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Non-invasive brain stimulation combined with neuroimaging: Towards precision medicine in the treatment of addictions

Estimulación cerebral no invasiva combinada con neuroimagen: Hacia una medicina de precisión en el tratamiento de las adicciones

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Addictive disorders are thought of as heterogeneous psychiatric conditions caused by the interaction of genetic, neurobiological, psychological, socioeconomic and environmental factors. These types of disorders are among the main causes of decreasing disability-adjusted life years (WHO, 2018), and smoking and alcoholism are considered to be among the most frequent causes of preventable death in the United States (Mokdad, Marks, Stroup & Gerberding, 2004). Spanish data are no less discouraging, with 5% of the population presenting this condition, resulting in an estimated cost of €1,500 per person per year (Miquel et al., 2018).

Despite the enormous social and financial burden that it generates, addiction is one of the disorders which has seen the least progress in the development of new treatments, most of which are of limited efficacy. Currently, approaches to treating addiction basically involve psychosocial and pharmacological interventions. Nevertheless, development of new drugs has been scarce in recent years. What is more, we lack pharmacological treatments for cocaine or cannabis, and, in the case of alcohol, no drugs surpass disulfiram, which was developed nearly a century ago and whose pharmacological action has a deterrent effect. Similarly, drugs with an anti-craving effect, such as acamprosate, naltrexone, nalmefene, which aim to reduce intense desire to consume a substance, have maintained only residual sales levels, a sure sign of their limited use in clinical practice.

The complexity associated with the pathophysiology of addiction is one of the main problems in finding an effective treatment for such conditions. However, the salience of the brain circuits involved in addictive behaviour in humans, which has been progressively recognized in recent years (e.g., Joutsa et al., 2022; Koob & Volkow, 2016), permits glimpses of new therapeutic approaches aimed at modifying the activity of these networks underlying addiction.

Neuroimaging studies have shown that two of the different existing brain networks are particularly involved in addictive behaviour (Dunlop, Hanlon & Downar, 2017). The first is the salience network (SN), which has several key nodes: the dorsolateral prefrontal cortex (DLPFC), the anterior cingulate cortex, and the anterior fraction of the insulae. This system, which is central to cognitive control and response inhibition (Dosenbach et al., 2006; Menon & Uddin, 2010), has been identified as a common pathophysiological substrate of various psychiatric illnesses

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(e.g., addiction, depression, and obsessive-compulsive disorder; Goodkind et al., 2015). In addictive disorders, this circuit is hypoactive. Abnormal functioning of this network could be behind the difficulty experienced by addicted people of curbing the impulse to consume when exposed to drug-related stimuli. The second brain network of key interest in addictions is the ventromedial network (VMN), which primarily encompasses the ventromedial prefrontal cortex (VMPFC), orbitofrontal cortices, and nucleus accumbens. This circuit is known as the brain's dopaminergic reward pathway. In addition, the network is hyperactive, thereby governing craving, i.e., the powerful need to consume the addictive substance (Volkow, Michaelides & Baler, 2019; Volkow, Wang, Fowler, Tomasi & Telang, 2011). In addictive disorders, not only is the intrinsic functioning of these networks altered, but the functional dynamics between them are also compromised (Hu, Salmeron, Gu, Stein & Yang, 2015; Zhang et al., 2015).

Looking at it in this way, addiction can be thought of as a psychiatric condition associated with an imbalance in brain networks, in particular a perturbation of two central circuits that play opposite roles in behaviour regulation. While the NS makes it possible to exercise control over decision-making processes, the VMN has the potential to generate craving. To simplify the treatment perspective, it can be said that psychosocial interventions seek to enhance the NS and avoid the stimuli that trigger the VMN, while pharmacological interventions seek to inhibit the VMN to make control of craving more viable.

In this framework, neuromodulation techniques have emerged as a promising therapeutic alternative given their ability to restore the homeostatic functioning of brain networks by modulating their main nodes (e.g., Antonenko et al., 2018; Meinzer et al., 2015; Orlov et al., 2017; for a review of this aspect in cognitive aging, see Abellaneda-Pérez, Vaqué-Alcázar, Solé-Padullés & Bartrés-Faz, 2022b). Most of the research involving non-invasive brain stimulation (NIBS) procedures in the field of addictive disorders has focused on the use of transcranial magnetic stimulation (TMS) and on transcranial direct current stimulation (tDCS). These techniques, particularly TMS, have also emerged with great translational potential, and protocols approved by the *Food and Drug Administration* (FDA; https://www.fda.gov/), to treat other psychiatric disorders, for example treatment-resistant depression and obsessive-compulsive disorder.

Before moving on to the application of these techniques to brain networks, let us take a look at how they work. Firstly, TMS is a technique that allows non-invasive stimulation of the cerebral cortex by generating brief and powerful magnetic pulses to produce a secondary electrical current in the brain, modifying its excitability (e.g., Ridding & Rothwell, 2007; Rossini et al., 2015). TMS can be applied in single, paired and repetitive pulses. In clinical practice, single and paired pulses have been used mainly for diagnostic purposes (for example, in multiple sclerosis: Conte et al., 2009; or in pathological aging: Benussi et al., 2017; 2020), while repetitive pulse trains (repetitive TMS, rTMS) have been applied for therapeutic purposes (Burke, Fried & Pascual-Leone, 2019). There are two main types of rTMS protocols: classic and patterned. In classical, depending on the stimulation parameters, rTMS can increase or decrease cortical excitability (Hallett, 2007). Procedures that use specific patterns of rTMS, such as 'theta-burst stimulation' (TBS), also allow mechanisms associated with neuronal plasticity to be induced (Huang, Edwards, Rounis, Bhatia & Rothwell, 2005). Secondly, tDCS is characterized by producing weak direct and tonic currents in the brain (Nitsche & Paulus, 2000). Similarly, new-generation electrical stimulation procedures called multifocal stimulation protocols have recently been developed which allow different brain regions to be stimulated simultaneously (Abellaneda-Pérez et al., 2021; Ruffini, Fox, Ripolles, Miranda & Pascual-Leone, 2014).

The studies performed to explore the clinical efficacy of neuromodulation techniques in addictions have followed two complementary approaches (e.g., Dunlop et al., 2017; Hanlon et al., 2015). The first focuses on boosting different nodes of the salience network through excitatory stimulation techniques. In line with the above, this should increase the cognitive control of the patients involved. One example is the classic study by Eichhammer et al. (2003), in which excitatory stimulation of the DLPFC was associated with significant reductions in cigarette smoking. Other studies have gone further by simultaneously stimulating different nodes of the SN, such as the DLPFC and the anterior insulae, with a special rTMS method which allows deep regions to be reached (e.g., by using H7-type coils); this also produced a reduction in drug use (Dinur-Klein et al., 2014). It is important to mention that research in this area, with exceptions where more refined procedures have been applied with the help of neuronavigation (e.g., Li et al., 2020), have primarily been able to control the behavioural spectrum of addiction, with only a minor impact on craving. This suggests that these protocols would mainly allow the cognitive control network (i.e., SN) to be modulated, but not so clearly its anti-network, the reward network (i.e., VMN).

The alternative approach, focusing on attenuating craving by reducing the activity of the ventromedial network, began development later. Initially, Hanlon et al. (2013) demonstrated, in a healthy sample, that by using TMS combined with neuroimaging it was possible to modulate the neural pathways governing executive control differentially from those associated with reward by stimulating dissimilar brain nodes. The DLPFC was stimulated in one way and the VMPFC in another. Once confirmed that was possible to modulate the VMPFC and the ventral striatum in a specific

way, the authors replicated the study with cocaine users. In this case, they applied inhibitory rTMS while the patients performed a craving induction task. Results showed that, as hypothesized, inhibitory rTMS significantly reduced brain activity in these ventromedial and striatal regions in study subjects (Hanlon et al., 2015). Nevertheless, subsequent studies have shown that the effect of these protocols is not the same in all subjects, and the observed effects may depend on various baseline neurobiological aspects (Kearney-Ramos et al., 2019). At a generic level, this is because neuromodulation techniques, both in their basic and clinical application, show notable inter- and intra-individual variability (Hamada, Murase, Hasan, Balaratnam & Rothwell, 2013; Martín-Trias et al., 2018).

To date, several biological factors contributing to such individual variability have been identified. Among them, we have found differences in the activation of intracortical networks (Hamada et al., 2013), in the basal functional connectivity of the modulated network (Nettekoven et al., 2015), in cortical excitability (Jannati, Block, Oberman, Rotenberg & Pascual-Leone, 2017), in the induced current in the brain (Abellaneda-Pérez et al., 2021; Saturnino, Thielscher, Madsen, Knösche & Weise, 2019) and even in genetic endowment (Abellaneda-Pérez et al., 2021; Pérez et al., 2022a; Di Lazzaro et al., 2015). In the context of the clinical application of these techniques, the studies reveal two crucial elements: on the one hand, the importance of offering applied interventions with the highest possible level of personalization, and, on the other, the possible existence of individual predictors of treatment efficacy. Taking these elements into consideration when applying neuromodulation protocols would presumably maximize treatment success, allowing subjects in whom a high probability of therapeutic response is estimated to receive the most personalized interventions possible.

With reference to the personalization of interventions, it is important to consider that rTMS can be applied with different levels of precision. At this point, it should be noted how crucial the combined use of brain stimulation with neuroimaging has been, since it has made it possible to reveal the neurobiological pathways mediating the therapeutic effects of this type of intervention in different psychiatric disorders. One of the disorders which has seen more research in this regard is depression, where the location of the stimulation point has been perfected in recent years. Specifically, this has changed from determining the stimulation target with simple calculations on the scalp based on the motor cortex or following the 10-20 international system to the use of neuroimaging, first structural, and then functional, to determine the optimal stimulation point in the DLPFC according to its level of connectivity (anti-correlation) with the subgenual nucleus (Cash et al., 2021; Fox, Buckner, White, Greicius & Pascual-Leone, 2012; Weigan et al., 2018). This optimization in target location, which has led to a substantial improvement in the response to treatment in depression, could also be effective in addictions, given the shared pathophysiology at the level of macroscopic networks between both conditions (Dunlop et al., 2017). A second element of personalization that has gradually become more important is related to the possibility of determining the exact stimulation dose that needs to be applied to each patient in order to suitably modulate the selected region, going beyond what is related to the threshold of the motor cortex. In this sense, in the future, the application of finite element calculation methods applied to structural images will probably be a relevant element to take into account in increasing the individualization of these interventions (Abellaneda-Pérez et al., 2021; Saturnino et al., 2019). Finally, it is worth mentioning the possibility of using neuromodulatory procedures that require fewer pulses and shorter treatment sessions, such as those using patterned rTMS (i.e., TBS). Being equally effective (e.g., Blumberger et al., 2018), these may be tolerated much better and can thus increase treatment adherence, essential in addictive disorders. Furthermore, given that TBS induces brain plasticity mechanisms, it could reverse the lasting neural effects due to psychiatric pathology on the one hand and, on the other, produce beneficial long-term effects, an essential aspect in the treatment of addictions.

Moving on to the second line of action, this focuses on carefully characterizing patients so that they can receive the most effective treatment option in each case. Here, we may consider that initial patient assessment, aimed at collecting as much data as possible on the predictive variables of treatment response, can be essential in guiding clinical decisions based on the markers identified. In this sense, structural examination of brain atrophy (Wagner et al., 2008), exploration of the basal functional state of brain networks (Nettekoven et al., 2015), together with the plasticity or malleability shown by them (Abellaneda-Pérez et al., 2019; Perellón-Alfonso et al., 2022), the specific ability to affect deep areas of interest (Vink et al., 2018), and even the genetic profile associated with synaptic plasticity (i.e., Abellaneda-Pérez et al., 2022a) would be key factors in estimating the chances of success of a specific neuromodulation protocol in a specific patient. This characterization should not be aimed solely at determining which patients are candidates for stimulation or not. That is, rather than being a go/no-go decision, it would make it possible to determine which patients would be candidates for which particular type of intervention. This line of action could lead to a radical change in the clinical use of neuromodulation, allowing the principles of personalized medicine to be applied to the field of psychiatry. However, these approaches are currently in the process of neuroscientific development, pending the identification of markers that are scalable to daily clinical practice.

All of the above suggests an approach involving a new perspective in the clinical implementation of neuromodulation. This new paradigm arises from the need to leave behind the notion that the heterogeneity associated with neuromodulation techniques are a limiting factor in clinical application, instead beginning to see it as an opportunity. It is an element that we can take use to our own ends in optimizing, and thus maximizing, treatment success in each patient. The fundamental idea behind this perspective is that the variability observed through stimulation techniques does not, of course, inform us of the differences in the techniques per se, but of the different ways in how each brain responds to them. And knowing how each brain responds is essential in determining how to apply the best therapy. Future research should thus focus not only on the clinical efficacy of this type of intervention, but also on the customization capacity that these protocols present and on the identification of their treatment efficacy markers. All this is key for making effective progress in the application of such interventions. In this way, we will be able to integrate advances in precision neuroscience into the clinical context of addictive disorders, with the ultimate goal of promoting treatment success in these patients.

In conclusion, it is reasonable today to imagine that in the near future it will be possible to study the addicted patient using neuroimaging techniques to establish exactly which brain networks to stimulate in order to reduce craving and increase cognitive abilities to deal with drugs. Undoubtedly, clinical work focusing on the patient and tackling the complex comorbidities and social situations that accompany addictive processes will continue to be essential, but it is clear that, if this new scenario is realized, it will not only constitute an important scientific advance, but will also contribute greatly to reducing the stigma associated with addictive behaviours.

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Factors associated with frequent marijuana consumption in young people before admission to juvenile detention centers in Peru

Factores asociados al consumo frecuente de marihuana en jóvenes antes de su ingreso a centros juveniles de diagnóstico y rehabilitación en Perú

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Abstract

Marijuana is the most widely used illicit drug in the world, especially among young people. This study is relevant to policy makers because it expands the knowledge regarding drug use in vulnerable youth, allowing health authorities to reduce marijuana consumption via educational, family, and governmental strategies and policies. The objective of this study was to determine the prevalence of frequent marijuana consumption and its associated factors in young people before admission to juvenile detention centers in Peru. The data was taken from the 2016 National Population Census of the Youth Diagnostic and Rehabilitation Centers in Peru. The final sample was made up of 1,848 people with ages between 14 and 22 years old, with a median age of 17 (95.6% males). The variable *frequent marijuana consumption* was defined as the use of marijuana at least once a week, prior to entering the center. The main factors associated with frequent marijuana use were male sex, running away from home before the age of 15, physical abuse during childhood, having a family member who consumed alcohol or drugs frequently, and the presence of criminal gangs in the housing area. Additionally, it was found that living with parents up to a specific critical age decreases the probability of frequent use of marijuana in young people. These results could aid the development of strategies and public policies that help prevent the consumption of marijuana and other drugs from an early age.

Keywords: Cannabis; marijuana use; substance-related disorders; Peru; vulnerable populations.

Resumen

La marihuana es la droga ilícita más consumida en el mundo, especialmente entre jóvenes. El presente estudio es relevante para la toma de decisiones en salud porque expande el conocimiento sobre el uso de drogas en la juventud vulnerable y permite a las autoridades sanitarias reducir el consumo de marihuana mediante estrategias educativas, familiares y gubernamentales. El objetivo de este estudio fue determinar la prevalencia del consumo frecuente de marihuana y sus factores asociados en jóvenes antes de su ingreso a centros juveniles de diagnóstico y rehabilitación en Perú. Los datos fueron tomados del Censo Nacional de Población en los Centros Juveniles de Diagnóstico y Rehabilitación del año 2016 en Perú. La muestra final estuvo compuesta por 1848 personas entre 14 y 22 años, con una mediana de edad de 17 años (95,6 % hombres). La variable *consumo frecuente de marihuana* fue definida como el consumo de marihuana de al menos una vez por semana por parte de los jóvenes, previo a su ingreso al centro. Los principales factores asociados al consumo frecuente de marihuana fueron el sexo masculino, huir de casa antes de los 15 años, haber sufrido abuso físico durante la infancia, tener un miembro de la familia que consuma alcohol o drogas frecuentemente y la presencia de pandillas criminales en la zona residencial. Asimismo, se halló que vivir con los padres hasta cierta edad crítica disminuye la probabilidad de consumo frecuente de marihuana en jóvenes. Estos resultados podrían ayudar a desarrollar estrategias y políticas públicas que ayuden a prevenir el consumo de marihuana y otras drogas desde edades tempranas.

Palabras clave: Cannabis; uso de la marihuana; trastornos relacionados con sustancias; Perú; poblaciones vulnerables.

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According to the United Nations Office on Drugs and Crime (UNODC) and the World Health Organization (WHO), cannabis is the most commonly used illicit drug in the world, with approximately 188 million people having used the drug in 2017 (United Nations Office on Drugs and Crime, 2019; World Health Organization, 2019). Globally, the prevalence of marijuana use ranges from 2.7-4.9%, with the highest rates of use reported in Australia and North America. In South America, the highest rates of cannabis consumption were found in Brazil and Chile (Degenhardt, Ferrari & Hall, 2017; Degenhardt et al., 2013; United Nations Office on Drugs and Crime, 2015; World Health Organization, 2016). In Peru, marijuana is also the most commonly used illicit drug. Overall rates of marijuana use in the past year are estimated between 2-3% (Inter-American Drug Abuse Control Comission, 2019). Furthermore, a national survey on the general population found that 47.1% of marijuana consumers in Peru have signs of dependency, which was similar to what was found for cocaine consumers (Comisión Nacional Para el Desarrollo y Vida sin Drogas, 2012).

Marijuana use has been associated with acute and long-term adverse effects. Acute effects are developed over a short period of time after consuming the drug and include psychiatric effects, such as impaired attention, dyschronometria, and psychosis; and physical signs such as conjunctival hyperemia, increased appetite, xerostomia, increased blood pressure and increased heart rate (Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2020; García Álvarez, Gomar, García-Portilla & Bobes, 2019; Karila et al., 2014; Levine,Clemenza, Rynn & Lieberman, 2017; National Institute on Drug Abuse, 2019; World Health Organization, 2019). Long term effects involve psychological impairment, cognitive deficits and respiratory consequences (Guxens, Nebot, Ariza & Ochoa, 2007; Karila et al., 2014; Martínez-Torres et al., 2016; World Health Organization, 2019). In addition, cannabis dependency is accountable for a decreased participation in academic activities and relationships, a lower income, unplanned pregnancies, mental diseases, increased rates of unemployment, and involvement in other risky behaviors (Khalsa & Baler, 2019; United Nations Office on Drugs and Crime, 2018). Nonetheless, cannabis has been associated with some beneficial effects, the most common conditions for which physicians recommend marijuana are pain, persistent nausea and vomiting, improvement of sleep and anxiety (Burggren, Shirazi, Ginder & London, 2019; Fiz , Durán, Capella, Carbonell & Farré, 2011).

Adolescence (~12 to 17 years old) is a period of critical risk for initiation of substance use (United Nations Office on Drugs and Crime, 2018). Its easy availability, coupled with perceptions of a low risk of harm, makes cannabis the drug of choice in this age group (Comisión Nacional para el Desarrollo y Vida sin Drogas, 2012; Comisión Nacional para el Desarrollo y Vida sin Drogas, 2013; United Nations Office on Drugs and Crime, 2018). In Peru, the average age of onset of cannabis use is 14.4 years old, and the prevalence per year of marijuana use between the ages of 12 and 17 years is 2% (only surpassed by the age group between 19 and 25 years, with 2.1%) (Comisión Nacional para el Desarrollo y Vida sin Drogas, 2012). The regular use of marijuana during adolescence is of particular concern, since use by this age group is associated with an increased likelihood of experiencing the deleterious consequences described previously (Volkow, Baler, Compton & Weiss, 2014). Among adolescents in juvenile detention centers of Peru, the prevalence per year of marijuana consumption was found to be around 29.3%, which is more than ten times higher than what was found for the general Peruvian population (Comisión Nacional para el Desarrollo y Vida sin Drogas, 2013).

