOLF and UOLF diets had a higher reinforcing effect than the control diet for both sexes and induced a higher compulsion-like behavior. Male and female animals from both HFD exhibited a higher breaking point than control animals, and in both sexes, it was higher for UOLF than SOLF animals. On the other hand, SOLF and UOLF animals from both sexes had a higher addiction score than control animals. In the case of the females, UOLF animals had a higher score than SOLF. These data constitute a first glimpse at the potential addictive properties of both saturated and unsaturated HFD. Animals under the same protocol are being studied after THC administration in the adolescence. Collaboration is ongoing with CIBEROBN to explore the role of diet as a vulnerability factor in relation to perinatal metabolic programming.

Various activities have been carried out to observe how physical exercise reduces alcohol and cocaine consumption in socially defeated mice, increasing the levels of BDNF and IL-6. Additionally, environmental enrichment has been shown to reverse the alcohol-induced loss of memory in the hippocampus-dependent memory and restore CB1-eLTD. Mechanisms involved in the recovery of this plasticity at medial perforant path synapses have been characterized, mediated by the endocannabinoid 2-arachidonoylglycerol (2-AG) and group I metabotropic glutamate receptors. Using genetic models and administering an inhibitor of RPTP ß/? MY10, the effects of pharmacological inhibition of this receptor have been evaluated, showing that MY10 treatment reduces alcohol consumption.

Furthermore, relapse in the consumption of cocaine and alcohol in adolescent rats of both sexes after simultaneous self-administration of cocaine and alcohol has been studied as a preclinical model of polydrug use. At 30 days of abstinence, both sexes experience relapse. 3-way ANOVA yielded an extensive volume of data that revealed significant differences in amino acids concentrations. Some amino acids that could be critical for comprehending the phenomenon of craving incubation are L-Aspartate, L-Leucine, L-Threonine, and L- Serine. We also have correlated the plasma concentrations of several amino acids with behavioral parameters of craving incubation at 30-day period of abstinence. A positive correlation between plasma L-Leu concentration (μM/L) and drug-seeking behavior was found. However, after the consumption of combined cocaine and alcohol we observed a negative correlation between the plasma concentration of L-Glu (μM/L) and drug-seeking behavior. We believe that these data might contribute to a better understanding of the neurobiological processes that might involve in the relapse of polydrug use of combined cocaine and alcohol.

We have developed a valid preclinical model to study the response to social stress in females through vicarious social defeat (VSD). Using surveys and the design of a mobile app, we have investigated eating patterns during the COVID-19 pandemic and food addiction by validating the mYFAS 2.0 questionnaire in Spanish, which is used to assess food addiction. The results suggest the importance of eating styles and food addiction in overall health during stressful situations such as COVID-19 lockdowns. In regard to various behaviors, including anxiety, aggressive behavior, and social behavior, we have observed the effects of two emerging psychostimulants, N-ethyl-pentylone (NEP) and N-ethyl-pentedrone (NEPD), in an acute and intermittent manner, resulting in an increase in FosB expression and various behavioral alterations.

A mouse model of postpartum depression has been developed to compare the effectiveness of allopregnanolone and ketamine in this model. Postpartum depressed females due to the exposure to the maternal separation protocol exhibit behaviors of despair, anhedonia, and disrupted maternal care. Both treatments have been observed to be effective. Additionally, a fetal alcohol syndrome model has been developed in mice, to evaluate the modulatory role of the expanded endocannabinoid system in the cognitive impairments induced by alcohol in the offspring. For that, mice of the

C57BL/6J strain, both males and females, were exposed to a paradigm of voluntary alcohol consumption for one month. The offspring were weaned and separated by sex to evaluate the consequences of this exposure on various behavioral and brain aspects. Studies reveal that both male and female mice exhibit elevated levels of anxiety and depression, as well as heightened emotional reactivity. Alterations in recognition memory and aversive memory retention are observed in both sexes. Our results demonstrate that repeated administration of cannabidiol, URB597 and pioglitazone improves memory impairments. Therefore, PPAR-g activation during childhood could be a promising therapeutic target for memory deficits.