Factors that have been linked to cannabis use in adolescents in the scientific literature include a variety of social, interpersonal, and individual factors. Social factors include urbanization and availability of drugs in the environment; interpersonal factors include affiliation with marijuana-using peers and peer-pressure; and individual factors include gender, level of study, risk perception, perceived stress, self-esteem, impulsivity and emotional discomfort (Ameth et al., 2017; Casajuana et al., 2021; Rial et al., 2019; Zapata Roblyer, Betancourth & Grzywacz, 2015).

The present work aimed to find the prevalence, characteristics, and associated factors of marijuana use among young people in juvenile detention centers of Peru. Although international literature regarding factors associated to marijuana consumption in adolescents is available, our review did not find studies regarding marijuana use in young people from juvenile detention centers.

Materials and Methods

The present study has a cross sectional analytical design, based on secondary analysis of the data obtained from the National Population Census in the Diagnostic and Rehabilitation Youth Centers in Peru, carried out from March to April 2016 by the National Institute of Statistics and Informatics (INEI, from Spanish acronym), in coordination with the Ministry of Justice. The census included all men and women admitted in the country's 10 juvenile detention centers spread out across the nation (United Nations Office on Drugs and Crime, 2019). Considering a marijuana consumption prevalence of 2.5% (World Health Organization, 2019) and 95% of significance, we estimated the statistical power for two scenarios of comparison of proportions (depression and tobacco use) (Bahorik et al., 2018; Leatherdale, Ahmed & Kaiserman, 2006) in OpenEpi version 3.01. Thus, we obtained a statistical power higher than 90% in both scenarios.

The information was collected through a face-to-face questionnaire by a printed census card, and the answers were registered by the pollster. The census card was composed of one cover and five chapters, which included 179 questions distributed in 16 pages. The chapters of the survey were: social and family conditions, the situation of the criminal offense, living conditions, role of the institutions, and expectations of the inmate. A pilot test was carried out to evaluate the operability, structure, phrasing and understanding of the questions, and answer alternatives stated in the census card. As a result, the number of questions was reduced from 213 to 179 to shorten the duration of the questionnaire. Coordinators of youth centers and census enumerators were trained to ensure the quality of the data obtained. They were also given a manual that served as a guide for an adequate collection of information by the enumerator (Instituto Nacional de Estadística e Informática, 2016).

The outcome variable "frequent marijuana consumption" (FMC) was constructed based on three questions from the health section of the questionnaire. The first question asked was: "Did you use drugs before entering the juvenile detention center?". If the answer was affirmative, the inmate would answer: "What type of drug did you use?". Thirdly, they were asked: "How often did you consume before entering the youth center?". Participants who answered "yes" to the first question; "marijuana" to the second one; and "daily", "2 to 6 times per week", or "weekly" to the third one, were considered as having the outcome. This way, the possible factors associated with frequent marijuana use in young people before entering the detention centers could be evaluated.

The variables were divided into sociodemographic and familial characteristics, morbidities, and harmful habits. The region variable was divided according to the place of origin of the inmate. They were classified as coming from Lima or other regions. The level of education was classified as uneducated, elementary (complete or incomplete) and secondary (complete or incomplete). Child labor was considered in those who reported having worked at age 14 or earlier. The age until which the inmate lived with the mother and father was classified as: he never lived, he lived until he was 14 and he lived beyond the age of 14. In addition, sex, age, ran away from home before the age of 15, physical abuse during childhood, having during childhood a family member who consumed alcohol or drugs frequently, presence of gangs in the area where he lived, discrimination or abuse before admission, has belonged to some criminal gang, and juvenile detention center readmission were considered in the independent variables. Depression, substance abuse disorder and asthma were evaluated using two questions. The first one asked the respondent to self-report whether he had the condition or not. The second one asked whether a health professional had diagnosed this condition. Only those who responded affirmatively to both of these questions were considered as having the disease. Permanent limitations on learning and concentration were evaluated through self-report. Harmful habits prior to the admission (consumption of alcoholic beverages, tobacco, and their starting ages) were self-reported. The self-reporting of diseases has been used in previous studies carried out in vulnerable populations (Feinstein et al., 1998; Salazar-De La Cuba, Ardiles-Paredes, Araujo-Castillo & Maguiña, 2019). One study concluded that the prevalence of self-reported diseases was more sensitive and specific than the incidence (Oksanen et al., 2010).

The database was downloaded from https://observatorio.mininter.gob.pe/proyectos/censo-nacional-de-centros-juveniles in dbf format and was transferred to Stata 14.0 (Stata Corporation, College Station, TX, USA) for analysis. In the univariate analysis, the absolute and relative frequencies of each variable of interest were described. The numerical variables were described through the median and interquartile range (IQR), due to their abnormal distribution, previously tested by Shapiro-Wilk test. The bivariate analysis was performed using Pearson's chi-square test for categorical variables and Mann-Whitney U test for numerical variables. The magnitude of the association was calculated through crude prevalence ratios (cPR) and adjusted prevalence ratios (aPR), computed for each variable. The epidemiological and statistical criteria were taken into consideration to select the variables of the multivariable model. Both models were estimated employing generalized linear models, Poisson family, log link function, with robust variance. This statistical model allows us to study associations between exposures and binary outcomes, through point estimates and comparable standard errors (Chen, Qian, Shi & Franklin, 2018). This enables us to determine relative risks, that based on the design of the present study would be interpreted as prevalence ratios. The multivariable model was adjusted for all the previously selected variables, and it was adjusted by clusters conformed by juvenile detention centers. All statistical analyzes were conducted with a level of significance less than 0.05 and a 95% confidence interval (95% CI). This work was approved by the institutional ethics committee of the Universidad Peruana de Ciencias Aplicadas (registration code PI081-17).

Results

The population from the 10 juvenile detention centers was 2,203. Of these, 58 were excluded because they were absent during the survey or turned in blank forms. Out of the 1,965 remaining, 117 did not fill the variables of interest and therefore were excluded. 1,848 participants were included, which represents 91.3% of the total population (see Figure 1).

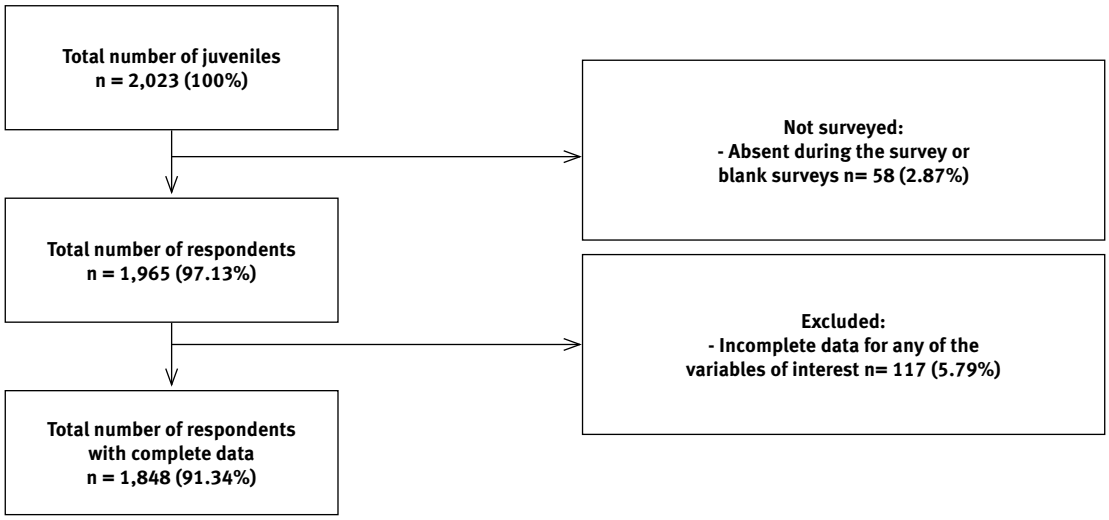

Figure 1. Flow chart.

The prevalence of FMC, as defined above, was 32.8% (n=606). The age range was 14 to 22 years old with a median age of 17 years old (IQR: 16-18). In addition, 95.29% (n=1,761) of the respondents were male and 67.26% (n=1,243) had secondary level education. Statistically significant (p value <0.05) association was found between FMC and being born in Lima, running away from home before the age of 15, presence of the father, physical abuse during childhood, having a family member who consumed alcohol or drugs frequently, presence of criminal gangs in the area where one lived, belonging to a criminal gang, and readmission to the juvenile detention center (see Table 1). Statistically significant associations were also found between FMC and a medical diagnosis of substance abuse disorder, consumption of alcoholic beverages, and tobacco use. An association between the age at which consumption of both alcohol and tobacco was started and FMC was also found (see Table 2).

When adjusted per all model variables and juvenile detention centers as clusters, we found that male sex (aPR: 1.31, 95%CI: 1.21-1.40), being born in Lima (aPR: 1.64, 95%CI: 1.36-1.95), running away from home before age 15 (aPR: 1.28, 95%CI: 1.11-1.47), physical abuse during childhood (aPR: 1.23, 95%CI: 1.07-1.40), having a family member who consumed alcohol frequently (aPR: 1.08, 95%CI: 1.01-1.15), having a family member who consumed drugs (aPR: 1.19, 95%CI: 1.05-1.34), presence of criminal gangs in the area where they lived (aPR: 1.63, 95%CI: 1.46-1.82), readmission to juvenile detention center (aPR: 1.18, 95%CI: 1.02-1.38), medical diagnosis of substance abuse disorder (aPR: 1.38, 95%CI: 1.13-1.67) and consumption of alcoholic beverages (aPR: 1.40, 95%CI: 1.18-1.66) increased the likelihood of FMC in a statistically significant way. We also found that when compared to never having lived with one's mother, living with her up to age 14 (aPR: 0.79, 95%CI: 0.64-0.95) or further (aPR: 0.83, 95%CI: 0.69-0.99) decreased the likelihood of FMC. In the case of the father, only living with him further than age 14 (aPR: 0.83, 95%CI: 0.73-0.93) decreased the likelihood of FMC (see Table 3).

Discussion

According to the World Drug Report of 2015, men are three times more likely than women to use marijuana (United Nationals Office on Drugs and Crime, 2015). In our country, marijuana use in men is three to ten times higher than in women (Comisión Nacional para el Desarrollo y Vida sin Drogas, 2012). This was also seen in our study, where male participants were 1.31 times more likely to use marijuana at least once a week than females. The prevalence of marijuana use among age groups vary among regions and socioeconomic level. According to the World Health Organization, in the United States marijuana use peaks at the early twenties and declines throughout the late twenties. In Brazil, the prevalence of use is highest among the adolescent population (World Health Organization, 2016). In the present study, subjects ranged from 14 to 22 years old, this age group is ideal for studying marijuana consumption because, as stated above, the highest prevalence is among adolescents and early adults.

Various studies have shown that interpersonal interactions influence the likelihood of marijuana utilization. In Peru, the most common initiation environment for marijuana use is among neighborhood groups, accounting for 57.9% of the consumption initiation environments (Comisión Nacional para el Desarrollo y Vida sin Drogas, 2012). Furthermore, a study conducted in North Carolina showed a positive correlation between gang membership

Table 1. *Prevalence of frequent marijuana consumption (FMC) at Peruvian Juvenile Detention Centers according to sociodemographic and familiar characteristics.*

Characteristics	Study population (n=1,848) n (%)	FMC*† (n=606)	Prevalence (% row)	95% CI	p value
Age (IQR)	17 (16-18)	17 (16-18)			0.127
Sex					
Male	1,761 (95.29)	579	32.88	30.72-35.11	0.721
Female	87 (4.71)	27	31.03	22.17-41.54	
Region					
Lima	866 (46.86)	375	43.30	40.03-46.63	‹0.001
Other regions	983 (53.14)	231	23.52	20.97-26.28	
Education level					
No education	22 (1.19)	6	27.27	12.54-49.50	0.183
Elementary	583 (31.55)	208	35.68	31.88-39.65	
Secondary	1,243 (67.26)	392	31.54	29.00-34.17	
Child labour					
Yes	932 (50.43)	298	31.97	29.05-35.04	0.450
No	916 (49.57)	308	33.62	30.63-36.75	
Ran away from home before 15 years old					
Yes	717 (38.80)	307	42.82	39.23-46.47	‹0.001
No	1,131 (61.20)	299	26.44	23.94-29.08	
Age until he lived with the mother					
Never lived	58 (3.14)	26	44.83	32.51-57.80	0.030
≤14 years	534 (28.90)	189	35.39	31.44-39.55	
›14 years	1,256 (67.97)	391	31.13	28.62-33.74	
Age until he lived with the father					
Never lived	280 (15.15)	114	40.71	35.09-46.58	‹0.001
≤14 years	724 (39.18)	251	34.67	31.28-38.21	
›14 years	844 (45.67)	241	28.55	25.60-31.70	
Physical abuse during childhood					
Yes	866 (46.86)	329	37.99	34.81-41.27	‹0.001
No	982 (53.14)	277	28.21	25.47-31.10	
Having during childhood a family member who consumed alcohol frequently					
Yes	580 (31.39)	234	40.34	36.41-44.39	‹0.001
No	1,268 (68.61)	372	29.34	26.89-31.90	
Having during childhood a family member who consumed drugs					
Yes	81 (4.38)	49	60.49	49.43-70.57	‹0.001
No	1,767 (95.62)	557	31.52	29.39-33.72	
Presence of gangs in the area where he lived					
Yes	975 (52.76)	426	43.69	40.60-46.83	‹0.001
No	873 (47.24)	180	20.62	18.06-23.43	
Discrimination or abuse before admission					
Yes	166 (8.98)	66	39.76	32.57-47.41	0.045
No	1,682 (91.02)	540	32.10	29.91-34.37	
Belonged to some criminal gang					
Yes	337 (18.24)	154	45.70	40.43-51.05	‹0.001
No	1,511 (81.76)	452	29.91	27.65-32.27	
Juvenile detention center readmission					
Yes	253 (13.69)	112	44.27	38.24-50.46	‹0.001
No	1,595 (86.31)	494	30.97	28.74-33.28	

Note. * Chi-square test was used for categorical variables and Mann-Whitney's U for numerical variables.
† FMC: Frequent marijuana consumption, meaning at least once a week.

Table 2. *Prevalence of frequent marijuana consumption (FMC) at Peruvian Juvenile Detention Centers according to morbidities and harmful habits.*

Characteristics	Study population (n=1848) n (%)	FMC*† (n=606)	Prevalence (% row)	95% CI	P value
Morbidities‡					
Depression					
Yes	69 (3.73)	31	44.93	33.58-56.82	0.029
No	1,779 (96.27)	575	32.32	30.18-34.53	
Substance abuse disorder					
Yes	64 (3.46)	39	60.94	48.45-72.13	‹0.001
No	1,784 (96.54)	567	31.78	29.66-33.98	
Asthma					
Yes	105 (5.68)	42	40.00	31.04-49.67	0.105
No	1,743 (94.32)	564	32.36	30.19-34.59	
Permanent limitations to understand or learn					
Yes	289 (15.64)	106	36.68	31.30-42.40	0.126
No	1,559 (84.36)	500	32.07	29.79-34.43	
Harmful habits†					
Age of onset of marijuana use (IQR)		14 (13-15)			‹0.001
Consumption of alcoholic beverages					
Yes	1,507 (81.55)	535	35.50	33.12-37.95	‹0.001
No	341 (18.45)	71	20.82	16.83-25.46	
Age of onset of alcohol consumption (IQR)		14 (13-15)			‹0.001
Tobacco use					
Yes	925 (50.05)	344	37.19	34.12-40.35	‹0.001
No	923 (49.95)	262	28.39	25.56-31.38	
Age of onset of tobacco use (IQR)		14 (13-15)			‹0.001

Note. * Chi-square test was used for categorical variables and Mann-Whitney's U for numerical variables.
† FMC: Frequent marijuana consumption, meaning at least once a week.
‡ Autorreported diseases diagnosed by a healthcare professional.
† Use prior to admission at the juvenile detention center.

and frequency of marijuana consumption. The same study also showed a higher probability of consumption in early adolescence compared to those without gang membership (Wechsberg et al., 2015). These results are consistent with ours because we described an increase of 63% of probability of having FMC among those who live in a neighborhood with gang presence. Another study found that adolescents whose peers were involved in drug use, including marijuana, had almost six times higher chances of using cannabis, most likely because of peer pressure (Mehanovič et al., 2020).

Family background has been reported to have an influence over marijuana use, and this is consistent with the results of our study. Having parents who consume alcohol and drugs increases the probability of FMC in 1.08 and 1.19 times, respectively. It has been described that closeness of young people to their parents reduces the consumption of marijuana and other substances (Kosterman, Hawkins, Guo, Catalano & Abbott, 2000; Velleman, Templeton & Copello, 2005). Furthermore, a systematic review found that having a single-parent family, in addition to a problematic relationship with parents, are important risk factors to marijuana consumption in young people (Guxens et al., 2007). Physical abuse during childhood has also been shown to be a risk factor for marijuana consumption, as demonstrated by a study carried out in young adults from Mexico, using the Social Cohesion Survey for the Prevention of Violence and Crime. Similarly, other studies also reported the same association (Hornor, 2010; Hser, Longshore & Anglin, 2007; Huang et al., 2011; Vega-Cauich, Heredia & García, 2018). Our study found that running away from home before the age of 15 had 1.28 more probability of FMC, which is consistent with prior research carried on homeless and runaway adolescents, where it was found that the prevalence of marijuana use was much higher in this group compared to the general population, regardless of their reasons for running away (Rew, Taylor-Seehafer & Fitzgerald, 2001; Tyler, Gervais & Davidson, 2013; Wang, Chen, Lew-Ting, Chen & Chen, 2010). In a study in early adolescence a

Table 3. *Associated factors to frequent marijuana consumption (FMC) at Peruvian Juvenile Detention Centers.*

	Crude analysisa			Adjusted model b		
	cPR*	**P value**	**CI 95%**	**aPR‡**	**P value**	**CI 95%**
Age	1.02	0.370	0.97-1.06	0.96	0.034	0.92-0.99
Sex						
Male	1.06	0.724	0.76-1.45	1.31	‹0.001	1.21-1.40
Female	Ref	Ref	Ref	Ref	Ref	Ref
Region						
Lima	1.84	‹0.001	1.60-2.10	1.64	‹0.001	1.36-1.95
Other regions	Ref	Ref	Ref	Ref	Ref	Ref
Ran away from home before 15 years old						
Yes	1.62	‹0.001	1.42-1.84	1.28	0.001	1.11-1.47
No	Ref	Ref	Ref	Ref	Ref	Ref
Age until he lived with the mother						
Never lived	Ref	Ref	Ref	Ref	Ref	Ref
≤14 years	0.79	0.132	0.58-1.07	0.79	0.014	0.64-0.95
›14 years	0.69	0.016	0.51-0.93	0.83	0.049	0.69-0.99
Age until he lived with the father						
Never lived	Ref	Ref	Ref	Ref	Ref	Ref
≤14 years	0.85	0.069	0.71-1.01	0.91	0.337	0.74-1.10
›14 years	0.70	0.000	0.58-0.83	0.83	0.002	0.73-0.93
Physical abuse during childhood						
Yes	1.35	‹0.001	1.18-1.53	1.23	0.002	1.07-1.40
No	Ref	Ref	Ref	Ref	Ref	Ref
Having during childhood a family member who consumed alcohol frequently						
Yes	1.38	‹0.001	1.20-1.56	1.08	0.016	1.01-1.15
No	Ref	Ref	Ref	Ref	Ref	Ref
Having during childhood a family member who consumed drugs						
Yes	1.92	‹0.001	1.58-2.31	1.19	0.005	1.05-1.34
No	Ref	Ref	Ref	Ref	Ref	Ref
Presence of gangs in the area where he lived						
Yes	2.12	‹0.001	1.82-2.45	1.63	‹0.001	1.46-1.82
No	Ref	Ref	Ref	Ref	Ref	Ref
Discrimination or abuse before admission						
Yes	1.24	0.036	1.01-1.51			
No	Ref	Ref	Ref			
Belonged to some criminal gang before admission						
Yes	1.53	‹0.001	1.32-1.75			
No	Ref	Ref	Ref			
Juvenile detention center readmission						
Yes	1.43	‹0.001	1.22-1.67	1.18	0.027	1.02-1.38
No	Ref	Ref	Ref	Ref	Ref	Ref
Depression						
Yes	1.22	0.019	1.03-1.44			
No	Ref	Ref	Ref			
Substance abuse disorder						
Yes	1.92	‹0.001	1.55-2.35	1.38	0.001	1.13-1.67
No	Ref	Ref	Ref	Ref	Ref	Ref
Consumption of alcoholic beverages						
Yes	1.71	‹0.001	1.37-2.12	1.40	‹0.001	1.18-1.66
No	Ref	Ref	Ref	Ref	Ref	Ref
Tobacco use						
Yes	1.31	‹0.001	1.14-1.49			
No	Ref	Ref	Ref			

Note. [a] Poisson regression with robust variance.
[b] Poisson Regression with robust variance adjusted per selected variables, and adjusting juvenile detention centers as clusters.
*cPR: Crude prevalence ratio.
‡ aPR: Adjusted prevalence ratio.

moderate association was found between having a sibling who consumed alcohol or who consumed marijuana during childhood and marijuana use in the last year (Heerde, Bailey, Toumbourou & Catalano, 2019; Terry-McElrath, O'Malley & Johnston, 2013). Having positive parental attitudes towards drug use increased 1.35 times the probability of substance use among young people (Heerde et al., 2019; Terry-McElrath et al., 2013). Furthermore, having parents with a positive attitude towards alcohol and tobacco use, increased the probability of marijuana consumption five-fold (Mehanovič et al., 2020).