Furthermore, alterations in the gene expression of cannabinoid receptors CB1 and CB2, as well as the peroxisome proliferator-activated receptor beta (PPARb/d), have been studied. The effects of perinatal exposure to stress or alcohol on anxious-depressive behaviors in adulthood, memory, and hippocampal function in adulthood have also been investigated.

D19 Preclinical Models of the Long-Term Consequences of Drug and/or Environmental Factor Exposure (Stress, Aggression, Diet) During Pregnancy: Impact on Vulnerability to Chronic Diseases.

2022

doi: 10.1016/j.biopha.2022.113598.

doi: 10.1016/j.pnpbp.2021.110508.

2023

doi: 10.1016/j.phrs.2023.106655.

doi.org/10.1101/ 2023.01.20.524912.

doi: 10.1038/s41380-023-02191-z

D20 Preclinical Models of the Long-Term Consequences of Drug and/or Environmental Factor Exposure (Stress, Aggression, Diet) During Adolescence: Impact on Vulnerability to Chronic Diseases

2022

doi.org/10.1186/s40337-022-00624-8 .

doi: 10.1016/j.pnpbp.2021.110460.

doi: 10.3390/biomedicines10030593.

doi: 10.1016/j.biopha.2022.112708.

doi: 10.1080/1028415X.2020.1821519.

doi.org/10.3390/biomedicines10051137.

doi: 10.1016/j.neulet.2022.136670.

doi.org/10.1016/j.microc.2022.107738

doi: 10.1016/j.biopha.2022.113333

doi: 10.1016/j.biopha.2022.113333.

doi: 10.3389/fnana.2022.1004702.

doi: 10.1002/npr2.12289.

doi: 10.1016/j.biopha.2022.113598.

doi: 10.1016/j.pnpbp.2021.110462.

doi.org/10.3390/biomedicines10102373.

doi.org/10.1016/j.pnpbp.2022.110562.

doi.org/10.1111/jnc.15542

doi: 10.1523/JNEUROSCI.2514-21.2022.

doi: 10.1007/s00418-022-02139-4.

2023

doi.org/10.1016/j.neulet.2022.136972

doi: 10.1038/s41398-023-02378-6

doi: 10.3389/fnut.2023.1068343

doi: 10.3389/fncel.2023.1068472

doi: 10.1111/febs.15907.

doi: 10.1016/j.euroneuro.2023.01.005

doi: 10.1186/s12993-023-00210-1.

doi.org/10.1016/j.pnpbp.2023.110722

doi.org/10.3390/biomedicines11020502

doi.org/10.1186/s40337-023-00772-5

doi.org/10.1016/j.chroma.2023.464047

doi: 10.1016/j.euroneuro.2023.05.005

doi: 10.1016/j.biopha.2023.115194.

doi: 10.1038/s41598-023-45476-7.

SCHEDULED MILESTONES.

Models of vulnerability to chronic diseases resulting from perinatal drug exposure:

- Development of a postpartum depression model: Effective pharmacological treatment with allopregnanolone and ketamine.

- Development of a fetal alcohol syndrome model: Observing behavioral alterations and gene expression changes in CB1 and CB2. Administration of URB597 and pioglitazone improves memory impairments.

Models of vulnerability to chronic diseases resulting from adolescent drug exposure:

- We have observed how a ketogenic diet, the lipid oleoylethanolamide (OEA), or the consumption of polyunsaturated Omega-3 fatty acids can reduce alcohol and cocaine consumption and reverse cognitive deficits.

- Physical exercise reduces alcohol and cocaine consumption in socially stressed mice through social defeat, increasing BDNF and IL-6 levels.

- Environmental enrichment reverses the memory loss caused by alcohol consumption during adolescence.

- We have developed a valid preclinical model to study the response to social stress in females through vicarious social defeat (DSV).

- We have observed the importance of eating styles and food addiction in overall health during stressful situations such as COVID-19 lockdowns.

- We have observed the acute and chronic effects of two emerging psychostimulants, N-ethyl-pentylone (NEP) and N-ethyl-pentedrone (NEPD), on various behaviors, including anxiety, aggressive behavior, and social behavior.

- We have observed the effect of relapse in a preclinical model of polydrug use of cocaine and alcohol on plasma levels of various amino acids.

PhD Thesis:

2022:

Tamara Escrivá Martinez.

Relationship between dysfunctional eating patterns and binge drinking in young people and associated risk factors.

Supervisors: Rosa M. Baños Rivera and Marta Rodríguez Arias.

Excellent.

Collaboration with: CIBEROBN OCB06/03/0052

Elisa Blanco Martín

Demencia frontotemporal: genética, estudio evolutivo clínico, neuropsicológico y conductual.

Supervisors: Pedro Grandes Moreno and Manuel Fernández Martínez

2023:

Aitor Medrano Peral

Relación topográfica entre la localización subcelular de los receptores metabotrópicos de glutamato del grupo II (mGlu2/3) y del receptor cannabinoide CB1 en la región del hilus del giro dentado del ratón

Supervisor: Sonia María Gómez Urquijo

Laura Sánchez Marín.

Alcohol y estrés en la adolescencia como factores de vulnerabilidad en los trastornos de ansiedad: papel del sistema endocannabinoide.

Supervisors: Antonia Serrano and Fernando Rodríguez de Fonseca.

Laia Alegre Zurano

Phytocannabinoids and endocannabinoids as modulatriors of cocaine reinforcement in mice. Excellent "Cum Laude", International Mention.

Supervisor: Olga Valverde

Alba García Baos

The role of the expanded endocannabinoid system in cognitive impairments induced by prenatal and lactation alcohol exposure in mice. Excellent "Cum Laude", International Mention.

Supervisor: Olga Valverde

María Roca Outeiro

The role of THC in the addiction score of diets enriched in saturated and unsaturated fats.

Supervisors: Nuria del Olmo and Emilio Ambrosio

Mario Moreno Fernández

Exploración de las alteraciones conductuales, transcriptómicas y en la función cerebral relacionadas con esquizofrenia debidas a posibles efectos sinérgicos de la activación inmune materna y la exposición a THC durante la adolescencia en ratas de ambos sexos. Excellent "Cum Laude" mention.

Supervisors: Alejandro Higuera and Emilio Ambrosio

Master thesis:

Darlying Ginner

Biomarcadores neuronales asociados al binge drinking en adolescentes mediante técnicas de neuroimagen. una revisión sistemática.

Supervisor: Laura Orío

Máster: Psicofarmacología y drogas de abuso. UCM.

Maria Llach Folcrà

Evaluating the Effects of Cannabidiol on Cocaine Abuse in a Conditioned Punishment Model with Mice.

Supervisor: Olga Valverde

Master of Neuroscience. UB-UPF

Yunes Mohamed

Study of the reinforcing potential of high-fat diets and the effect of their intake on hippocampus-dependent spatial learning and memory in aged animals.

Supervisor: Nuria del Olmo

Master of Research in Psychology. UNED

WP 10: Implement the use of PROMs and PREMs in addiction care resources

The main objective of WP10 is the implementation in clinical practice for addictions of the set of self-reported measures by patients (PROMs) proposed by the ICHOM initiative, and to implement a PREM following the recommendations of the Patient-Reported Indicator Surveys (PaRIS) initiative of the Organization for Economic Co-operation and Development (OECD).

Deliverables (Expected delivery date in month 36):

D21 Report on Patient-Reported Outcome Measures in Outpatient Clinical Settings

D22 Report on Patient-Reported Experience Measures in Outpatient Clinical Settings

To obtain these reports following the grant award and the formal creation of the Primary Care Research Network in Addictions (RIAPAd), the following activities related to WP10 were carried out:

Activities:

1. Formation of the WP10 working group with the following members of RIAPAd:

2. RD21/0009/0001; RD21/0009/0003; RD21/0009/0004; RD21/0009/0007; RD21/0009/0010; RD21/0009/0025; RD21/0009/0029.

3. Evaluation of the impact for WP10 of not including the associated clinical groups in the network:

- Gonzalo Haro Cortes from San Pablo CEU University (Valencian Community)
- Francisco Javier Zamora Rodríguez from Badajoz Hospital (Extremadura)
- Maria Candelaria Martin Gonzalez from the University Hospital Complex Of Canaries (Canary Islands)

4. Creation (RD21/0009/0001) and review (All) of the ADD_PROMs study protocol (January-April 2022)

5. Activation of REDCap software in participating centers for use in the study. (All)

- Each center must request the free REDCap software from Vanderbilt University and install it on secure servers that comply with current regulations (LOPD).