Our study described that alcohol consumption increases 1.40 times the probability of FMC. In addition, we found a great prevalence of tobacco use (50.05%) in our population, in contrast with the low prevalence of tobacco use in the general population in Peru (World Health Organization, 2016). A 2019 study found that consumption of either alcohol or cigarettes increased the probability of simultaneous use of marijuana. It is of note that this study found that marijuana use also increased the probability of alcohol and/or cigarette use (Roche et al., 2019). Furthermore, a population-based study in Canada found that teenagers who had used both alcohol and tobacco were 188 times more likely to have tried marijuana (Leatherdale, Hammond & Ahmed, 2008). These studies are consistent with ours, since we found that alcohol consumption increases the probability of FMC 1.40 times. A study in high school seniors found that simultaneous alcohol and marijuana use was strongly linked to perceived dependency (Mehanovič et al., 2020), which supports our findings of an association between self-reported substance abuse disorder and marijuana consumption. Earlier age of onset of both alcohol and tobacco use has also been found to increase FMC prevalence, which is consistent with previous studies in incarcerated populations (Racz et al., 2016). Early onset of substance use has been associated with polysubstance use, higher risk of substance abuse and criminal behaviors later in life (Gordon, Kinlock & Battjes, 2004; Moss, Chen & Yi, 2014). This association is particularly strong in incarcerated young adults (Harrison, Ramo, Hall, Estrada-Gonzales & Tolou-Shams, 2019). Youth involved in the penal system are therefore at a higher risk for these disorders and should merit evaluation and further interventions.

We found that juvenile detention center readmission increases 1.18 times the probability of FMC compared to those who were not readmitted. This correlates well with studies that indicate that drug use overall is associated with faster recidivism (Aalsma et al., 2015). This indicates that drug use, in this case marijuana, could be an important factor for reentry to the youth detention center. A possible explanation for this could be that they were detained because of their illegal marijuana use, or because the drug use provoked them to commit an illegal act.

This study, due to the coverage of the entire population of juvenile detention centers, allows extrapolating the statistical data found on this population group at that of the level of Peru. The findings of this research should be interpreted in the light of its limitations. Since the variable FMC was generated using questions from the questionnaire, it represents only an approximation of the marijuana consumption pattern, since it has not been validated. It must be considered that some of the data obtained refers to events that occurred in childhood, so a memory bias may arise. The diseases analyzed were self-reports of diagnosis by health professionals, so they are subject to information bias. The use of a face-to-face interview to collect information about risky behaviors produces desirability bias. Because this is a cross-sectional study, there will be no temporality and it is impossible to determine causation. We encourage the development of longitudinal studies with the aim of evaluating marijuana consumption as a possible risk factor to juvenile detention centers admission. In addition, we suggest evaluating risk factors among this population through censuses in other countries.

The present study found important sociodemographic factors and life experiences associated with frequent marijuana consumption in Peruvian youths before their admission to detention centers. These results are relevant to policy makers because it expands the knowledge regarding drug use in vulnerable youth, such as those living in neighborhoods with gang presence and in single-parent families. Allowing health authorities to reduce the prevalence of factors associated with more frequent marijuana use via educational, family and governmental strategies and policies. At an educational level, programs could be made that promote healthier life styles, that shed a light on the dangers of marijuana and other drugs, or that allow testimonies from past drug users. In the family, the results could allow parents to be more watchful of their children and aware of which factors could lead their children to consume marijuana or other drugs. At a governmental level, the government could make television or radio commercials that educate the population on drug use, or they could also make policies that help reduce the frequency of use, like adding more security around the communities to help reduce marijuana use in vulnerable neighborhoods.

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Conflict of interests

The authors declare no conflicts of interest regarding the publication of this article.

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Psychological recovery stages of alcohol dependent patients after an intensive outpatient treatment: A 4-year follow-up study

Fases de la recuperación psicológica en pacientes dependientes del alcohol tras un tratamiento intensivo: Un seguimiento de 4 años

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Abstract

The aim of this work is to determine if relapses can hinder the sequence of psychological recovery and to rebuild this sequence in patients with severe alcohol dependence that seek treatment. The sample was comprised of 159 patients seeking an intensive outpatient treatment of two years duration and who were subject to follow-up during four years after discharge. Patients were grouped according to the presence of relapse during follow-up, resulting in abstainers (n = 80) and relapsers (n = 79). Assessments were carried out in the following periods: baseline, at discharge, and at the second- and fourth-year follow-ups. The measurement variables were avoidance behavior, anxiety, depression, impulsivity and meaning in life (MiL). A control group (n = 74) was evaluated at the same periods as the patients. Results indicate a slower recovery in relapsers in comparison to abstainers in all psychological dimensions and periods assessed. At the second-year follow-up, the abstainers achieved similar scores in depression as the control participants, in addition to higher scores in Meaning in Life at the end of treatment. In patients with severe alcohol dependence, our data supports a sequence of recovery that could continue beyond the four years of follow-up after treatment. This sequence would begin with the avoidance of risk situations and continue with the rest of dimensions (anxiety, depression, impulsivity).
Keywords: Alcohol dependence; recovery; meaning in life; abstinence; affective symptoms; impulsivity.

Resumen

El objetivo de este trabajo es comprobar si las recaídas dificultan la secuencia de la recuperación psicológica y reconstruir la secuencia de la recuperación de pacientes graves que solicitan tratamiento. Los participantes fueron 159 pacientes tratados durante dos años en un programa ambulatorio intensivo y tras ser dados de alta fueron seguidos durante cuatro años. En función de la presencia o no de recaída durante el seguimiento se configuraron dos grupos, el de abstinentes (n = 80) y el de pacientes que recaen (n = 79). Las evaluaciones se realizaron: basal, al alta del tratamiento, al 2.º y 4.º año de seguimiento. Las variables fueron: conductas de evitación, ansiedad, depresión, impulsividad y sentido de la vida. Se incluyó un grupo de control (n = 74) que fue evaluado con la misma cadencia que los pacientes. Los resultados indican una recuperación más lenta en el grupo con recaídas frente a los abstinentes, en todas las dimensiones psicológicas y los períodos estudiados. A los dos años de seguimiento, los pacientes abstinentes obtuvieron puntuaciones en depresión similares a los controles, además de puntuaciones superiores en sentido de la vida (MiL) a partir del final del tratamiento. Al menos en pacientes con dependencia grave del alcohol, nuestros resultados apoyan una secuencia de recuperación que podría continuar más allá de los cuatro años de seguimiento. Se inicia con la evitación de situaciones de riesgo y continúa con el resto de las dimensiones (ansiedad, depresión, impulsividad).
Palabras clave: Dependencia de alcohol; recuperación; sentido de la vida; abstinencia; sintomatología afectiva; impulsividad.

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The Substance Abuse and Mental Health Services Administration (SAMHSA) (2011) defines recovery as "a process of change through which individuals improve their health and wellness, live a self-directed life, and strive to reach their full potential" and includes four major dimensions: health, home, purpose and community. Psychological health, comprising depressive and anxiety symptoms or life purpose, has been one of the most studied dimensions related to recovery, although as an abstinence or relapse predictor. In fact, they represent dimensions that have been found to be altered during the dependence process, being associated to a poorer quality of life (Ugochukwu et al., 2013), psychological wellbeing and treatment success in general (Amodeo, Kurtz & Cutter, 1992; Laudet, Becker & White, 2009). Specifically, alcohol dependent individuals show anxiety and/or depression-like symptoms along the dependence process (Ghorbani, Khosravani, Bastan & Ardakani, 2017), as well as a lack of motivation, decision-making problems, coping and impulsivity, among others (Ando et al., 2012; Brown, Vik, Patterson, Grant & Schuckit, 1995; Courtney et al., 2012). It has been assumed that with continued abstinence a normalization/stabilization of these variables starts to take place (White, 2012), however, little is known with respect to recovery sequence and whether the patients ever reach values similar to healthy population (Kelly, Greene & Bergman, 2018).

An important aspect of recovery could be the avoidance behavior, as a coping strategy regarding substance exposure, meaning the avoidance of risky situation, that is, where alcohol is present or alcohol-related contexts (e.g. bars, parties, etc). Avoidance coping is a key element to relapse prevention goals, among other coping strategies (Marlatt, 1990; Marlatt & Witkiewitz, 2005), since it has an intense presence from early stages of psychotherapeutic treatment.

Studies regarding anxiety evolution in alcohol dependent patients seeking for treatment have determined that after several months of abstinence, a decrease of *anxiety* scores is produced; and that the higher the baseline scores are, the larger is the risk for relapse (Brown, Irwin & Schuckit, 1991; Rubio et al., 2017). With respect to depression symptoms, research has also shown a reduction in *short and long-term depression* scales (Wilcox, Pearson & Tonigan, 2015; Worley, Tate & Brown, 2012). These lower depression scores have been associated with a greater level of attendance to mutual-help groups, although its persistence or sudden presence in an intense form represents a challenge in the recovery of these patients (Kelly, Stout, Magill, Tonigan & Pagano, 2010a). Lower levels of *impulsivity* have also been observed, at least during the first year of abstinence (Blonigen, Timko, Moos & Moos, 2009). Studies carried out in subjects with alcohol dependence that attended mutual-help groups indicate a decrease in impulsivity up to fifteen months of follow-up (Blonigen, Timko, Finney, Moos & Moos, 2011; Kelly, Stout, Tonigan, Magill & Pagano, 2010b). Our previous research results also indicate an improvement of these symptoms, that could last over two years of treatment (Rubio et al., 2018).

At the same time, *values acquisition* like *spirituality* and *meaning in life* have been considered as essential variables in alcohol dependence recovery, especially in studies carried out in the field of programs based on the 12 steps , such as Anonymous Alcoholics (AA) (Tonigan, McCallion, Frohe y Pearson, 2017; Wilcox et al., 2015). Kelly, Hoeppner, Stout and Pagano's (2012) research with two samples from the MATCH project showed that spirituality correlated with groups attendance, particularly in patients included in the continuing care sample (n = 774), that is, the most severe cases. Another value involved in recovery is *meaning in life* that has been related to a better social functioning (Witkiewitz et al., 2019), life quality (Laudet & White, 2008) and long-term abstinence maintenance (Rubio et al., 2018). A recent study (Kelly et al., 2018) performed in a community sample of alcohol dependent patients found that within the first months of recovery the indexes of *life quality* and *psychological well-being* were low at the beginning but then got higher, although they did not reach general population levels up until 10 years after.

In summary, up to these days, research points to a bidirectional relation between abstinence length and an improvement in avoidance behavior, anxiety, depression, impulsivity, spirituality and life purpose. Nevertheless, we do not fully understand how the sequence of psychological recovery takes place and if we could identify different stages and duration. There is also a lack of results on whether this recovery, after several years of abstinence, would imply similar scores to general population, regarding the mentioned psychological dimensions.

In this way, the aim of this study was to determine the progress of behavioral variables (avoidance) and psychological ones (anxiety, depression, impulsivity and life purpose) during the period of intensive treatment of two years duration and four years of follow-up. In this study we used a sample from a previous study (Rubio et al., 2018) divided by the presence of relapse, forming two groups (relapsers and abstainers), and followed-up during four years. We also included a control group formed by participants from the general population.

Our hypothesis is that the presence of relapse would slow-down the psychological recovery process, and that even abstainers would not reach similar scores to control participants in the measured psychological dimensions (Kelly et al., 2018).

Method

Participants

The sample was selected over a period of 14 months from patients attending the alcohol dependence treatment

program from "12 de Octubre" Hospital (Rubio et al., 2018).A total number of 249 patients were included the study, with 42 abandoning it at different moments of the study (third (N = 11), sixth (N = 12), ninth (N = 9), twelfth (N = 4) and eighteenth month (N = 5)) . By the end of the follow-up, we had incomplete information regarding 41 subjects, either because it was difficult to contact them over time or they had passed away (n = 7). The final sample included in the analysis was comprised by 233 subjects. Patient's group was divided according to the presence of relapses during the study, giving rise to a first group of abstainers and a second group of relapsers. Relapse is defined as the consumption of more than 4 units of standard drinks in males and 2.5 units in women, during at least three times a week or lower quantities more than three times a week.

With respect to the control group, participants were recruited through ads placed in two health centers, asking for participation in a study for emotional states progress evaluation. Once they were interviewed, those individuals who met criteria for abuse or substance use disorders, or any other psychiatric or neurological condition, were discarded. Participants were explained the tests instructions and the follow-up procedure of the study. The initial sample had 167 candidates, but 46 were discarded due to abuse or substance use disorders and 4 denied participation regarding the follow-up measures, whereas 32 did not attend to the second year of follow-up assessment. We disposed from complete data from 85 cases, although the final sample was composed by 74 patients, since they had to be similar in age and gender to the clinical sample.

Table 1 shows sociodemographic and clinical characteristics for all participants. 66% of the total sample were men and the average age was of 42.86 (8.35) years. 59.9% completed secondary education, 23.3% had a higher education level and 16.8% of them only went to primary school. Half of the sample had a job during the assessment. Regarding alcohol consumption data, patients reported high levels of daily consumption and their scores in EIDA (Rubio, Urosa & Santo Domingo, 1998) indicated a severe alcohol dependence, with over 10 years of evolution. While examining these sociodemographic differences between all three groups we did not find statistical significant differences for most variables, with the exception of study level, and abstinence levels in months between abstainers and relapsers (p<0.01, see Table 1).

Treatment programs and follow-up interviews

Details regarding the therapeutic program can be read in Rubio et al (2017). The clinical groups were treated as outpatients and intensively, along 24 months, and they were sequentially included in the following programs: detoxification and motivation for abstinence, relapse prevention, social abilities, consolidation of healthy habits and lifestyle and preparation for discharge. Annually, we disposed from data regarding each patient's evolution. After discharge, every two years participants were interviewed in order to fill out psychological scales, gave a blood sample to determine GGT and the information relative to months of abstinence and attendance to follow-up appointments was registered. Half of the sample (n = 91), in addition to attending the outpatient program, also went to mutual-help groups of the Federation of Alcoholics from the Community of Madrid (FACOMA), which is based on the "help yourself-help-us" program (FACOMA, 2016).

Clinical assessment instruments

Patients were interviewed and diagnosed according to DSM-IV-TR criteria (American Psychiatric Association, 2000). A Spanish version (Rubio et al., 1998) of Severity of Alcohol Dependence Questionnaire (SADQ) (Stockwell, Murphy & Hodgson, 1983) was used to asses alcohol dependence intensity (EIDA) and it is composed by 30 Likert items with four answer options. Total EIDA scores can indicate low (<20), moderate (21-37) or severe (>37) dependence. This scale has good reliability values, with Cronbach's alpha values of 0.91 in the adapted scale and 0.87 in this study. The follow-up for alcohol consumption was: it was carried out through the Alcohol Timeline Followback (TLFB) interview designed by Sobell, Sobell, Leo and Cancilla (1988) in order to determine the daily consumption. Through this interview the presence of relapse was determined, in addition to period of consumption and accumulated abstinence.

Coping strategies regarding alcohol dependence were assessed through a Spanish version (García González & Alonso Suárez, 2002) of The Coping Behavior Inventory (CBI) (Litman, Stapleton, Oppenheim & Peleg, 1983). This self-informed measure consists of 36 items and it aims to identify the frequency of coping strategies use in order to maintain abstinence in risk situations. Reliability values are of 0.78 for the Spanish validation and 0.76 in this study. Taking into account that one of the least used strategies by Spanish patients is avoidance of risk situation, and its particular cultural relevance in this country, we decided to include in this study the 5 items of the avoidance subscale (items 5, 8, 18, 20 and 30).

Affective symptomatology was assessed through Hamilton anxiety (HARS) (Hamilton, 1959) and depression (HDRS) (Hamilton, 1967) scales, with Cronbach's alpha values of 0.78 and 0.82, respectively, for this study. Self-informed impulsivity was evaluated by the Barrat Impulsiveness Scale (BIS-11) (Patton, Stanford & Barratt, 1995), which has 30 items that evaluate cognitive, motor and non-planned impulsivity. The Spanish version (Oquendo et al., 2001) has a good alpha coefficient and maintains the three factors structure. In this study alpha's value is of 0.79.

Another measure used in this study was the Meaning in Life Questionnaire (MLQ), an instrument thought

Table 1. *Sociodemographic and clinical characteristics.*

	Participants n = 233	Relapsers n = 79	Abstainers n = 80	Controls n = 74	*F. Welch/ chi²*
Sex. no. (%)					
Men	154 (66.1)	56 (79.9)	49 (61.3)	49 (66.2)	1.68
Age. Mean ± SD	42.8± 8.35	41.6 ± 8.3	43.4 ± 8.4	43.5 ± 8.3	1.24
Civil Status. N (%)					
Single	56 (35.2)	30 (38)	26 (32.5)	--	
Married	68 (42.8)	33 (41.8)	35 (43.8)	--	
Separated/Divorced	33 (20.8)	16 (20.3)	17 (21.2)	--	2.37
Widow	2 (1.3)	0 (0)	2 (2.5)	--	
Study level. N (%)					
Primary	39 (16.8)	14 (17.7)	15 (19)	10 (13.5)	
Secondary	139 (59.9)	41 (51.9)	37 (46.8)	61 (82.4)	27.59**
Superior	54 (23.13)	24 (30.4)	27 (34.2)	3 (4.1)	
Employment situation. N (%)					
Active	81 (50.9)	35 (44.3)	46 (57.5)	--	
Unemployed	32 (20.1)	21 (26.6)	11 (13.8)	--	
TIW	28 (17.6)	14 (17.7)	14 (17.5)	--	
Pensioners	11 (6.9)	5 (6.3)	6 (7.5)	--	4.84
Homemaker	7 (4.4)	4 (5.1)	3 (3.8)	--	
Group of received treatment. n (%)					
Regular	68 (29.2)	46 (58.2)	22 (27.5)	---	15.33**
Mixed type with FACOMA	91 (39.1)	33 (41.8)	58 (63.7)	---	
Type of consumption. N (%)					
Social	33 (21.2)	16 (20.8)	17 (21.5)	--	
Solitary	47 (30.1)	27 (35.1)	20 (25.3)	--	1.89
Mixed	76 (48.7)	34 (44.2)	42 (53.2)	--	
Frequency of use. N (%)					
Daily excessive	134 (84.8)	69 (88.5)	65 (81.2)	--	
Weekend excessive	8 (5.1)	3 (3.8)	5 (6.2)	--	1.59
Sporadic excessive	16 (10.1)	6 (7.7)	10 (12.5)	--	
Beverage preference. N (%)					
Beer	82 (51.9)	40 (51.3)	42 (52.5)	--	
Wine	10 (6.3)	4 (5.1)	6 (7.5)	--	0.48
Liquors	66 (41.8)	34 (43.6)	32 (40)	--	
Initial age of alcohol consumption. Mean ± SD	17.24 ± 5.35	17.4 ± 6.07	17.9 ± 6.4	16.3 ± 2.31	3.07
Age of alcohol dependence diagnosis. Mean ± SD	29.79 ± 9.33	29.8 ± 9.31	29.7 ± 9.4	--	0.007
Years of alcohol consumption. Mean ± SD	12.82 ± 10.07	11.8 ± 9.05	13.8 ±10.9	--	1.54
Abstinence in the first year (in months). Mean ± SD	11.09 ± 1.82	10.6 ± 2.2	12 ± 0	--	53.5**
Abstinence in the second year (in months). Mean ± SD	10.24 ± 2.54	8.46 ± 2.59	12 ± 0	--	149.7**
Abstinence in the fourth year (in months). Mean ± SD	9.14 ± 3.4	6.24 ± 2.55	12 ± 0	--	407.1**
Tobacco dependence. N (%)					
Yes	129 (81.2)	61 (77.2)	66 (82.5)	21 (29.6)	
No	20 (12.6)	12 (15.2)	8 (10)	50 (70.4)	131**
Abandonment	10 (6.3)	6 (7.6)	6 (7.5)	0 (0)	
Cocaine Consumption. N (%)					
No	107 (67.3)	49 (62)	58 (72.5)	--	
Abuse	22 (13.8)	13 (16.5)	9 (11.2)	--	2.01
Dependence	30 (18.9)	17 (21.5)	13 (16.2)	--	

Note. Sociodemographic and clinical descriptive data and statistic comparison indexes (either Welch. F and Chi-Squared) values for the three groups of study (abstainers and relapsers and control group). TIW stands for Temporary Inability to Work. "--" indicates that this data was not available in case of the control group.*,** indicates p values ‹0.05 and 0.01, respectively.

to measure life significance, that is, the meaning of the subject's own nature and existence (Steger, Frazier, Kaler & Oishi, 2006). This scale evaluates two aspects of life meaning, through two subscales of 5 items: Presence and Search. Presence refers to the extent to which people understand, give or see a meaning of their own life, together with the grade of purpose, mission or aims perception. The Spanish version has a good alpha value 0.80 and in the present study reaches the value of 0.87. Concurrent validity shows a good association with psychological well-being, where meaning in life was related to a committed and significant life (Góngora & Castro Solano, 2011).

Procedure

This is a follow-up study of a group of patients attending treatment for severe alcohol dependence, evaluated in four different occasions over 6 years: a baseline evaluation (before treatment), at treatment discharge and at 2 and 4 years after treatment. A group of control subjects were also evaluated in four occasions every two years (with a baseline, and at 2, 4 and 6 years after) in order to obtain an equivalence to patients' group periods of assessment.

Statistical analysis

Continuous demographic variables were evaluated using one-way analysis of variance (ANOVA). When the variances of the dependent variables were not equal across groups, we used the Welch test as a more robust and conservative alternative to the usual *F*-test.

We used 2x4-way ANOVAs repeated measures for avoidant coping, incorporating group (abstainers and relapsers) X time (baseline, at discharge, 2, and 4, years of follow-up). We used 3x4-way ANOVAs repeated measures dependent variables (i.e. anxiety, depression, impulsivity and MiL), incorporating group (abstinents, relapsers and controls) X time (baseline, at discharge, 2 years and 4 years of follow-up). Significant main and interaction effects were further analyzed by post-hoc comparisons with Bonferroni adjusted alpha level. All statistical analyses were performed using the SPSS v.22 package (IBM, 2013). An additional descriptive and ANOVA for repeated measures analysis was carried out for impulsivity subscales, which can be consulted in the supplementary material of this work.

Results

Table 2 and Figure 1 show self-informed measures data of clinical (abstainers and relapsers) and control groups, along the several periods of evaluation.

Avoidant coping during the study

The results of this scale only refer to patients' groups. Abstainers had significantly higher scores compared to relapsers ($F = 166.44$; $p = 0.0001$; *partial eta*$^2 = 0.51$). This study also revealed a significant effect regarding the moment of measuring: at the end of the study (at the 4th year of follow-up), scores were significantly higher for both abstainers and relapsers comparing to the three previous moments of measuring (*Wilk's* $\lambda = 0.80$; $F = 12.46$; $p = 0.001$; *partial eta*$^2 = 0.19$). Particularly, in the group of abstainers, avoidant coping scores were significantly increased at discharge and the fourth year of follow-up, comparing to baseline and the second year of follow-up. For relapsers, significant differences were found between baseline, the fourth year of follow-up and the measurements at discharge, as well as the second year of follow-up (*Wilk's* $\lambda = 0.97$; $F = 1.55$; $p = 0.20$; *partial eta*$^2 = 0.03$).

Table 2. *Psychological evaluation scores.*

Groups	Baseline	At discharge	2 years- follow-up	4 years- follow-up
Avoidant Coping				
Abstainers (n=80)	6.60 ± 1.51	7.06 ± 0.87	6.85 ± 0.91	7.37 ± 0.98
Relapsers (n=79)	5.37 ± 1.64	5.24 ± 1.35	5.18 ± 1.14	5.87 ± 1.12
Hamilton Anxiety Rating Scale				
Abstainers (n=80)	11.31 ± 5.51	10.24 ± 3.30	9.19 ± 1.61	9.90 ± 2.32
Relapsers (n=79)	11.4 ± 5.63	12.68 ± 4.81	10.03 ± 6.85	15.72 ± 5.79
Controls (n=74)	8.51 ± 1.87	8.38 ± 1.88	8.32 ± 1.77	8.05 ± 2.08
Hamilton Depression Rating Scale				
Abstainers (n=80)	10.92 ± 7.33	8.03 ± 3.64	6.11 ± 3.23	5.55 ± 2.82
Relapsers (n=79)	10.57 ± 7.92	9.76 ± 4.60	10.2 ± 3.87	11.3 ± 3.11
Controls (n=74)	5.97 ± 2.04	5.82 ± 2.07	5.89 ± 2.07	5.80 ± 2.06
Barrat Impulsiveness Scale				
Abstainers (n=80)	49.5 ± 14.45	46.3 ± 12.06	42.7 ± 9.96	41.2 ± 8.32
Relapsers (n=79)	57.7 ± 10.27	51.6 ± 9.14	48.4 ± 6.14	49.7 ± 7.48
Controls (n=74)	38.12 ± 11.7	37.2 ± 11.73	37.2 ± 11.4	36.7 ± 11.17
Meaning in Life Questionnaire				
Abstainers (n=80)	38.5 ± 7.73	47 ± 6.52	51.04 ± 5.4	58.4 ± 5.95
Relapsers (n=79)	39.1 ± 7.22	41.7 ± 6.85	41.6 ± 5.23	46.3 ± 6.05
Controls (n=74)	44.3 ± 7.13	42.4 ± 8.00	44.1 ± 8.04	45.3 ± 7.06

Note. Descriptive data (mean ±SD) for self-informed measures at the different moments of evaluations (columns), in each group of study (rows).

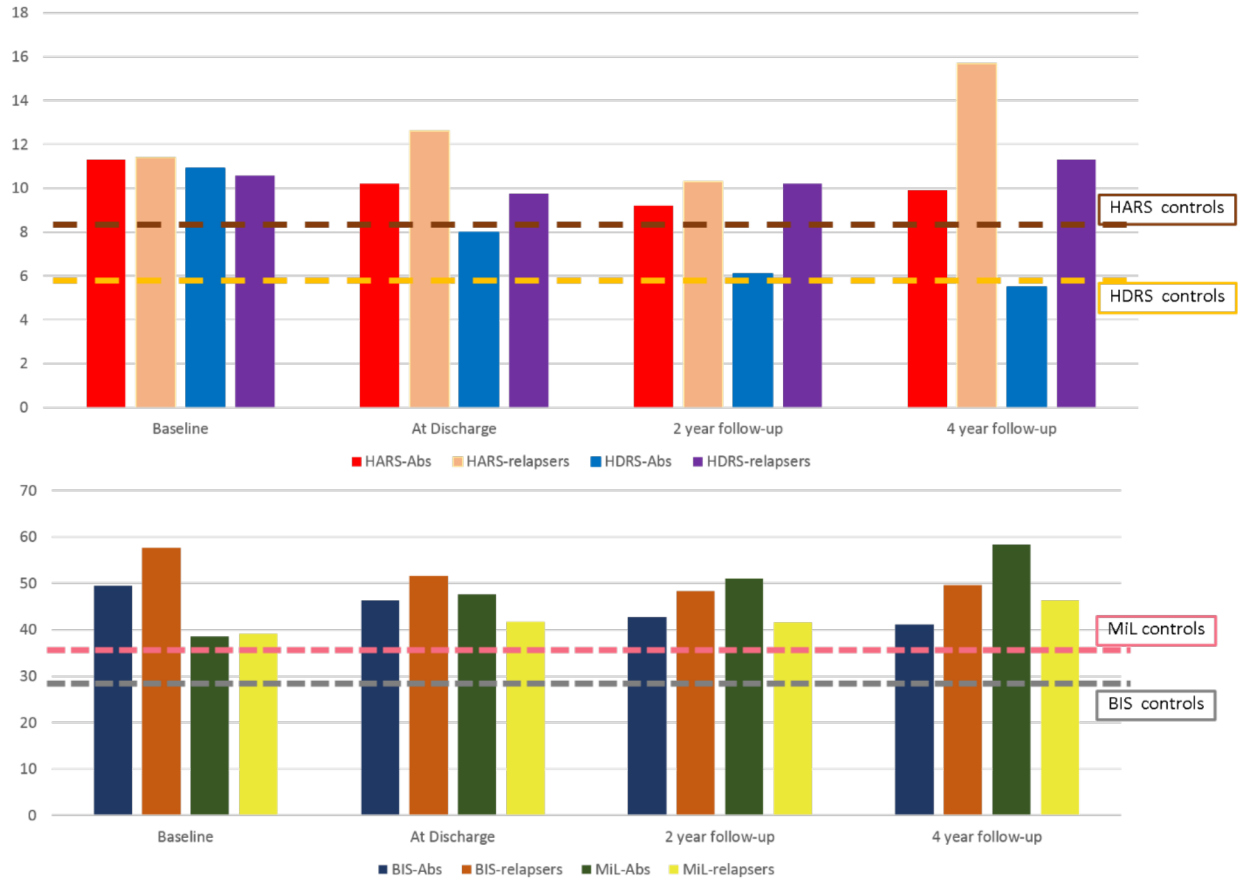

Figure 1. Changes in psychological symptoms.

Note. Mean scores for anxiety (HARS) and depression (HDRS), impulsivity (BIS) and meaning in life (MiL) at several moments of evaluation. Red, blue, dark blue and green columns represent mean scores for abstainers' group (Abs) in HARS, HDRS, BIS and MiL, respectively. Whereas salmon, purple, brown and yellow colors represent relapsers' scores for the same measures. For the sake of brevity, we represented an average value of these measures obtained by control subjects by using discontinuous lines (dark brown, orange, pink and grey for HARS, HDRS, BIS and MiL, respectively).

Recovery of anxiety symptoms

A main significant effect of the group factor was observed ($F = 62{,}17$; $p = 0{,}0001$; *partial eta*$^2 = 0{,}35$); control subjects had lower scores than abstinents and relapsers. This study also found a significant main effect for moment of evaluation, revealing significantly lower scores for the 2nd and 4th year of follow-up comparing to baseline and discharge moments (Wilk's $\lambda = 0{,}72$; $F = 28{,}89$; $p = 0.001$; *partial eta*$^2 = 0.27$). A significant decline in anxiety was observed for the group of abstainers at the 2nd year of follow-up, although no differences were observed at the 4th year. Regarding the relapsers' group, anxiety levels increased at discharge, decreased at the 2nd year of follow-up and then increased again significantly at the 4th year of follow-up. Control subjects showed no significant differences in anxiety scores across the 4 moments of evaluation.

Last, an interaction effect was observed between group and the moment of evaluation regarding anxiety (*Wilk's* $\lambda = 0.65$; $F = 17.97$; $p = 0.0001$; *partial eta*$^2 = 0.19$). Specifically, at baseline, both relapsers and abstainers showed significant higher anxiety levels comparing to control participants. Whereas, at discharge, the group of abstainers showed significantly lower anxiety scores comparing to relapsers, although higher comparing to control subjects. These same results were observed at the 2nd and 4th years of follow-up.

Recovery of depressive symptoms

In a similar way as anxiety symptoms, control group showed significantly lower depression scores, followed by abstainers and relapsers ($F = 43.1$; $p = 0.0001$; *partial eta*$^2 = 0.27$). Diminished depression scores are observed from the baseline assessments to the discharge moment, and they are maintained along the follow-ups (Wilk's $\lambda = 0.90$; $F = 8.01$; $p = 0.001$; *partial eta*$^2 = 0.09$). In the abstainers group, scores reached until the 2nd year of follow-up maintained without significant changes to the 4th year of follow-up, although they were significantly lower compared to baseline and discharge moments. Relapsers had significantly lower

levels of depression at discharge, although they increased after this moment. Control participants maintained similar levels of depression along the study. A significant interaction between group and moment of evaluation was found (*Wilk's* $\lambda = 0.78$; $F = 9.86$; $p = 0.0001$; *partial eta*$^2 = 0.11$), in such a way that ,at the moment of discharge, abstainers showed significantly lower levels of depression comparing to relapsers, although higher than control subjects. At the 2nd and 4th years of follow-up, abstainers reached similar depression scores to control participants and maintained the lower scores comparing to relapsers.

Recovery of impulsivity symptoms

Regarding impulsivity, control subjects had the lowest scores, followed by abstainers and relapsers ($F = 41.1$; $p = 0.0001$; *partial eta*$^2 = 0.26$). The moment of evaluation also influenced the scores (Wilk's $\lambda = 0.59$; $F = 52.87$; $p = 0.001$; *partial eta*$^2 = 0.41$), in such a way that impulsivity levels at discharge and 2 years after treatment were significantly smaller comparing to the baseline evaluation, and remained stable at the 4th year after the treatment. Specifically, abstainers descended significantly in impulsivity levels across all moments of measuring. In a similar manner, relapsers went reducing their impulsivity scores across all moments, with the exception of the 4th year, where impulsivity was higher comparing to the 2nd year of follow-up. With respect to control subjects, they had no changes in impulsivity levels across all 4 moments. Finally, a significant interaction effect was observed between group and moment of evaluation regarding impulsivity (*Wilk's* $\lambda = 0.67$; $F = 16.42$; $p = 0.0001$; *partial eta*$^2 = 0.17$). In this way, relapsers presented significantly higher impulsivity levels compared to abstainers and control subjects, at all moments of evaluation. In the same way, the abstainers showed a higher impulsivity compared to control individuals at all moments of evaluation.

Meaning in Life and recovery

Meaning in Life (MiL) scores for the abstainers were significantly more elevated comparing to the other two groups ($F = 39.32$; $p = 0.0001$; *partial eta*$^2 = 0.25$). A significant main effect of moment of evaluation was found, where MiL scores were significantly higher at the follow-up moments during the 2nd and 4th years (*Wilk's* $\lambda = 0.50$; $F = 74.14$; $p = 0.001$; *partial eta*$^2 = 0.49$). On one hand, abstainers had significantly increasing levels of MiL during the 2nd and 4th year of follow-up comparing to previous moments of evaluation. Relapsers, on the other hand, showed significant increases in MiL across all moments, with the exception of discharge and the 2nd year after treatment moments, where they remained stable. Last, MiL levels for control subjects showed no differences across the moments of evaluation, with the exception of the difference found between the 2nd and 4th evaluation, showing an increase in the latter.

Additionally, an interaction effect was observed between group and moment of evaluation regarding MiL scores (*Wilk's* $\lambda = 0.55$; $F = 25.99$; $p = 0.0001$; partial eta$^2 = 0.25$). Post hoc comparisons show that, at baseline, both abstainers and relapsers had significantly lower MiL levels comparing to control subjects. Whereas, at discharge, abstainers had significantly higher MiL scores comparing to relapsers and to control participants. Similar results were maintained at the 2nd year of follow-up and the 4th year.

In summary, abstainers showed superior levels of MiL after treatment comparing to the other two groups of study and they went increasing progressively across the follow-up moments.

Discussion

Data coming from this study can partially confirm the initial hypothesis. On one side, the group with relapses had a slower recovery comparing to abstinent patients, in all the psychological dimensions assessed. Nonetheless, and contrary to our hypothesis, the abstinent patients reached similar scores to control participants in the depression scale, at 2 years of follow-up. They also showed higher meaning in life scores comparing to controls, from the point of treatment discharge onwards. On the other side, with respect to the stages of psychological recovery sequence, while analyzing the situation for abstainers, we observed that the avoidance behavior was maintained along the treatment and follow-ups; that dimensions depending less on personality such as depressive symptoms remained stable and were even similar to control subjects 2 years after the treatment; whereas variables more related to personality such as anxiety and impulsivity continued to diminish during the follow-up period, although with higher scores than control individuals. In this group meaning in life was increased after finishing the treatment, with superior scores even to control participants.

Why relapses suppose a slowing-down of the recovery process?

From a neurobiological point of view, relapses or the interruption of abstinence suppose a re-activation of neurotoxic damage processes (Crews, 2008), stress activation (Beracochea, Mons & David, 2019), neuroinflammatory processes (Crews et al., 2005; Venner et al., 2006) and neurogenesis interruption (Crews & Nixon, 2009), giving rise to a worsening of anxiety symptoms (Brown et al., 1991; Rubio et al., 2017) and depression (Kelly et al., 2010a).

Relapses usually suppose an impact on the psychological state of the patient (Marlatt & Gordon, 1985), that could prolong in a significant manner through time. They regularly lead to a fast appearance of negative emotions, such as guilt and shame, which increase the sense of inefficacy and facilitate the relapse process, with the

consequent exacerbation of anxiety and depression symptoms (de Hooge, Zeelenberg & Breugelmans, 2010).

Patients did not reach similar scores to controls in the assessed psychological dimensions

As it was hypothesized, patients from both groups had higher anxiety and impulsivity levels compared to control participants, along all the assessments. Our findings are in line with those published by Kelly et al. (2018), although the evaluated dimensions were not entirely the same. In their study, patients in recovery took an average of 10 years to achieve similar life quality levels to a control sample. Since life quality is not the same as anxiety or impulsivity, we could think that these higher scores have several origins: it has been shown that high scores in anxiety or impulsivity are a risk factor for substance dependence development in adolescence (Chow et al., 2018; Dyer, Heron, Hickman & Munafó, 2019; Stautz & Cooper, 2013), although they may also result from neurotoxic effects of alcohol (Beracochea et al., 2019; Mons & Beracochea, 2016). Hence, the differences in anxiety and impulsivity with the control group might be due to a mix of personality factors, previous to alcohol dependence development and they could also rise from alcohol damaging effects.