6. Participation in the initial study meeting on May 3, 2022, for the review and approval of the study protocol. Attendees:

- Marta Torrens RD21/0009/0001
- Juan Ignacio Mestre RD21/0009/0001
- Fernando Rodríguez de Fonseca RD21/0009/0003
- Roberto Muga RD21/0009/0004

- Gabriel Rubio RD21/0009/0007
- Laia Miquel RD21/0009/0010
- Manuel Cuesta RD21/0009/0025
- Carlos Roncero RD21/0009/0029

7. Approval of the protocol by the PSMar's CEIC

- The research project no. 2022/10478/I, promoted by Consorci Mar Parc de Salut de Barcelona and titled: "ADD_PROMs: Feasibility study of the application of the ICHOM standard set for addictions: a mixed-methods assessment in outpatient addiction treatment settings in primary care" was approved on June 1, 2022.

8. Creation of the REDCap project with specifications recommended by the International Consortium for Health Outcomes Measurement (ICHOM), an international initiative to create a standard set of measures that allow the evaluation and monitoring of interventions in addictions. It includes the tools (PROMs) to be used, the times they should be administered, and risk adjustment factors for each pathology.

9. Once created, it can be exported to the servers of other research groups for use in data collection for the study.

In May 2022, the development and testing of the REDCap application with ICHOM's addiction standard set PROMs were completed. (Milestone 19)

In June 2022, the development and testing of the REDCap application with a generic PREM were completed due to the delay of the Patient-Reported Indicator Surveys (PaRIS) initiative in creating the initially proposed one.

The progress indicators for objective 5 expected by month 30 of implementation are:

1. The evaluation of the implementation of the PREM.
2. The evaluation of the implementation of the PROMs.

Currently, we have developed two REDCap projects for the implementation of both PROMs and the PREM in the care resources of the network.

During the process, we have encountered three problems:

1. Collaborating institutions were required to implement the free REDCap program on their servers following an agreement with Vanderbilt University. In the case of Dr. Cuesta's group from the Navarra Health Research Institute, this has not been possible

yet, and the current solution involves using the resources of the institution of the coordinator and PI of this WP10.

2. One of the premises of the study is the immediate visualization of part of the results and their evolution by the participants, as well as the visualization of the complete data of the questionnaires by the care professionals for use during baseline and follow-up visits. This visualization is not possible with REDCap, and alternative solutions (PDFs, data visualization web, etc.) through REDCap's API found so far are not affordable due to their high economic cost. Active alternatives are being sought through platforms such as Tableau. A definitive solution is expected by January 2024 to start the recruitment and follow-up of patients.

3. The delay of the Patient-Reported Indicator Surveys (PaRIS) initiative in creating a PREM has been resolved by creating an evaluation PREM based on a literature review, which we will test from December 2023 by administering it to 20 patients from PSMar centers and conducting focus groups to evaluate with the patients both the formal issues and usability as well as the content.

WP 11: Improvement of diagnosis through the application of the Dual Diagnosis Screening Interview (DDSI) in Primary Care clinical settings

Primary goal: To assess the utility of the Dual Diagnosis Screening Instrument in a online format, at Primary Care centers, and to estimate the prevalence of psychiatric comorbidities among patients with addiction from this network. At this moment, this objective has reached 30% completion, since adaptations of the instrument and initial steps for patients' recruitment and evaluation are being carried out.

With respect to the activities performed until the date, the following lines detail the development process and updates for the project phases:

May 2022. First meeting of clinical groups from the network: Torrens 0001; Rodríguez 0003, Rubio 0007, Miquel 0010, Cuesta 0025 y Roncero 0029. Sociodemographic and clinical variables were incorporated (in terms of substance use and medical comorbidities of responders), in order to obtain a better sample characterization and for the posterior analysis.