Something different happened with depression and meaning in life scores for the abstainers. The recovery of these variables seems more related to abstinence duration and attendance to mutual-help groups (Kelly et al., 2010a). So, the score normalization in depression or MiL for abstainers might be explained by their greater attendance to mutual help groups (Kelly et al., 2012; Kelly et al., 2010a).

The fact that several years of abstinence were needed in order to achieve depression normalization levels or meaning in life boost, agrees with the opinions that patients attending mutual-help groups have (FACOMA, 2016). Other models exploring the recovery of bio-psycho-social dimensions also agree with the need for several years to pass in order to achieve personality changes that would enable the adaptation to a new lifestyle (Chapman, 1991; Freyer-Rose, 1991; Gorski, 1990)

Can a sequence of psychological recovery be established in severe alcohol dependence?

If we think of the abstainers group as a recovery model for severe dependence, where the impact of relapse has been eliminated, our results would allow to hypothesize upon a sequence of some psychological variables represented in Figure 2. Behavioral changes (avoidant coping) initiated in a significant manner at the first moments of the treatment, are those that would allow for a secure environment, indispensable in order to avoid relapses and to keep introducing new healthy habits.

Conceivably, self-efficacy perception in relapse avoidance might facilitate the managing of emotions such as anxiety, depression and control of impulsive behavior. Since many of these dimensions are closely related to personality factors and with a long list of learned habits, it would be plausible to presume that it would take months or even years for patients to improve their scores in these dimensions. Over time, individuals would become capable of changing their motivation for abstinence maintenance, so that external motivations (worrying for

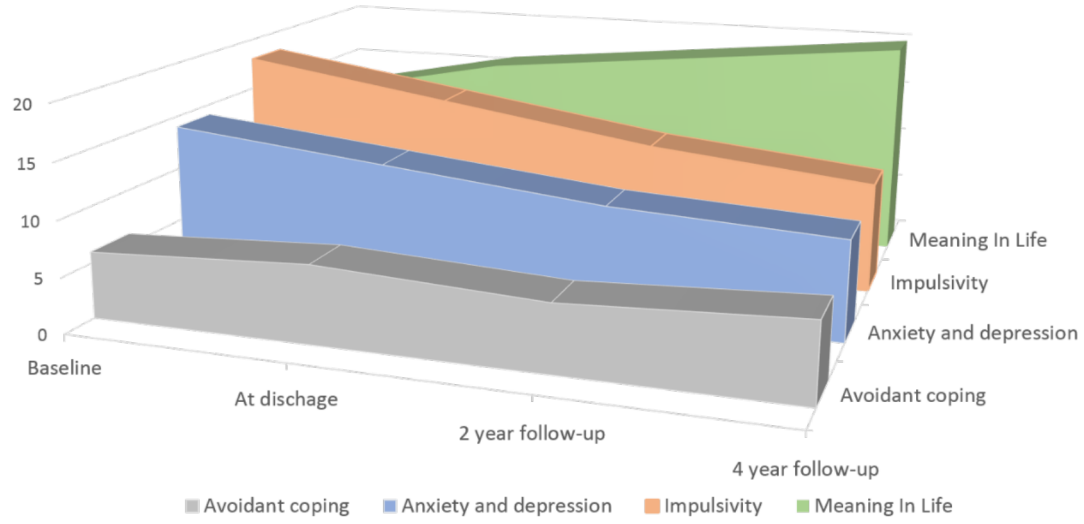

Figure 2. Psychological recovery stages along the study: behavioral-emotional-meaning in life.

Note. A visual representation of psychological recovery sequence across each moment of evaluation (X axis): baseline, at discharge of treatment, followed by 2 and 4 years after. Y axis would represent theoretical changes across these periods in several psychological dimensions (Z axis) (Meaning in Life, impulsivity, anxiety and depression and avoidant coping).

alcohol consumption-related consequences in physical and psychological health, as well as work and family areas) are replaced by internal ones (coherence, meaning in life, sense of belonging in the mutual-help groups). This hypothesis is in line with motivational approaches based on behavioral change maintenance (Kwasnicka, Dombrovski, White & Sniehotta, 2016).

Empirically, there has now been rigorous scientific studies conducted on how exactly mutual-help groups, like AA or FACOMA, confer recovery benefits. These studies suggest that the main ways that AA aids remission and recovery is through facilitating changes in the social networks of attendees and by boosting abstinence self-efficacy, coping, and by maintaining abstinence motivation (Kelly et al., 2010a; Kelly et al., 2010b). Evidence suggests too that these broad benefits may depend on severity of dependence (Kelly et al., 2012) and also gender (Kelly & Hoeppner, 2013) whereby for more severely addicted individuals, in addition to facilitating important social network changes, AA may also aid recovery by reducing negative affect and increasing spiritual practices. It is also possible that MiL could be a determinant variable, even from the first moments of treatment, by favoring the abstinence through an increase of avoidance strategies and lowering of the depression levels

Regarding the limitations of this study, it is possible that our results would not be applicable to a mild form of dependence, nor to individuals that do not seek for treatment, since this study is carried out in patients with severe alcohol dependence seeking for treatment. Another limitation could be represented by the fact that an important percentage of patients attended mutual help therapy groups. This might give rise to differences between subjects in several psychological dimensions and aspects of recovery. In fact, we already addressed this matter (Rubio et al., 2017) and found that patients that attended FACOMA self-help groups, besides the psychotherapeutic treatment, improved in affective symptoms and meaning in life, accumulating more months of abstinence.

All the patients had family support, being one of the requirements to enter the study, therefore we ignore if the course of the studied variables would have been the same with other conditions of support. Abstinence was recorded based on self-informed reports, therefore we could not assure a total lack of consumption that could have been hidden by patients; although it is also true that self-reports usually have a good correlation with real amounts of consumption. Given the considerable number of patients that were not able to complete these measures, we could hypothesize that the observed changes in this work would correspond to the group with better outcomes. Although this is a possibility, at least we dispose from a sequence for recovery in a group of patients, though less vulnerable to relapse.

Last, an additional limitation could be constituted by the fact that we did not dispose from civil status and employment situation in control subjects. While this kind of sociodemographic information could be of use regarding its possible influence on several psychological variables, they were not the main concern of the aims of this study and further research on this topic should account for these variables.

Implications of this study: Given that the psychological dimensions of impulsivity and anxiety studied in this work were not stabilized until 2+2 years of abstinence, we think is important to emphasize the need for follow-ups by primary care teams, in order to impulse the revision of patients in recovery.

We think that it would be important to recommend or insist in the advisability to attend mutual-help groups as a strategy of usefulness to improve emotional states related to anxiety, depression and impulsivity, and what is more important, to breed or boost values such as meaning in life (Kelly & Yeterian, 2013; Rubio et al., 2018). From our standpoint, recovery in severe patients would begin with a behavioral component (changes in lifestyle), followed by an emotional one (anxiety and depression) and a final step based on purpose in life and spirituality.

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Conflict of interests

None of the authors had conflicts of interest with public or private entities.

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Cannabinoid receptor type 2 gene is associated with comorbidity of schizophrenia and cannabis dependence and fatty acid amide hydrolase gene is associated with cannabis dependence in the Spanish population

El gen del receptor cannabinoide tipo 2 se asocia con la comorbilidad entre esquizofrenia y dependencia de cannabis y el gen de la enzima amidohidrolasa de ácidos grasos se asocia con la dependencia de cannabis en población española

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Abstract

The endocannabinoid system has been associated with various psychiatric disorders, such as schizophrenia or addictive disorders. Recent studies have found that some polymorphisms in the cannabinoid receptor type 2 (*CNR2*), cannabinoid receptor type 1 *(CNR1*) and fatty acid amide hydrolase (*FAAH*) genes could play an important role as risk factors in the etiology of these diseases. We analysed different cannabinoid gene polimorphisms from non-substance using patients diagnosed with schizophrenia (n = 379), schizophrenic patients with cannabis use disorders (n = 124), cannabis users who did not have psychoses (n = 71), and 316 controls from various Spanish hospitals and health centres. We found a statistical association between polymorphisms rs35761398 and rs12744386 in the *CNR2* gene and comorbidity of schizophrenia and cannabis dependence, as well as an association between loss of heterozygosity (overdominance) for polymorphism rs324420 in the *FAAH* gene and cannabis dependence in a Spanish population sample. The rs35761398 and rs12744386 polymorphisms in the *CNR2* gene are genetic risk factors for schizophrenia in cannabis-dependent subjects. Loss of heterozygosity for polymorphism rs324420 in the *FAAH* gene is a genetic risk factor for cannabis dependence in this population.

Keywords: Cannabis use disorder; schizophrenia; polymorphisms; cannabinoid receptor type 2 gene; cannabinoid receptor type 1 gene; fatty acid amide hydrolase gene.

Resumen

El sistema cannabinoide se ha asociado con varios trastornos psiquiátricos como la esquizofrenia y las adicciones. Diversos estudios han observado que algunos polimorfismos del receptor cannabinoide tipo 2 (*CNR2*), del receptor cannabinoide tipo 1 *(CNR1*) y del gen de la enzima amido hidrolasa de ácidos grasos (*FAAH*) pueden ser factores de riesgo de estos trastornos. Hemos analizado diversos polimorfismos del sistema cannabinoide en pacientes diagnosticados de esquizofrenia sin trastorno por uso de sustancias (n = 379), esquizofrenia con trastorno por uso de cannabis (n = 124), dependientes de cannabis sin psicosis asociada (n = 71) y un grupo de control (316) procedentes de diversos hospitales y centros de asistencia sanitaria españoles. Hemos encontrado una asociación entre los polimorfismos rs35761398 y rs12744386 del *CNR2* con la presencia de esquizofrenia y trastorno por uso de cannabis comórbido y una pérdida de heterocigosidad en el polimorfismo rs324420 del gen *FAAH* con la dependencia de cannabis en población española. Los polimorfismos rs35761398 y rs12744386 en *CNR2* son factores de riesgo para esquizofrenia en sujetos dependientes de cannabis. La pérdida de heterocigosidad en el polimorfismo rs324420 en el gen *FAAH* es un factor de riesgo para la dependencia de cannabis.

Palabras clave: Trastorno por uso de cannabis; esquizofrenia; polimorfismos; gen del receptor cannabinoide tipo 2; gen del receptor cannabinoide tipo 1; gen de la enzima amido hidrolasa de ácidos grasos.

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Schizophrenia is a severe mental disorder with a worldwide prevalence of 0.5–1.0% and it has an enormous social and economic impact (Andreasen, 1995; Dong et al., 2019). Different epidemiologic studies have suggested that cannabis could be a risk factor for the development of schizophrenia (Marconi, Di Forti, Lewis, Murray & Vassos, 2016). Moreover, the well-known psychotropic effects of cannabinoids and the distribution of cannabinoid receptors in the brain suggest that the endocannabinoid system may be involved in schizophrenia (Fakhoury, 2017; Minichino et al., 2019) and addictive disorders (Manzanares et al., 2018; Van Hell et al., 2012). A study identified an association between early cannabis use, lower cortical thickness and high polygenic risk for psychosis in adolescents. This finding implicates processes underlying cortical maturation in mediating the link between cannabis use and proneness to schizophrenia (French et al., 2015), indicating that cannabis could potentially play a role in the development of psychosis by altering neural circuits in genetically vulnerable subjects (Aas et al., 2017; Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2019; French et al., 2015; García-Álvarez, Gomar, García-Portilla & Bobes, 2019; Parkar et al., 2011).

CNR1, CNR2 and *FAAH* are the genes that encode some of the proteins associated with the endocannabinoid system. CB1 receptors are mainly located in the central nervous system and are abundant in the basal ganglia, hippocampus, cerebellum and cortical areas (Herkenham et al., 1991). CB2 receptors were initially found in the immune system (Galiègue et al., 1995), however, their presence has also been demonstrated in neurons and glial cells of multiple brain areas (cerebral cortex, hippocampus, amygdala, striatum, thalamus, cerebellum...) (Gong et al., 2006; Onaivi et al., 2006). Fatty Acid Amide Hydrolase (*FAAH*) is the enzyme responsible for the hydrolysis of anandamide, an endogenous ligand of this system (Deutsch, Ueda & Yamamoto, 2002).

Some studies have suggested an association between the *CNR1* gene (that encodes the CB1 receptor) and incidence of schizophrenia (Chavarría-Siles et al., 2008; Leroy et al., 2001; Martínez-Gras et al., 2006; Ujike et al., 2002) and substance use disorders, such as cannabis use disorder (Gerra et al., 2018; Hartman et al., 2009). However, evidence remains heterogeneous and controversial for both outcomes. Gouvêa et al. (2017) systematically analysed all the existing trials on *CNR1* gene variants and schizophrenia and emphasized the high heterogeneity of the results. A polymorphism consisting of nine alleles containing (AAT) 7-15 repeat sequences has been used in association studies on the *CNR1* gene and mental illness and drug abuse among different populations, with contradictory results (Ballon et al., 2006; Chavarría-Siles et al., 2008; Comings et al., 1997; Martínez-Gras et al., 2006; Tsai, Wang & Hong, 2000; Ujike et al., 2002).

In recent years, the CB2 receptor has gained attention due to its function as a modulator of neuroinflammation (Javed, Azimullah, Haque & Ojha, 2016; Kong, Li, Tuma & Ganea, 2014; Malfitano, Basu, Maresz, Bifulco & Dittel, 2014), memory processes (García-Gutiérrez et al., 2013), and reward processing, and for its role in drug addiction, and psychosis-(Onaivi, Ishiguro, Gu & Liu, 2012; Xi et al., 2011). The frequency of the CC allele of rs35761398 (R63 variant), the C allele of rs12744386, the haplotype of the CC allele of rs35761398 and the C allele of rs12744386 (CC/C) was found to be significantly increased among a Japanese population sample with schizophrenia compared with control subjects (Ishiguro et al., 2010). A significantly lower response to CB2 ligands in cultured cells transfected with the CC allele of rs35761398 compared with those transfected with the TT allele was observed, and significantly lower CB2 receptor mRNA and protein levels were found in the human brain with the C/C and C/T genotypes of rs12744386 compared with T/T genotypes (Ishiguro et al., 2010).

On the other hand, a common Single Nucleotide Polymorphism (SNP) rs324420 (C385A) in the human *FAAH* gene has been related to drug abuse, for instance, cannabis (Tyndale, Payne, Gerber & Sipe, 2007), cocaine (Patel et al., 2018) and methamphetamine (Zhang, Liu, Deng, Ma & Liu, 2020).

The aim of this study was to investigate genetic association between the *CNR1* gene $(AAT)_{7\text{-}15}$ repeat polymorphism, the *FAAH* gene SNP rs324420, the *CNR2* gene rs35761398 and rs12744386 polymorphisms, and schizophrenia and cannabis dependence in a sample of Spanish subjects.

Methods

Participants

In this study, 379 schizophrenic patients, 124 schizophrenic and cannabis use disorder (CUD) patients (Dual group), 71 CUD subjects without psychoses (cannabis group) and 316 controls who were not related to each other were analysed. Diagnoses were made according to DSM-IV-TR by clinical interview. The patients (outpatients and inpatients) were recruited from different hospitals in the Community of Madrid and Castilla-La Mancha. Cannabis users without psychosis were recruited from addiction centres or user associations in the Community of Madrid. Inclusion criteria were: being over 18 years of age, being Spanish and Caucasian, and signing the informed consent. Exclusion criteria were: being themselves or having first-degree relatives of another ethnic origin, from countries other than Spain, presence of mental disorders other than those being studied, dependence on drugs other than cannabis or tobacco, presenting comorbid organic brain pathology or other serious medical conditions and refusing to participate or failing to sign the informed consent.

Patients with a diagnosis of dependence on drugs other than cannabis or tobacco were excluded, although subjects were included if they used drugs but were not dependent.

The control population consisted of 316 individual volunteers who were not related to each other and were recruited from the Spanish population. They were health and administrative personnel from the health centres attended by the patients and companions of the patients. A clinical interview was carried out on all of them to exclude other psychiatric pathologies.

Assessment instruments

Sociodemographic variables, personal and family history and data related to substance use were obtained through a clinical interview. In addition, in that first interview psychotic symptomatology was assessed using the Positive and Negative Syndrome Scale (PANSS).

PANSS Scale (Positive and Negative Syndrome Scale). The Positive and Negative Syndrome Scale, developed by Kay, Fiszbein and Opler (1987), the Spanish version of which was created by Peralta and Cuesta (1994), is one of the most frequently used tools for assessing symptoms in schizophrenic patients. It is a clinician-administered scale that is completed based on a semi-structured interview, which takes approximately 45 minutes. In its original version, the PANSS consists of 30 items grouped into three factors: positive syndrome (which includes 7 items), negative syndrome (which also includes 7 items) and general psychopathology (which includes 16 items). In this study, in addition to using the PANSS total score, we also used the three subscales (positive, negative and general psychopathology).

Study procedure

Inpatients and outpatients treated at different mental health centres (University Hospital Fundación Alcorcón (Madrid), Ramón y Cajal Hospital (Madrid), Virgen de la Luz Hospital (Cuenca), University Hospital of Guadalajara, Nuestra Señora de La Paz Clinic (Madrid)), who met the inclusion and exclusion criteria and were willing to participate in our study, were prospectively recruited and signed an informed consent. Cannabis dependent subjects were recruited from different Drug Treatment Centres in the Community of Madrid (Majadahonda, Alcorcón, Arganzuela, Vallecas, Latina).

A total of 27 subjects were excluded either because they refused to participate in the study or to sign the informed consent.

DNA extraction and genotyping

DNA was obtained from leukocytes present in peripheral blood samples anticoagulated with EDTA, using the Sambrook Method and the DNeasy Blood & Tissue kit (Qiagen).

After extraction of DNA from peripheral blood, analysis of the different polymorphisms was carried out using PCR-based methods. The genotyping of the rs324420 polymorphism in the *FAAH* gene was performed using the SSCP (Single Strand Conformation Polymorphism) method (GeneGel Excel 12.5/24 Kit, GE Healthcare) (See Table 1 for primer sequences). The genotyping of the $(AAT)_{7\text{-}15}$ 3'UTR polymorphism was performed using a capillary electrophoresis fragment analysis technique (ABI Prism 310 Genetic Analyzer - Applied Biosystems) (See Table 1 for primer sequences). The standard GeneScan-500 LIZ, was used as a size marker (Applied Biosystems). Analysis of the results was carried out using GeneMapper 4.0 software. The genotyping of the rs35761398 and rs12744386 polymorphisms in the *CNR2* gene was performed using allelic discrimination with TaqMan probes in an iCycler Thermal Cycler (Bio-Rad) (see Table 1 for primer and TaqMan probe sequences).

Ethical concerns

Participation in this study was voluntary and all participants gave their written consent to taking part in the project. The study was approved by the Clinical Research Ethics Committee of the University Hospital Fundación Alcorcón (Madrid).

Statistical analyses

Genotype distribution was compared to the predictable value from Hardy-Weinberg equilibrium. The control and case groups were at Hardy-Weinberg equilibrium in terms of allele and genotype frequencies for the polymorphisms studied (Table 2).

Table 1. *Primers and techniques used for sample analysis.*

Gene	Polymorphism	Primer 5` 3`	Techniques
CNR1	(AAT)n	A: 5' GCTGCTTCTGTTAACCCTGC 3' B: 5' ATTCCCACCTATGAGTGAGAAC 3'	Capillary electrophoresis fragment analysis (ABI Prism 310 Genetic Analyzer - Applied Biosystems)
CNR2	rs35761398	A: 5' AAGACCACACTGGCCAGGAAG 3' B: 5' CACTCTTCTGGGCCTGCTAAG 3'	Allelic discrimination with TaqMan probes in an iCycler Thermal Cycler (Bio-Rad)
			SSCP
FAAH	rs324420	A: 5' GGCCAGCCTCCTTTTATCTTATG 3' B: 5'GACGATGGAGGCCTGGCGA 3'	SSCP (Kit GeneGel Excel 12.5 / 24, GE Healthcare)

Note. Single Strand Conformation Polymorphism (SSCP).