June-December 2022. Several proposals for the design and variables information have been discussed and proposed for an effective measurement, also considering the optimal administration time for the instrument.

February-March 2023. The project's design and writing process were set up according to specific aims derived from the main objective. Study design, recruitment method for respondents and researchers were discussed and written, as well as selection criteria for participants and methods of evaluation, including: additional variables to DDSI interview, type and mode of the assessments and informed consent preparation. All documentation was adapted to the online format of the study.

April-June 2023. Documentation was selected and sent for the approval of the project by the Ethical Committee of "12 de Octubre" Hospital Research Foundation. The protocols of evaluation were implemented and revised in the correspondent online platforms.

June-September 2023. The project has been approved by the Ethical Committee of "12 de Octubre" Hospital Research Foundation. An initial version of the updated instrument was tested by the technical staff; links for the interviewers (researchers) were tested. Comprehension of items of evaluation was discussed and tested, as well as time administration of the complete interview.

October-December 2023. During this period, the online interview was tested by several health care professionals from 12 de Octubre Hospital, with a reduced set of responders (patients with alcohol dependence). This initial step was carried out in order to discuss and determinate the easiness and simplicity of items' design, format and wording. Also, the instructions for the interviewers are being revised, together with clinical impressions about the technical and theoretical aspects of the interview, and the report that professionals receive at the end of the assessment. All these will be considered to improve the instrument's comprehension and easiness for the assessment.

Currently, the project has started the search for the recruitment of medical professionals from Primary Care centers. Finding possible interested collaborators from these centers and obtaining their participation in the project has been a challenging process, since contact with them has been quite scarce. Nonetheless, we recently contacted with the Primary Care medical residents coordinator in order to find possible collaborators.

Considering the complexity of this recruitment process and the time-consuming characteristics of an online interview for psychiatric comorbidities, our group has initiated the steps towards an online format for the responders. The psychological assessment with DDSI and additional variables is being adapted to a self-report format: items and instructions are being revised and adapted, and additional information for participants is being considered. In this way, the complete instrument will have two possible formats: one link with the full interview for researchers of professionals and an alternative, with a link for the participant or patient, with the items adapted to a self-report of the psychological evaluation. A pilot phase will be carried out in the next months, with the aim to compare and revise their possible equivalence in terms of results and psychometric properties. To this date, 50 participants have been interviewed by health care professionals, and a similar sample size will be recruited in the next weeks, for the self-informed alternative of the psychological assessment.

WP 12: Adapt CANreduce to Primary Care clinical settings. Comparison with standard brief interventions in addiction (alcohol and tobacco)

Enhancing Interventions: Implementation of CANReduce in Primary Clinical Settings. Comparison with Standard Brief Interventions for Addiction (Alcohol and Tobacco).
As part of Objective 6, WP12 addresses the need for the incorporation and improvement of e-health tools within the addiction field, encompassing prevention, detection, and treatment.
This report evaluates the effectiveness of the CANReduce tool in enhancing treatment adherence and reducing cannabis consumption. The study builds upon the 2019/8901/I study commissioned by the MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL. The project's aim was to assess the effectiveness of the CANReduce intervention, adapted to Spanish, in two versions (with and without psychological support) for reducing cannabis use in problematic consumers.
The initial steps involved translation, back-translation, and cultural adaptation of the CANReduce interface and intervention, followed by the development of a mobile application. Led by M. Torrens's group, the results were published in a preliminary article (doi: 10.1186/s13063-022-06399-2).

In parallel, to enhance user engagement with the platform, focus groups were conducted to improve various aspects, including target population, platform usage purposes, content, design, motivation, and adherence. A focus group involving professionals (n=6) and two focus groups with users (n=3 each) were conducted to improve the platform and subsequently enhance user adherence. Currently, the results from these focus groups are under analysis, with the intention of publishing an article detailing the qualitative findings and incorporating the improvements suggested by the focus groups to increase user adherence.

In addition to the aforementioned developments, there have been further advancements resulting from collaborations with other groups in e-health-related aspects:

1. PI20/00760. INSTITUTO DE SALUD CARLOS III. IBM-ABJ: Intervención Breve Motivacional combinada con Aprendizaje Basado en el Juego para mejorar la retención en tratamiento de pacientes con daño hepático relacionado con el alcohol. IP: López

Pelayo, Hugo. Collaboration with R. Muga (RD0021/0009/0004). 01/01/2021 - 31/12/2023. Objective: This project aims to design and evaluate an intervention to improve treatment retention for patients with alcohol-related liver damage who are initiating treatment for addiction. The intervention combines a brief motivational in-person session with the use of a gamified web app (6 weeks in duration).

2. Digital and blood biomarkers based on Addictions Neuroclinical Assessment framework and thiamine metabolism in patients affected by Alcohol Use Disorders with and without Alcohol Liver Disease. Objective: We aim to validate digital biomarkers (BD) based on the "Addictions Neuroclinical Assessment" approach and blood biomarkers based on thiamine metabolism to predict the prognosis of patients with Alcohol Use Disorders (AUD), with or without Alcohol-Related Liver Disease (DHrA).

3. Project Cahly: 2022I037. Influencia de la introducción del constructo de "consumo de riesgo de cannabis" con una intervención formativa cocreada sobre la alfabetización en salud respecto al cannabis en jóvenes y adolescentes. IP: Mercè Balcells. (Plan Nacional Sobre Drogas). The project aims to explore the level of health literacy regarding cannabis risk consumption in students aged 16 to 25 and to investigate if a psychoeducational intervention can enhance this literacy. The intervention consists of a structured session led by an educator, and students complete it in small groups using digital support (https://view.genial.ly/64f850d53c4b7e001199acb9/learning-experience-didactic-unit-cahly).

4. Project Muninn: Virtual Reality for Early Cognitive Rehabilitation through Physical and Cognitive Activity in Patients with Alcohol Use Disorder in Recent Abstinence. IP: Hugo López Pelayo. 2022/008916 (Instituto de Salud Carlos III). The project's objective is to identify cognitive and metabolic digital biomarkers that can assess individual risk factors for relapse in alcohol consumption among patients with Alcohol Use Disorder (AUD) and patients with alcohol-related liver damage who are beginning detoxification. Cognitive markers will be assessed through a digitalized protocol.

WP 13: Dissemination to professionals, the scientific community, patients, society at large, and policymakers

Justification: Objective 7 corresponds to the work package "Objective: Dissemination to addiction care professionals, the scientific community, patients and their associations, society in general, and policy makers," and has been implemented following the three deliverables committed in the proposal:

- D25 Dissemination to the scientific community and primary care professionals in addictions.
- D26 Dissemination to patients and Patient Associations.
- D26 Dissemination to the General Society and political decision-makers.

To achieve these deliverables, a set of actions have been carried out, grouped into 4 indicative variables, with full listings available on the RIAPAd website, as they exceed the volume allowed in the following report. These indicative variables are:

- Scientific publications
  Access: [RIAPAd Collaborative Publications](https://riapad.es/publicaciones-colaborativas-destacadas-de-la-riapad/)
- Communications at professional congresses
  Access: [RIAPAd Congresses](https://riapad.es/congresos/)
- Direct Communication Actions towards Patients, Associations, and the General Public
  Access: [RIAPAd Patients and Society](https://riapad.es/pacientes-y-sociedad/)
- Communication Actions on Social Networks, Written Press, Radio, and Television
  Access: [RIAPAd Media](https://riapad.es/medios-de-comunicacion/)

Activities Performed:

Communication in RIAPAd is a joint activity carried out by ALL members of the Network, configured as a daily commitment to communicate to society the studies and findings made by its members, or achieved through collaborations with other networks or CIBER in the field of addictions. In addition, all RIAPAd members have contributed to the dissemination of the network activity, by interacting directly with national/international drug problem-related stakeholders, editorials, policy makers, higher education representatives etc…

Achievement Dates: As it is a continuous activity, there is no achievement date, but a date for each communication action. Considering the volume of actions (over 400), RIAPAd members have been continuously working to openly disseminate the work done, explaining its impact on the approach to addictions from primary care, without neglecting studies on the biological bases of its pathogenesis, improvements in diagnostic processes, staging and classification, and improvements in therapeutic and social health approach. Use of social networks has been encouraged for all scientists engaged in RIAPAd's activities.