Table 2. *Hardy-Weinberg equilibrium*.

GENE	Polymorphism	Gender	χ^2	p-value
CNR1	(AAT)n	Women	.5389	.7638
		Men	3.2414	.1978
CNR2	rs35761398	Women	.0467	.9769
		Men	.1874	.9106
FAAH	rs324420	Women	1.5451	.4183
		Men	.1229	.9404

Note. Two degree of freedom except rs6323 and rs1799836 in man (hemizygosity), calculated for 1 degree of freedom.

The nine alleles containing $(AAT)_{7\text{-}15}$ repeat sequences were distributed in accordance with the article by Comings et al. (1997) in a group of short alleles with less than 11 AAT triplet repeats (genotype <5) and another group of long alleles ≥ 11 repeats (genotype ≥ 5). Thus, the patients and controls were subdivided into three groups according to their genotype: individuals with <5/<5, ≥ 5/≥ 5, and <5/≥ 5. These data were used as qualitative variables. The hypothesis of an association between genotypes and groups was tested using Pearson's chi-squared test and where cell sizes were equal to or smaller than 5, Fisher´s exact test was used. Bonferroni correction was applied.

A two-sided P-value test was used and P-values of < 0.05 were considered statistically significant. The analysis was carried out using OpenEpi (Open Source Epidemiologic Statistics for Public Health) online software.

Results

Sociodemographic and clinical data are summarized in tables 3 and 4. No statistically significant differences were observed in any of the polymorphic variants studied in the population analysis based on variables such as sex or age at initiation of cannabis use or psychotic symptoms.

CNR1

Regarding the $(AAT)_{7\text{-}15}$ 3'UTR polymorphism in the *CNR1* gene, we did not find statistically significant differences between the schizophrenic, dual and cannabis groups and the control population when allele and genotype frequencies were analysed (Table 5).

FAAH

Regarding the rs324420 polymorphism in the *FAAH* gene, non-statistically significant differences were found between the control population and both subjects with schizophrenia and comorbid schizophrenia and cannabis dependence when comparing genotype and allele frequencies (Table 5). Assuming an overdominance model, statistically significant differences were found between the cannabis dependent subjects and the control population (Table 6).

CNR2

Regarding the analysis of the rs35761398 polymorphism in the *CNR2* gene, when we compared the dual group with the schizophrenia and control groups, statistically significant deviations in genotype frequencies were found (Table 7). Assuming a dominant model for the less frequent allele (TT), differences in the presence of TT were statistically significant when we compared the dual group to the controls. In both cannabis users and controls, no statistically significant differences were found in genotype and allele frequencies between the rs35761398 and rs12744386 polymorphisms. There was an interaction between the rs35761398 polymorphism in the *CNR2* gene and the rs324420 polymorphism in the *FAAH* gene (Table 8).

Literature on the rs35761398 polymorphism places its origin in linkage disequilibrium within this gene. The functional linking implication of these polymorphisms

Table 3. *General description of the sample*.

	Controls N=316	Schizophrenia N=379	Schizophrenia + cannabis dependence N=124	Cannabis dependence N=71
Male (%)	42.72	60.16	87.90	70.42
Mean age at testing (p25 -p75)	31 (28 - 37)	37 (31 - 50)	29 (26 - 36)	28 (25 - 34)
Mean age at diagnosis (p25-p75)		25 (20 - 32)	25 (20 - 28)	23 (19 - 30)
Mean age of first cannabis use (p25-p75)			16 (15 - 18)	16 (15 - 17)
PANSS score: mean (95% CI)				
Positive Scale		22.6 (20.7-24.5)	21.5 (18.8-24.1)	
Negative Scale		23.8 (22.0-25.6)	20.1 (17.0-23.2)	
Global Scale		36.3 (34.2-38.3)	33.5 (31.0-35.9)	

Note. PANSS: Positive and Negative Syndrome Scale. P=percentile. CI=confidence interval. Male predominance in schizophrenia+cannabis dependence vs schizophrenia (chi^2 = 32,53, p < 0.001, OR: 4,81, IC: 95%: 2,70-8,58).

Table 4. *Percentages of drug use among groups.*

	Schizophrenia and Cannabis dependence N=124	Cannabis dependence N=71	Schizophrenia N=379	Controls N=316
Cannabis (cigarette/day): mean; median	7.5; 6	6; 6	0	0
Tobacco (%)	92.1	64.3	48.4	36.8
Alcohol (%)	48.0	21.4	-	-
Cocaine (%)	32.7	10.7	-	-
Opioids (%)	9.3	0.0	-	-
Amphetamines (%)	1.3	0.0	-	-
Others (%)	12.0	0.0	-	-

Note. Percentage of use of alcohol, cocaine, opioids, amphetamines or other drugs without dependence criteria. In the subgroup of schizophrenia + cannabis dependence, 52 % of the subjects only used tobacco and cannabis.

Table 5. *Distribution of genotype and allele frequencies among subgroups.*

Polymorphism (gene)	Genotype/Allele		Controls N (%)	Schizophrenia N (%)	Schizophrenia + cannabis dependence N (%)	Cannabis dependence N (%)
(AAT)n (CNR1)	Genotype	LL	171 (54.11)	190 (50.13)	58 (46.77)	33 (57.89)
		LS	116 (36.71)	145 (38.26)	52 (41.94)	20 (35.09)
		SS	29 (9.18)	44 (11.61)	14 (11.29)	4 (7.02)
	Allele	L	458 (72.47)	525 (69.26)	168 (67.74)	86 (75.44)
		S	174 (27.53)	233 (30.74)	80 (32.26)	28 (24.56)
rs35761398 (CNR2)	Genotype	CC/CC	101 (31.96)	116 (30.61)	24 (19.35)	21 (29.58)
		CC/TT	152 (48.10)	181 (47.76)	70 (56.45)	34 (47.89)
		TT/TT	63 (19.94)	82 (21.64)	30 (24.19)	16 (22.54)
	Allele	CC	354 (56.01)	413 (54.49)	118 (47.58)	76 (53.52)
		TT	278 (43.99)	345 (45.51)	130 (52.42)	66 (46.48)
rs324420 (FAAH)	Genotype	CC	202 (63.92)	254 (67.02)	90 (72.58)	53 (75.71)
		CA	104 (32.91)	107 (28.23)	31 (25.00)	11 (15.71)
		AA	10 (3.16)	18 (4.75)	3 (2.42)	6 (8.57)
	Allele	C	508 (80.38)	615 (81.13)	211 (85.08)	117 (83.57)
		A	124 (19.62)	143 (18.87)	37 (14.92)	23 (16.43)

Note. L=long allele. S=short allele.

Table 6. *Association results for frequency contrast between cannabis dependent group and controls/schizophrenia + cannabis dependence groups.*

		Polymorphism	Model-Adjustment procedure	χ^2	D.F.	p-value	ODDS-R (95% IC)
Cannabis dependent	Schizophrenia + cannabis dependence	rs35761398 (CNR2)	Codominant	2.0365	2	.3612	
			Alelles	.9904	1	.3196	1.23 [.82; 1.86]
			Dominant	2.0075	1	.1565	1.63 [.83; 3.23]
		rs324420 (FAAH)	Codominant	5.4918	2	.0642	
			Alelles	.1559	1	.6930	.89 [.51; 1.57]
			Heterocygosis	2.2743	1	.1315	.56 [.26; 1.20]
	Controls	(AAT)n (CNR1)	Codominant	.3618	2	.8345	
			Alelles	.3177	1	.5730	.88 [.56; 1.38]
		rs35761398 (CNR2)	Codominant	.4757	2	.7883	
			Alelles	.4793	1	.4887	1.14 [.79; 1.64]
		rs324420 (FAAH)	Codominant	1.9360	2	.0042	2.74 [1.45; 5.31]
			Alelles	.7574	1	.3842	.81 [.49; 1.31]
			Heterocygosis	8.1024	1	.0044	2.63 [1.33; 5.22]

Table 7. *Association results for frequency contrast in rs35761398 between dual group and controls/schizophrenia groups.*

Gene	Polymorphism	Model	Groups		χ^2	P value.	ODDS-R (95% IC)
CNR2	rs35761398	Dominant (CC/TT+TT/TT)	Dual	Controls	6.9595	.0083	1.96 [1.18; 3.24]
				Schizophrenia	5.8892	.0152	1.84 [1.12; 3.02]

Table 8. *Association analysis between CNR2 and FAAH genes.*

Genotype rs35761398 – rs324420	Controls (a) N (%)	Schizophrenia + Cannabis dependence (b) N (%)	Ratio (%a /% b)	χ^2	p- value	ODDS-R (95% CI)
CC/CC – CC	51 (16.14)	16 (12.90)	.7995	.7224	.3953	.77 [.42; 1.41]
CC/CC – A carrier	50 (15.82)	8 (6.45)	.4077	6.8337	.0089 (1)	.37 [.17; .80]
TT carrier – CC	151 (47.78)	74 (59.68)	1.2489	5.0407	.0248	1.62 [1.06; 2.46]
TT carrier – A carrier	64 (20.25)	26 (20.97)	1.0353	.0279	.8672	1.04 [.63; 1.74]
				9,031	.0289 (*)	

Note. (1) Bonferroni correction implies that significant values are those p-values below 0.0125. (*) X^2 = 9,031; GL= 3; p = 0,0289.

in receptor action and the descriptions of infrequent haplotypes in other populations was the reason for genotyping this second polymorphism in the *CNR2* gene, in order to determine whether those haplotypes were present in the sample included in this study. They were genotyped in both the control group and the dual diagnosed patients. The haplotype linkage between the rs12744386 and rs35761398 polymorphisms in the population studied was 100%, with the following haplotypes found to be present: C - CC y T - TT. Alternative haplotypes, that is, T - CC and C - TT, were not found in the population included in this study.

Discussion

Different epidemiological studies have suggested that cannabis use could be a risk factor for the development of schizophrenia (Marconi et al., 2016). However, only a small proportion of cannabis users develop psychosis, which can be partially explained by genetic factors. Converging evidence from animal and human studies suggests that the endocannabinoid system (ECS) is involved in the pathophysiology of psychosis (Fakhoury, 2017; Minichino et al., 2019; Rodriguez-Muñoz, Sánchez-Blázquez, Callado, Meana & Garzón-Niño, 2017). Thus, logical candidate genes that could influence the likelihood of developing psychosis include *CNR1*, *CNR2*, and *FAAH*.

CNR1

We found no evidence of association between the *CNR1* microsatellite and schizophrenia, which is consistent with findings in other studies (Ballon et al., 2006; Dawson, 1995; Seifert, Ossege, Emrich, Schneider & Stuhrmann, 2007; Tsai et al., 2000). An association has been found between the hebephrenic subtype of schizophrenia and the AAT-repeat polymorphism in a Japanese population and in a family-based association study on a Costa Rican population (Chavarría-Siles et al., 2008; Ujike et al., 2002). Our sample of schizophrenic subjects mainly included paranoid-type patients (data not shown), as hebephrenic-type schizophrenia is very uncommon in the Spanish population. The Ujike and Chavarría-Siles studies did not find significant differences in the frequency of genotype or alleles between subjects with paranoid-type schizophrenia and controls.

While no association has been found here between schizophrenia and other different *CNR1* polymorphisms (Leroy et al., 2001; Zammit et al., 2007), another Spanish group (Martínez-Gras et al., 2006) did find significant differences for this polymorphism between 113 patients and 111 healthy controls. Allele 4 was more frequent in controls, suggesting a protective effect against schizophrenia development. The sample was more heterogeneous, including comorbid substance abuse in the schizophrenic group, which could explain the discrepancies with our findings. On the other hand, the frequency of the (AAT)12 repeat allele was increased in schizophrenic cocaine dependent subjects in an African-Caribbean population (Ballon et al., 2006).

Although we did not find an association between this polymorphism and schizophrenia, many other data suggest that the CB1 receptors could play a key role in its pathogenesis, or it could be linked with some of the phenotypes related to this disease. In this regard, an association has been described between some of the *CNR1* gene polymorphisms and the psychomimetic effects of cannabis in a healthy population (Krebs, Morvan, Jay, Gaillard & Kebir, 2014), the cognitive function of psychotic first-episodes (Rojnic et al., 2019) and the pharmacogenetic response in psychosis (Hamdani et al., 2008). In addition, there have been changes described in *CNR1* gene expression (Tao et al., 2020) and in the methylation of the DNA of the *CRN1* gene in schizophrenia-(D'Addario et al., 2017),

as well as reduced availability of CB1 receptors in different brain areas in psychotic first-episodes (Borgan et al., 2019).

Comings et al. (1997) found that this polymorphism was significantly associated with a number of different types of drug dependence and intravenous drug use. In accordance with our findings, other authors did not find an association between the AAT polymorphism and substance abuse (Covault, Gelernter & Kranzler, 2001; Heller, Schneider, Seifert, Cimander & Stuhrmann, 2001; Li et al., 2000). Comparison of allele distributions among different ethnic groups showed marked genetic variation among populations (Comings et al., 1997; Li et al., 2000; Ujike et al., 2002). It is important to note that, in our sample, all patients were Caucasian.

FAAH

When comparing schizophrenic patients with or without cannabis use disorder to controls, no significant differences were found with regard to allele frequencies or genotype distribution of the *FAAH* gene. This is consistent with the findings of Morita et al. (2005) in relation to a Japanese population, and the recently published results of Hindocha et al. (2020), which also failed to find a significant association between the rs324420 genotype and psychotic experiences in cannabis users. Bioque et al. (2019) analysed the genotypes of 321 patients with first-episode psychosis. A total of 15 *CNR1, CNR2* and *FAAH SNPs* were analysed, but they only found statistical significance in the case of the rs2295633 polymorphism of the *FAAH* gene. Homozygote carriers of the T allele who were cannabis users had a greater likelihood of presenting a psychotic episode than users of cannabis without this genotype. Sufficient statistical significance was not found with regard to the rs324420 polymorphism. Watts et al. (2020) recently found that lower levels of *FAAH* were associated with more severe psychotic symptoms. These results were independent of cannabis exposure.

We found an association between the rs324420 polymorphism in the *FAAH* gene and cannabis dependence. The presence of fewer heterozygotes in the rs324420 *FAAH* polymorphism was associated with cannabis dependence, which leads us to hypothesise that the heterozygous genotype confers some protection against this dependence, in accordance with an overdominance model. Heterozygosity could thus be a balance between the demands of flexibility and stability in the neural pathways involved. Just as in our research, other authors have found an association between the AA or CC homozygotes of this polymorphism and substance use disorders (Flanagan, Gerber, Cadet, Beutler & Sipe, 2006; Sipe et al., 2002), and different clinical manifestations in cannabis users (Haughey, Marshall, Schacht, Louis & Hutchison, 2008; Schacht, Selling & Hutchison, 2009).

FAAH is the critical regulator of the endogenous levels of anandamide (Fezza, De Simone, Amadio & Maccarrone, 2008). The *FAAH* polymorphism rs324420 predicts a substitution of proline at position 129 of the protein by a threonine residue (P129T), resulting in a protein that is more susceptible to proteolytic degradation (Sipe, Chiang, Gerber, Beutler & Cravatt, 2002). Thus, *FAAH 385A* is associated with lower enzymatic activity. FAAH knockout mice have shown altered cannabis tolerance and dependence (Falenski et al., 2010) suggesting that altered FAAH activity may modify endocannabinoid signalling in reward-controlling areas and contribute to addictive vulnerability (Van Hell et al., 2012).

Previous literature about the relationship between the rs324420 polymorphism and drug use patterns seems to be extremely heterogeneous and complex (Hindocha et al., 2019; Melroy-Greif, Wilhelmsen & Ehlers, 2016; Tyndale et al., 2007). Lower levels of FAAH have been identified in healthy A-carriers of rs324420 (Boileau et al., 2015). Reduced brain FAAH binding has been found in cannabis users compared to controls. In addition, lower binding has been associated with abstinence, impulsivity and increased cannabinoid blood levels (Boileau et al., 2016). In the cannabis user sample of the Hindocha et al. (2019) study, A carriers showed a greater bias towards appetitive stimuli in comparison with CC carriers. Hariri et al. (2009) found that there was an association in carriers of *FAAH 385A* with possible increased endocannabinoid signalling, and that there was increased reward-related ventral striatal reactivity and more impulsivity in comparison with C385 homozygotes. On the contrary, Filbey, Schacht, Myers, Chavez & Hutchison (2010) identified higher activation in reward areas in C-allele carriers in a sample of regular marijuana users.

Our findings should be interpreted with caution because significance levels for codominant and overdominance models were similar and the study population number was limited (the AA genotype was only present in few cases and the cannabis dependent control subgroups were small).

CNR2

Different studies have shown that CB2 receptors are present in neural progenitor cells, neurons and glial cells. In addition, CB2 receptor function has not only been linked to neurological disorders involving neuroinflammation but also to neuropsychiatric disorders like drug addiction, psychosis, depression, and eating disorders (Onaivi et al., 2012).

Nonetheless, we observed an association between the polymorphisms rs35761398 and rs12744386 in *CNR2* and comorbid schizophrenia and cannabis dependence. We found that the high function genotype of *CNR2* was associated with schizophrenia, but only in cannabis dependent subjects. We tested several models of inheritance and found that statistical association was enhanced when a dominant model for the TT allele was assumed. To our

knowledge, this is the first study performed on a Caucasian population. Ethnicity should be taken into consideration when interpreting our results because differential allelic distributions have been described in previous scientific literature on other ethnic groups. For instance, an association has been reported between schizophrenia and the low function haplotype in a Japanese population sample (Ishiguro et al., 2010) and other different *CNR2* polymorphisms in Chinese samples (Tong et al., 2013), whereas in Korean samples, no association was found (Bae et al., 2014).

Banaszkiewicz, Biala & Kruk-Slomka (2020) conducted a review on schizophrenia-like symptoms induced via CB2 receptor modulation in animal models, suggesting a key function in schizophrenia. Schizophrenia-related behaviours were observed in mice with deletion of CB2 receptors (Ortega-Alvaro, Aracil-Fernández, García-Gutiérrez, Navarrete & Manzanares, 2011). It is suggested that a lack of the CB2 receptor might impair neural development, thus inducing relevant alterations in several brain areas, based on findings supporting a pro-neurogenic role of the CB2 receptor in the control of fundamental neural cell processes (Galve-Roperh, Aguado, Palazuelos & Guzman, 2008). These results seem contrary to our data as they relate psychosis to lower function of CB2 receptors. Our data would support an alternative explanation: that excessive activity of these receptors could facilitate this psychotic phenotype. Therefore, cannabis use could disrupt neuronal differentiation during adolescence and provoke psychoses in vulnerable subjects through a mechanism involving CB2.

On the other hand, inflammatory and immunological processes interfering with brain development are discussed as a cause of schizophrenia, and the CB2 receptor is a main component of these processes (Sahu et al., 2019). Glia are implicated in schizophrenia pathogenesis, and the CB2 receptor is relevant (De Almeida & Martins-de-Souza, 2018). It has been hypothesised that an increased number of activated microglial cells in patients with schizophrenia contribute to disease pathogenesis (Juckel et al., 2011).

Furthermore, in Alzheimer´s disease, CB2 receptors are abundantly and selectively expressed in neuritic plaque-associated astrocytes and microglia, respectively (Benito et al., 2003), and activation of CB2 receptors expressed by immune cells is likely to reduce their antiviral response, thus favouring the CNS entry of infected monocytes with simian immunodeficiency virus (Benito et al., 2005).

Thus, overactivation of the CB2 receptor could be a psychosis vulnerability factor, and cannabis use could provoke psychosis in these vulnerable subjects. It has been found that THC inhibits the chemotactic response of microglia through activation of the CB2 receptor (Cabral, Raborn, Griffin, Dennis & Marciano-Cabral, 2008). Furthermore, cannabis use in the context of specific cannabinoid receptor genotypes may contribute to white matter abnormalities, which could in turn increase schizophrenia risk (Ho, Wassink, Ziebell & Andreasen, 2011). White matter alterations are relevant in schizophrenia, and adolescent cannabis use has specific effects on these abnormalities (Peters, Blaas & de Haan, 2010).

In addition, the expression of *CNR2* gene transcripts in animals treated with drugs of abuse is increased in comparison with controls (Ishiguro et al., 2007). Therefore, cannabis use could modify *CNR2* transcription, and in subjects with highly activated CB2 receptors, could contribute to psychotic symptoms through an unknown mechanism. It has also been reported that clinical remission from schizophrenia is accompanied by significant decreases in CNR2 mRNA levels in mononuclear peripheral blood cells (De Marchi et al., 2003).

The limitations of this study are related to the nature of association studies and therefore, our results must be interpreted with some caution. The strength of our results is limited by a small sample size, particularly in the cannabis dependent group. It would be preferable to replicate our genetic studies in independent samples, since this could clarify the possible role of the *CNR1, CNR2,* and *FAAH* gene variants. Secondly, the possibility of a result occurring by chance cannot be ruled out, although we did apply Bonferroni correction. These results should therefore be confirmed among a larger population. Likewise, it would have been useful to administer the PANNS scale to the controls and in particular to the CUD subjects, in order to rule out clinical psychotic symptoms. Urine tests for detecting drugs were not carried out on the control group so it is possible that some subjects were using cannabis. Drug testing was conducted on the non-cannabis using schizophrenia group.

Despite these limitations, we believe our study has identified a major genetic protective factor against cannabis-associated psychosis in the Spanish population, which deserves greater attention in future investigations. That research should also examine whether specific phenotypic characteristics, such as symptom profile, age at onset, and treatment response, are associated with the *CNR2* polymorphism. No previous reports on these polymorphisms in cannabinoid-associated psychosis are available. The mutation detected by this polymorphism results in a change in the amino acid sequence of the protein, so direct functional consequences are expected. Cannabis dependent subjects with the TT genotype exhibited a significantly higher risk of psychosis. These findings suggest that dysfunction of the endocannabinoid system due to genetic mutation may constitute a risk factor for cannabis-associated psychosis.

Apart from genetic variants, it would also be advisable to include epigenetic variables in future research. Changes in

DNA methylation in the promotor region of *CNR1* genes in schizophrenic patients have been described (D'Addario et al., 2017; Tao et al., 2020).

Finally, we did not find a relationship between *CNR1* and *FAAH* variants and psychosis. Overall, our findings suggest that *FAAH* variants are associated with cannabis dependence but not with schizophrenia in Spanish patients, which would imply that differences in endocannabinoid function could play a part in the pathophysiology of this illness. Confirmation of our findings among other populations and independent samples would be useful for the design of pharmacological strategies focused on prophylaxis and treatment of these patients.

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Conflict of interests

The authors confirm that there are no conflicts of interest.

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Impact of neuropsychological disorders on clinical aspects of smoking

Impacto de las alteraciones neuropsicológicas sobre aspectos clínicos en tabaquismo

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Abstract

Studies examining associations between cognitive measures and clinical aspects of smoking are scarce and generally limited to predicting risk profiles or relapses. However, it is essential to understand the influence of several measures of executive function in nicotine addiction in order to investigate factors associated with smoking maintenance. This study examined the ability of working memory and delay discount to predict years of smoking. The sample consisted of 180 smokers who were assessed at baseline with measures of cognitive impulsivity (Delay Discounting Task) and working memory [Visual Search and Attention Test (VSAT) and Letter-Number Sequencing (WAIS III)] while the outcome measure was years of smoking. Consistent with predictions, working memory evaluated with Visual Search and Attention Test was a statistically significant factor in predicting years of nicotine addiction. These findings suggest that working memory is clinically relevant in nicotine dependence and proposes a pattern of executive functioning associated with smoking.

Keywords: Smoking; addictive behavior; working memory; delay discount.

Resumen

Los estudios que examinan las asociaciones entre las medidas cognitivas y los aspectos clínicos del tabaquismo son limitados y, en general, se limitan a predecir perfiles de riesgo o recaídas. Sin embargo, es esencial comprender la influencia de varias medidas de la función ejecutiva en la adicción a la nicotina a fin indagar factores asociados al mantenimiento del tabaquismo. En el presente estudio se examinó la capacidad de la memoria de trabajo y el descuento por retraso para predecir los años de tabaquismo. La muestra consistió en 180 fumadores que fueron evaluados en la línea de base con medidas de impulsividad cognitiva (Tarea de Descuento de Retraso) y memoria de trabajo [Prueba de Búsqueda y Atención Visual (VSAT) y Secuenciación de Números de Letras (WAIS III)] mientras que la medida de resultado fue los años de adicción. De acuerdo con las predicciones, la memoria de trabajo evaluada con la Prueba de Búsqueda y Atención Visual fue un factor estadísticamente significativo para predecir los años de adicción a la nicotina. Estos hallazgos sugieren que la memoria de trabajo es clínicamente relevante en la dependencia de la nicotina y plantea un patrón de funcionamiento ejecutivo asociado al tabaquismo.

Palabras clave: Fumar; comportamiento adictivo; memoria de trabajo; descuento por retraso.

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The tobacco epidemic is one of the most persistent international threats to public health (WHO, 2019). Given that a sizeable percentage of smokers become dependent, nicotine has been shown to be one of the most addictive psychoactive substances (Detandt, Bazan, Quertemont & Verbanck, 2017). Specifically, the reinforcing effects of nicotine trigger the activation of the brain reward system that drives the probability of repeat consumption (Carlson, Birkett & Redolar Ripoll, 2018). Nicotine addiction therefore represents a disorder semiologically characterised by compulsive use, a gradual loss of control over use and the appearance of a characteristic clinical picture of syndromes associated with withdrawal (Zarrindast & Khakpai, 2019). The consolidation of dependence is the result of the confluence between earlier vulnerability factors and a specific configuration of neurological mechanisms driving the predominant neuroadaptive changes in addictive processes (Corominas, Roncero, Bruguera & Casas, 2007). The high addictiveness and toxicity resulting from chronic nicotine abuse modulate neural mechanisms involved in vital cognitive functions such as working memory, attention and inhibitory control (Zlomuzica et al., 2018). The controlled administration of nicotine has been shown to weaken certain attentional, cognitive and mood deficits associated with schizophrenia, attention-deficit/hyperactivity disorder, Alzheimer's, Parkinson's, late-life depression and mild cognitive impairment (Gandelman et al., 2018; Heishman, Kleykamp & Singleton, 2010; Newhouse et al., 2012). Chronic use, however, affects the functionality of connectivity and brain coordination, compromising cognitive processes subordinate to these structures (Durazzo, Meyerhoff & Nixon, 2010). Specifically, the impairment of working memory, understood as the ability to temporarily retain information while operating with it, (Wechsler, 1999), could favour smoking maintenance by predisposing to ruminative thoughts about the drug (Kübler, Murphy & Garavan, 2005). Wagner et al. (2013) examined the cognitive profile of smokers and non-smokers to investigate whether smokers showed cognitive deficits associated with chronic use. They assessed six domains: 1) episodic memory [Auditory Verbal Learning Test (AVLT; Helmstaedter, Lendt & Lux, 2001)], 2) visual attention [Trail Making Tests (TMT; Reitan, 1958)] and digit symbol [Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999)], 3) verbal fluency (letter fluency task S, A, B and N), 4) working memory measured with digit-span [Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999)] and sequence of numbers (Gold, Carpenter, Randolph, Goldberg & Weinberger, 1997) 5) impulsivity [The Continuous Performance Test (CPT-IP; Cornblatt, Risch, Faris, Friedman & Erlenmeyer-Kimling, 1988)] and 6) interference using a Stroop task (Stroop, 1935). The results showed smokers to have significant deficits in visual attention (TMT and WAIS digits) and impulsivity (CPT-IP) (Wagner et al., 2013). More recently, Hu et al. (2017) explored the link between smoking and cognitive performance in working memory between smokers and non-smokers, measured with the information, arithmetic and digit subtests [Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1999)], and in dysexecutive symptomatology [Dysexecutive Questionnaire (DEX; Bodenburg & Dopslaff, 2008)]. Smokers scored higher in dysexecutive symptoms and lower on the arithmetic and digit subtests (WAIS) compared to non-smokers. Similarly, a direct correlation was revealed between working memory (Digits) and the age of smoking onset (Hu et al., 2018).

Impulsive behaviour is a well-known etiological factor in the field of nicotine addiction (Billieux et al., 2010). One of the commonly explored impulsive dimensions is delayed discounting (De Wit, 2009), assessed in tasks with a choice between a smaller immediate reward or a greater but delayed reward (Verdejo-García, Alcázar-Córcoles & Albein-Urios, 2019). A recent meta-analysis examining performance in different neuropsychological domains between smokers and non-smokers concluded that smokers had higher rates of cognitive impulsivity. This was linked to a preference on the part of smokers for devaluing long-term in favour of immediate rewards on delayed-discounting tasks (Conti, McLean, Tolomeo, Steele & Baldacchino, 2019). Furthermore, delayed discounting tasks have emerged as powerful predictors of relapse in both adult (González-Roz, Secades-Villa, Pericot-Valverde, Weidberg & Alonso-Pérez, 2019; López-Torrecillas, Perales, Nieto-Ruiz & Verdejo-García, 2014; Reynolds, Richards, Horn & Karraker, 2004) and adolescent samples (Krishnan-Sarin et al., 2007; Sheffer et al., 2014). However, to our knowledge, research on its predictive powers in other clinical aspects of smoking is limited. Similarly, although smoking has been a focus of study in recent decades, most authors have concentrated on detecting the early factors that trigger onset (Gustavson et al., 2017; Harakeh et al., 2012; Lydon, Wilson, Child & Geier, 2014), on the adverse consequences of chronic smoking (Billieux et al., 2010; Detandt et al., 2017; Lyvers, Carlopio, Bothma & Edwards, 2014; Sheffer et al., 2014; Valentine & Sofuoglu, 2018), as well as on exploring variables that jeopardise abstinence (González-Roz et al., 2019; Harvanko, Strickland, Slone, Shelton & Reynolds, 2019; Krishnan-Sarin et al., 2007; Luijten, Kleinjan & Franken, 2016). Therefore, in comparison with the interest aroused by other stages of nicotine addiction such as onset or withdrawal, there is still a paucity of studies exploring factors linked to repeated tobacco use, in particular, research reporting on the influence of neuropsychological variables that perpetuate nicotine addiction. Moreover, it has been found that the therapeutic response is not homogeneous among smokers (Villalbi et al., 2019), in part because the factors that motivate smoking in different groups are unknown (O'Dell & Torres, 2014). Therefore, from a clinical and public health point of

view, it is essential to investigate the factors associated with smoking maintenance which could favour the development of new therapeutic approaches. The aim of this study is therefore to provide empirical evidence on the association between performance on neuropsychological tasks assessing working memory and impulsivity and years of addiction in a sample of smokers seeking to begin smoking cessation treatment. Based on the reviewed evidence highlighting the potential role of working memory in prompting ruminative thoughts about the drug, we hypothesise that the variables involved in working memory will be good predictors of years of addiction.

Method

Participants

The sample comprised 180 smokers who had requested treatment in the smoking cessation program of the Occupational Risk Prevention Service of the University of Granada. Mean participant age was 47.3 (SD = 8.31) within a range from 27 to 69 years, and 59% were women. The mean score of the sample on the Fagerström test was 4.49 (SD = 2.32) and mean smoking intensity was 17.9 (SD = 8.94) cigarettes per day. Inclusion criteria were: 1) being a smoker (Fagerström > 3), 2) aged over 18 years, 3) having a work relationship with the University of Granada, 4) voluntary participation in the treatment offered by the Occupational Risk Prevention Service and 5) completion of all questionnaires, inventories and tasks in the pre-treatment and monitoring assessment. Exclusion criteria were: being diagnosed with a serious mental disorder (bipolar and/or psychotic disorder, etc.) or one requiring medication on a regular basis (anxiolytics, antidepressants, etc.), as well as concurrent addiction to other substances (cocaine, heroin, alcohol, etc.). All participants were informed about the aims of the study and consented to take part. Prior to the assessment, participants were informed of the voluntary nature of the program, as well as of the confidential nature of data processing (article 7 of Law 41/2002); informed consent was thus obtained, ensuring that our research process was backed by the legislative framework established by the Code of Ethics (subject to the latest adaptation of Law 25/2009). In addition, the study was approved by the Ethics Committee in Human Research of Granada University.

Instruments

All neuropsychological assessments were carried out by duly trained psychologists.

- **Letter-Number sequencing** *(Wechsler Adult Intelligence Scale, WAIS III;* Wechsler, 1999, *Spanish adaptation, TEA Ediciones*). In this test a combined sequence of

Table 1. *Demographic characteristics of the sample.*

Category	Measurement	Percentage	Mean	SD	Range
Sociodemographic variables	Age		47.3	8.31	27-69
	Years of schooling		17.13	5.40	8-25
Professional career	Office worker	62.5%			
	Lecturer	19.5%			
	Researcher	4%			
	Service personnel	14%			
Smoking variables	Fagerström Nicotine Addiction Test		4.49	2.32	0-10
	Severe (TFDN >7)	22%			
	Moderate (TFDN<7)	78%			
Cigarette brands	Blond	83.5%			
	Dark	8.5%			
	Rolling	8%			
	Years of addiction		28.43	9.84	4-57
	Number of cigarettes a day		17.9	8.94	2-60
	Level of nicotine in mg per cigarette		.99	.13	,60-1.8
	Earlier attempts to quit		1.27	1.35	0-12
Working memory					
	Letter-Number Sequencing (WAIS III)		8.70	2.90	0-15
	Visual Search and Attention Test (VSAT) (Cues)		227.17	59.01	18-383
	Visual Search and Attention Test (Errors)		7.34	11.31	0-95
Delay discount	Now or later? task		.57	.22	0-1

Note. N = 180.

letters and numbers is read to the participant. The participant then has to reproduce this sequence by first repeating the numbers, from smallest to largest, and then the letters, in alphabetical order. The task involves maintenance and manipulation of information from working memory. The test contains six elements, each one consisting of three sequences of equal length. Administration is interrupted when the subject fails all three sequences of the same element. The total number of correct responses constitutes the variable score.

- ***Visual-search attention test*** (VSAT; Trenerry, Crosson, Deboe & Leber, 1990). In this visual search test, a target (a letter or coloured symbol) is identified in a matrix designed to explore sustained attention, understood as the ability to rapidly activate and inhibit motor responses. In this case, the total score of stimuli detected was used as an independent variable.
- ***Delay Discounting Task Questionnaire*** **Now or later?** (Delay Discounting Task, DDT; Kirby, Petry & Bickel, 1999). This is a 27-question monetary choice questionnaire that asks for preferences between smaller and immediate or larger but delayed rewards varying according to their value and time to be obtained. The area under the curve (AUC) was calculated using the Myerson, Green and Warusawitharana (2001) proposal. The AUC was estimated for the range of reward sizes covered in the questionnaire (small €5-35; medium €50-60; and large €75-85), according to the formula (x2-x1) [(y1-y2)/2], where x1 and x2 are successive delays, y1 and y2 are the subjective values associated with these delays (Myerson, Green & Warusawitharana, 2001). The predictive variable was AUC, with lower AUC values indicating greater impulsivity.

Tobacco use pattern

Semi-structured interview for smokers (López-Torrecillas, 1996) This is used to gather sociodemographic information, family history, years of addiction, number of cigarettes per day and smoking history in the first treatment session. The coding of the criterion variable "Years of addiction" was defined as the number of years from the date of onset to the beginning of smoking cessation treatment.

Fagerström Nicotine Dependence Test (FNDT) (Fagerstrom & Schneider, 1989) This consists of 6 items assessing the degree of physiological dependence. The maximum score is 10 points and is categorised into mild (0-3 points), moderate (4-7 points) and severe dependence (8-10 points).

Procedure

This quasi-experimental, observational and cross-sectional study employed non-random and incidental sampling since participants voluntarily requested to join the program. They were assessed individually before starting smoking cessation treatment (the measures of this study thus correspond to the baseline assessment), and the study instruments were part of a larger protocol aimed at neuropsychological assessment within a smoking cessation intervention. This subsequent intervention consisted of three phases: (1) psychoeducational phase (activity planning and target setting) to reduce smoking and to conduct neuropsychological tests and apply psychological instruments; (2) prescription and controlled administration of varenicline, a partial agonist/antagonist drug at the neuronal receptors for nicotinic-type acetylcholine α4β2 in the presence of nicotine and (3) clinical follow-ups with relapse prevention strategies, promotion of healthy lifestyle habits and strategies aimed at increasing motivation.

The program's initial session consisted of a semi-structured interview for smokers (López-Torrecillas, 1996) as well as a neuropsychological assessment with the measures described above. This initial evaluation was carried out in a single session, with appropriate breaks to avoid fatigue. Each participant was assigned a unique code to ensure individual monitoring while safeguarding anonymity, with the project leader as the person in charge of safeguarding the records.

Statistical analysis

Statistical analysis was performed using version 20.0 of the IBM SPSS program. Participants were characterised with descriptive statistics, and relationships between variables were assessed with Pearson's correlations, with statistical significance at $p<.05$. To analyse the specific contribution of the independent variables to years of addiction, a hierarchical regression analysis was performed. In all, the appropriate statistical procedures were performed to ensure that the assumptions required by the regression model were met.

Results

The Pearson test was applied to check for the existence of associations between the variables; this yielded inverse correlations in our study between the variables measuring working memory (WAIS and VSAT) and the criterion variable, with the relationship for WAIS (r = -.020; p = .05) being slight, but moderate for VSAT (r = -,415; p = .05). In this regard, smokers with low scores on working memory tests tend to be addicted for more years. In relation to the variable measuring delayed discount (Delay Discounting Task, DDT), a slight direct relationship is observed with the criterion variable (r = -.084; p = .05). In this test, therefore, the more smokers discount, that is, behave impulsively, the greater the number of years of addiction (Table 2).

Table 2. *Matrix of correlations between criterion and independent variables.*

Variables	Years	WAIS	VSAT	AUC
Year	1			
WAIS	-.020	1		
VSAT	-.415*	.162*	1	
DDT	.084	-.022	-.043	1

Note. N = 180. Years = Years of addiction; WAIS: Total score in the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale, WAIS III; VSAT = Total Stimuli in the Visual Search and Attention Test; DDT = Total score on the Now or Later Test.
*P<.05.

Regarding the hierarchical regression analysis (Table 3), it was observed that the variables measuring working memory (WAIS and VSAT) explained 17.5% of the variance. Finally, in the third step, when incorporating the AUC variable measuring delay discount, the model explained 17.9% of the criterion variance, leaving a statistically significant final model, $F_{(3,176)} = 12.80$; $p < .000$. In the final model, only the VSAT working memory variable was statistically significant ($\beta = -.070$, $p < .000$). In the regression equation it can thus be observed that the variable score in VSAT is the independent variable with the greatest weight in the regression equation. An increase of one standard deviation in VSAT means an increase in addicted years of .420. Finally, when observing the width of the confidence intervals of the partial regression coefficients, we find better adjusted estimates in the working memory tests (VSAT and WAIS), but greater interval width in the impulsivity test (Delay Discounting Task, DDT), which signals less precision when estimating the population value of this regression coefficient.