Progress Indicators: The indicators are basically numerical, i.e., the number of actions of each type. In this sense, the indicators of the network have been:
- Number of cooperative publications > 70
- Number of communications to congresses > 115
- Number of communication actions towards patients and general society > 90
- Number of communications on Social Networks, Written Press, Radio, and Television > 125

Challenges, difficulties, and solutions: The challenge of communicating scientific findings in a complex transversal network like RIAPAd has been solved through a layered communication design, in which communication contents have been structured from the most general to the most particular, understanding the contents as the scientific definition of the objectives and the analysis of their results. Similarly, a participation of the general society and of the patients and their associations has been designed to allow them to integrate these knowledge sequentially, gaining depth.

For instance, at the General Scientific Level, the Network was presented in the main Spanish and European forums related to the topic during 2022 and 2023, through structured sessions and symposiums where the integrated project of the network was presented. Highlights among these forums include:
- Lisbon Addictions Congress: organized by the European EMCDDA, it is the main European Congress on drugs.
- Socidrogalcohol Congress: The main Congress on Addictions in Spain.

- International Congress of Psychobiology: which also paid tribute to Consuelo Guerri, one of our most prominent scientists in the field of addictions.
- Congresses of the Dual Pathology Society.

For Dissemination to the General Society, dozens of activities were developed towards patient associations, conferences, book presentations in debate forums, technical days with patient associations, scientists, teachers, and students, etc. In all of them, the activity of the RIAPAd was presented and the message focused on the importance of addictions and the need to research and improve their primary care. Examples of these actions include book presentations, science debates, and scientific outreach programs.

For instance, and with the support of the National Plan Against Drugs**,** On May 30, 2023, the event "Alcohol, Science, and Society: Biomedical Research and Social Demand in Alcohol Use Disorders" took place in the auditorium of the Higher Technical School of the CEU San Pablo University on the Montepríncipe Campus (Alcorcón). The Institute of Addiction Studies at CEU San Pablo University (IEA-CEU) organized the event in collaboration with the Scientific groups of RIAPAd. This event was organize to give the floor to patients and patients' organizations dealing with alcohol-associated harms, and was open to citizens, students and health professionals.
https://riapad.es/jornada-alcohol-y-sociedad-iea-ceu-riapad-mayo-2023/

Specialized Communication: carried out at congresses and publications, as well as in the development of clinical practice guidelines and teaching manuals. In this sense, RIAPAd has been responsible and promoter of the latest teaching manual on addictions such as "Drogodepedencias" Colado MI et al., Ed. Panamericana
https://www.medicapanamericana.com/es/libro/drogodependencias-4ed
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The comprehensive approach in communication reflects the multidimensional and collaborative effort of the RIAPAd in disseminating knowledge and findings in the field of addictions.

Collaborative Publications

The RIAPAd is a collaborative scientific project committed to excellence in communication. RIAPAd groups have collaborated with each other and with other national groups to disseminate their scientific studies in leading journals in the field of addiction. You can see the list of the most notable collaborations here.

Mass media

Since its inception, RIAPAd has had a mission of dissemination, with frequent appearances in traditional media such as radio and television. This document summarizes the most notable appearances during the period 2022-2023.

Patients and society

All groups within RIAPAd demonstrate a clear commitment to disseminating results both to professionals in their respective fields and to patients, families, and society at large. This document highlights the most significant of all the activities carried out in the first 18 months of RIAPAd.

Congresses

One of the main activities of RIAPAd is the dissemination of results within the scientific community. This is what allows us to create new synergies with other groups, both national and international, and to advance in our objectives of improving prevention, treatment, and the maintenance of abstinence in addictive disorders. For these reasons, in this document, we share our most notable participations in the first 18 months of RIAPAd