Table 3. *Hierarchical regression analysis.*

Variable	R	R^2	gl	β	t	p	95% IC of β
Step 1							
WAIS	.020	.000	1	-.069	-.273	.786	-.570-.432
Step 2							
WAIS				.163	.697	.487	-.299-.626
VSAT	.418	.175	1	-.071	-6.113	.000	-.093- -.048
Step 3							
WAIS				.167	.049	.478	-.296-.630
VSAT				-.070	-.420	.000	-.093--.047
TDD	.423	.179	1	2.871	.067	.329	-2.919-8.66

Note. N = 180. WAIS: Total score in the Letter-Number Sequencing subtest of the Wechsler Adult Intelligence Scale. WAIS III; VSAT = Total Stimuli in the Visual Search and Attention Test; DDT = Total score on the Now or Later Test.
*P<.05.

Discussion

The aim of this study was to explore the relationship between years of nicotine addiction and performance in neuropsychological tasks in smokers seeking to initiate smoking cessation treatment. The results indicate that working memory tasks (WAIS and VSAT), together with a delayed discount task, make up a significant regression model explaining 17.9% of the criterion variance. However, in our sample only the VSAT variable serves as the main predictor of years of addiction, with an inverse correlation indicating that the lower the VSAT performance, the more years of addiction. These findings are similar to those reported by Wagner et al. (2013) showing significant deficits in visual attention in smokers compared to non-smokers (Wagner et al., 2013). They are also congruent with the functional-structural hypothesis, which posits a superposition of the chronic structural effects of smoking on the functional effects of acute administration of nicotine (Sutherland et al., 2016). Consequently, research attributing beneficial properties to nicotine cite groups distinguished by an altered cholinergic system or underlying nAChR dysfunction (Gandelman, Newhouse & Taylor, 2018). Specifically, controlled nicotine administration promotes improvements in functional performance in the lateral prefrontal cortex (LPF), anterior cingulate cortex (ACC), thalamus and cuneus, that is, regions traditionally associated with attention, working memory, and task execution, which require external-oriented processing (executive control network) (Gandelman et al., 2018; Sutherland et al., 2015). However, chronic nicotine use involves cognitive performance impairment (Durazzo et al., 2010) as well as neuroadaptations that lead to decreases in the grey matter of regions commonly identified in processes associated with addiction such as ventromedial PFC, insula, thalamus and cerebellum (Sutherland et al., 2016). Specifically, the insula as a substrate assigned to cognitive and attentional control (Bi et al., 2017) and involved in the need to smoke (Paulus & Stewart, 2014) seems to play a critical role in smoking maintenance (Sutherland & Stein, 2018). Furthermore, structural differences in the insula between smokers and controls are more easily seen in smokers with longer histories of smoking exposure (Li et al., 2015). As our results aim to contribute behavioural data to the discussion on structural alterations resulting from the harmful impact of smoking, our inferential hypothesis is that smokers with a greater history of addiction show poorer performance in the demanding tasks of working memory and attentional control which predispose towards ruminative thoughts of craving traditionally linked to addiction (Hester & Garavan, 2009; Kübler et al., 2005).

The Delay Discounting Task (DDT), on the other hand, did not yield statistical significance, which may indicate that this variable plays a significant role in other stages of addiction, an assumption which is consistent with the hypothesis held by Reynolds and Fields (2012) stating that the different dimensions of impulsivity can have various effects at the onset of use or in later stages (Reynolds & Fields, 2012). In this case, delayed discount has been widely

linked to treatment response (González-Roz et al., 2019; Krishnan-Sarin et al., 2007; López-Torrecillas et al., 2014; Reynolds et al., 2004; Sheffer et al., 2014). In summary, research indicates that, despite the coexistence of individual differences facilitating onset or risk of relapse, the effects of nicotine on cognitive aspects suggest that the causes of smoking maintenance are heterogeneous (Bedi et al., 2011; García-Rivas & Deroche-Gamonet, 2019; Hall et al., 2015).

Our results show that cognitive processes which need working memory, such as sustained attention and visual search, seem to have an influence on smoking maintenance. However, there are some limitations which need to be pointed out, such as the nature of the sample since, being non-random and incidental, it limits the generalisability of results. In addition, the cross-sectional nature of the study makes it difficult to obtain data showing development over time and the inferred causal relationship between the variables. Therefore, the importance is stressed of implementing longitudinal designs allowing the development of dependency to be considered. Finally, this study may stimulate interest in trying to clarify the implications of neuropsychological variables in clinical aspects of smoking behaviour as relevant and hermetic as habit maintenance. Therefore, identifying mediating variables that motivate nicotine use is crucial in developing more effective therapeutic strategies (O'Dell & Torres, 2014) which include these neuropsychological variables. Our results should thus be interpreted as a starting point for new research investigating the implication of cognitive variables both in the maintenance of chronic smoking and their possible role in obstructing of the path to abstinence; since the predictive capacity of neurocognitive factors has been occasionally explored in smoking cessation (Luijten et al., 2016) despite representing a priority objective in preventive policies (Villalbi et al., 2019).

Conflict of interests

The authors declare that no conflict of interest.

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Longitudinal associations between dispositional mindfulness and addictive behaviors in adolescents

Asociaciones longitudinales entre el rasgo de mindfulness y conductas adictivas en adolescentes

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Abstract

Adolescence is a vulnerable period for the development of addictive behaviors, and substance use (SU) and problematic Internet use (PIU) typically start during this developmental stage. Dispositional Mindfulness (DM) has been proposed as a protective factor for adolescents against numerous psychological problems. Previous studies have suggested that the Observing facet of DM may moderate the other facets' roles. The objective of this study was to longitudinally analyze whether the facets of DM could predict lower levels of PIU and SU among adolescents, and to assess whether the Observing facet moderated the associations between the other facets of DM and addictive behaviors. A total of 836 participants aged 11 to 18 completed measures of PIU, SU, and the five facets of DM. The results indicated that Acting with Awareness predicted lower SU, Describing predicted an increase in both PIU and SU, and Non-judging marginally predicted lower PIU. Furthermore, Observing was beneficial against PIU when combined with high levels of Acting with Awareness, but was not when combined with high levels of Describing. The implications and future directions for the empirical study of DM against addictive behaviors are discussed.

Keywords: Dispositional mindfulness; problematic Internet use; substance use; adolescents.

Resumen

La adolescencia es un período vulnerable para el desarrollo de conductas adictivas. El uso de sustancias (US) y el uso problemático de Internet (UPI) generalmente comienzan durante esta etapa de desarrollo. El mindfulness rasgo (MD) se ha propuesto como un factor protector para los y las adolescentes frente a numerosos problemas psicológicos. Estudios previos sugieren que la faceta Observar de MD puede moderar los roles de las otras facetas. El objetivo del presente estudio fue analizar longitudinalmente si las facetas de MD podían predecir niveles más bajos de UPI y US entre los y las adolescentes, y evaluar si la faceta Observar moderaba las asociaciones entre las otras facetas de MD y las conductas adictivas. Un total de 836 participantes de entre 11 y 18 años completaron medidas de UPI, US y las cinco facetas de MD. Los resultados indicaron que Actuar con conciencia predijo niveles más bajos de US, Describir predijo un aumento tanto de UPI como de US y No juzgar predijo marginalmente niveles más bajos de UPI. Además, la faceta Observar fue beneficiosa frente a UPI cuando se combinó con altos niveles de Actuar con conciencia, pero no fue beneficiosa cuando se combinó con altos niveles de Describir. Se discuten las implicaciones y direcciones futuras para el estudio empírico de MD frente a conductas adictivas.

Palabras clave: Rasgo de mindfulness; uso problemático de Internet; uso de sustancias; adolescentes.

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Adolescence is considered a developmental stage characterized by numerous changes at the biological, social, cognitive, and affective levels. These changes make this stage a vulnerable period for adolescents to develop higher levels of addictive behavior, as substance use (SU) normally begins in adolescence (Bava & Tapert, 2010). The average age at which SU begins to show an increased prevalence is 14 years, with first alcohol consumption typically occurring at this age, and first consumption of other illegal substances, such as cannabis and cocaine, occurring at 15 years (Spanish Drug Observatory, 2019). Additionally, in recent years, with the expansion of Internet use among young people, Internet addiction or problematic Internet use (PIU) has emerged. PIU is characterized by behaviors associated with poor control, continuous use, and cognitive concern regarding the Internet, which can carry a series of negative consequences in different areas of an individual's life (Caplan, 2010). The results of a study conducted with large sample of Spanish adolescents indicated that the prevalence of PIU was high, reaching 16.3% (Gómez, Rial, Braña, Golpe & Varela, 2017). These addictive behaviors are, in turn, related to higher levels of psychological and physical health problems (Brownlie et al., 2019; Restrepo et al., 2020). Further, different studies indicate that PIU and SU are related to each other (Gámez-Guadix, Orue, Smith & Calvete, 2013b).

Taking into account the rates of both risk behaviors and their early onset in adolescence, it is necessary to identify protective factors that help prevent the development of these problems. Recently, interest has increased in mindfulness-based interventions, with Dispositional Mindfulness (DM) serving as a beneficial factor in preventing the development of numerous psychological problems in different populations, including adolescents.

Dispositional Mindfulness, Substance Use, and Problematic Internet Use

DM has been defined as a multidimensional construct (e.g., Baer, Smith, Hopkins, Krietemeyer & Toney, 2006; Bishop et al., 2004). Baer et al. (2006) indicate that it is a trait consisting of five different facets: (1) Observing: The ability to attend to internal and external experiences such as perceptions, thoughts, sensations or feelings; (2) Describing: The ability to describe internal experiences through words; (3) Acting with Awareness: The ability to be focused to one's activities at the moment; (4) Non-judging: The ability not to judge internal experiences such as thoughts and feelings; and (5) Non-reacting: The ability to avoid getting carried away by internal experience (Baer et al., 2006). These facets may have different roles, depending on the nature of a psychological problem (Cortazar & Calvete, 2019), emphasizing the importance of evaluating the trait of mindfulness through its different facets. However, one of the limitations to drawing conclusions regarding the role that DM has in protecting against different psychological problems is that many previous studies focus on one or only some facets of DM. Additionally, there are numerous scales to evaluate the construct, some of which are one-dimensional or focus only on some facets of DM. However, previous studies indicate that there is overlap between some facets as measured with different instruments. For example, the Mindful Attention Awareness Scale (MAAS-A; Brown, West, Loverich & Biegel, 2011; Spanish version: Calvete, Sampedro & Orue, 2014) has shown associations with the Acting with Awareness facet of the Five Facet Mindfulness Questionnaire (FFMQ; Quaglia, Braun, Freeman, McDaniel & Brown, 2016), and the Child and Adolescents Mindfulness Measure (CAMM; Greco, Baer & Smith, 2011; Spanish version: Guerra et al., 2019; Turanzas Romero, 2013) has shown associations with the Acting with Awareness and Non-judging facets of the FFMQ (Calvete & Royuela-Colomer, 2016).

At the cross-sectional level, some studies found that Acting with Awareness was associated with lower levels of PIU (Gámez-Guadix & Calvete, 2016), such as compulsive use of mobile phones and social networks (Apaolaza, Hartmann, D'Souza & Gilsanz, 2019; Kircaburun, Griffiths & Billieux, 2019). At the longitudinal level, Calvete, Gámez-Guadix, and Cortazar (2017a) found that all facets of DM (except Non-reacting) predicted lower PIU levels in adolescents.

Regarding SU, a meta-analysis indicated that, although many studies showed negative relationships with DM, these results are mixed, as other studies have not found these relationships or even found positive relationships (Karyadi, VanderVeen & Cyders, 2014). For example, in adolescents, scores on the CAMM, which combines Acting with Awareness and Non-judging, were associated with lower alcohol and marijuana consumption (Robinson, Ladd & Anderson, 2014), and Describing was associated with lower alcohol consumption (Fernández, Wood, Stein & Rossi, 2010). Likewise, the results of another cross-sectional study conducted with an adult clinical sample showed that these three facets of DM were negatively associated with SU (Bowen & Enkema, 2014). However, Karyadi et al. (2014) did not find significant associations for Observing or Describing, while Acting with Awareness, Non-judging, and Non-reacting showed significant negative associations. Moreover, most extant studies have been cross-sectional, and very few have been conducted with adolescent samples. A recent study with an adolescent sample did not find significant predictions between MAAS scores (i.e., Acting with Awareness) and SU (Calvete, Orue & Sampedro, 2017b).

The role of the Observing facet of DM has been debated. Although many previous studies have found that the Observing facet can be maladaptive in samples of non-meditators (e.g., Baer et al., 2006; Calvete, Fernández-

González, Echezarraga & Orue, 2019; Royuela-Colomer & Calvete, 2016), some studies indicated that this facet can be beneficial when interacting with other DM skills for different psychological problems (e.g., Desrosiers, Vine, Curtiss & Klemanski, 2014; Eisenlohr-Moul, Walsh, Charnigo, Lynam & Baer, 2012). Specifically, in a sample of university students, Eisenlohr-Moul et al. (2012) found that Observing was associated with lower SU (i.e., tobacco and alcohol) only in interaction with other facets, such as Non-reacting. Contrastingly, Bowen and Enkema (2014) did not find significant support for this interaction. Furthermore, to our knowledge, there are no studies that evaluate the interactions between Observing and other facets of DM to examine changes in PIU. However, a recent meta-analysis (Sala, Rochefort, Priscilla Lui & Baldwin, 2020) suggested that Observing may be positively related to health behaviors when other DM skills are high, which indicates the need to evaluate how the combination of DM facets can influence health behaviors.

Overview of the Current Study

Although previous studies have evaluated the relationship between DM and risk behaviors such as PIU and SU, these studies generally used cross-sectional designs. Longitudinal studies are necessary to evaluate the extent to which facets of DM predict these risk behaviors. Furthermore, most previous studies have been conducted with adults; however, as mentioned above, these risky behaviors tend to emerge in adolescence. Finally, most existing studies examine DM through a single facet or a one-dimensional construct, making it difficult to determine the specific relationships between each facet and addictive behaviors or the potential interactions between Observing and the other facets.

Therefore, the main objective of the current study was to analyze whether the five facets of DM can predict lower levels of PIU and SU over time in a sample of adolescents. Based on a literature review, Describing, Acting with Awareness, Non-judging, and Non-reacting were expected to predict lower levels of PIU and SU over time. Likewise, the second objective was to evaluate potential interactions between Observing and the other facets of the DM construct in predicting changes in PIU and SU. The Observing facet was expected to predict lower levels of PIU and SU only when combined with high levels of other DM facets, thus mitigating the dysfunctional role that Observing may have in samples of non-meditators.

Method

Participants

A total of 836 students between the ages of 11 and 18 (M_{age} = 14.65 years, SD = 1.74) comprised the baseline of the current study (423 girls and 413 boys). The distribution by age was: 11 (7.4%), 12 (17.2%), 13 (9.9%), 14 (16.5%), 15 (24.4%), 16 (15.8%), 17 (8%), and 18 (0.7%). Of this initial sample, 650 students participated in the study's second wave (retention rate = 77.75%). The criteria suggested by the Spanish Society of Epidemiology (2000) were followed to calculate participants' socioeconomic status: 13.6% low, 15.5% low-medium, 29.1% medium, 16.2% high-medium, and 25.7% high.

Procedure

The participants were students at six randomly selected schools from the entire list of public and private schools in Araba and Bizkaia (Spain). More specifically, two public and four private schools participated in the study. The students participated voluntarily with the consent of their parents or legal guardians. The schools' directors were informed of the study's goals, and after receiving their approval, we sent them information about the research aims and their respective informed consent to the students and their parents. All students completed the questionnaires in their classrooms with a researcher present, and their responses were anonymous. We linked their answers over the two waves of the study (six months apart) using a code that only the participants knew. The Ethics Committee of the University of Deusto approved this study.

Measures

Dispositional Mindfulness. DM was assessed with the Spanish version of the FFMQ adapted to adolescents (Baer et al., 2006; Royuela-Colomer & Calvete, 2016). This self-report questionnaire assesses the five facets of DM (i.e., Observing, Describing, Acting with Awareness, Non-judging, and Non-reacting) with 39 items. Items are answered on a Likert scale ranging from 1 (*never or rarely true*) to 5 (*very often or always true*). Some sample items are "I can easily put my beliefs, opinions, and expectations into words;" "When I do things, my mind wanders off and I'm easily distracted;" and "I perceive my feelings and emotions without having to react to them." The psychometric properties of FFMQ in children and adolescent samples have been examined in previous studies (for a review, see Cortazar, Calvete, Fernández-González & Orue, 2020). In the present study, Cronbach's α coefficients were .75, .75, .82, .86, and .68, for Observing, Describing, Acting with Awareness, Non-judging, and Non-reacting, respectively.

Problematic Internet Use. PIU was assessed with the Generalized Problematic Internet Use Scale 2 (GPIUS2; Caplan, 2010). The GPIUS2 is a 15-item self-report questionnaire that measures generalized and PIU. Items are answered using a Likert scale ranging from 1 (*strongly disagree*) to 6 (*strongly agree*). Some sample items are "When I haven't been online for some time, I become preoccupied with the thought of going online" and "I find it difficult to control my Internet use." For the present study, total

PIU scores were used, and we used the Spanish version of the GPIUS2 (Gámez-Guadix, Orue & Calvete, 2013a). The psychometric properties of the GPIUS2 were found to be adequate in both the original and Spanish versions (Caplan, 2010; Gámez-Guadix et al., 2013a). In this study, Cronbach's α coefficients for the total score were .92 at Time 1 (T1) and .91 at Time 2 (T2).

Substance Use. SU was assessed with the Adolescents Drugs Abuse Inventory (Calvete & Estévez, 2009). This self-report scale comprises nine items about the frequency of consumption of different substances. In the present study, we assessed the frequency of consumption of alcohol, marijuana, hashish, cocaine, speed, and ecstasy. Items are answered using a Likert scale ranging from 0 (*never*) to 5 (*daily*). In the present study, Cronbach's α coefficients for the total score were .64 at T1 and .65 at T2.

Data Analyses

Little's MCAR test indicated that missing data was not random, χ^2 (103) = 218, $p < .000$. Those who only participated in the first wave scored lower on Acting with Awareness ($t = -2.81$, $p = .005$, $d = -0.23$) and Non-judging ($t = -3.31$, $p = .001$, $d = -0.27$) and higher on PIU ($t = 2.59$, $p = .01$, $d = 0.23$), SU ($t = 6.17$, $p = .000$, $d = 0.63$), and age ($t = 8.99$, $p = .000$, $d = 0.75$). Thus, to manage missing values, we used the Full Information Maximum Likelihood (FIML) method with MPLUS 8. The hypothesized model included: (1) cross-sectional associations between all study variables at T1 and T2, (2) autoregressive paths from variables at T1 to the same variables at T2 (PIU and SU), (3) cross-lagged predictive paths from T1 DM dimensions to T2 PIU and SU, and (4) predictive paths from the interaction terms between Observing and the other four DM dimensions (i.e., Acting with Awareness x Observing, Non-judging x Observing, Describing x Observing, and Non-reacting x Observing). Following the standard procedure for examining moderation effects, all DM dimensions were transformed into z scores at T1. The interaction figures were created by means of a macro by Dawson (2018).

The model's goodness-of-fit was evaluated using the comparative fit index (CFI), non-normative fit index (NNFI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Generally, CFI and NNFI values of .90 or higher reflect good fit, and RMSEA and SRMR values lower than .08 indicate excellent fit (Hu & Bentler, 1999).

Preacher and Coffman's (2006) calculator was used to conduct a power analysis, that is, to calculate the probability of detecting an effect, if there is a true effect present to detect. The power in the present study was 99.9% for a sample of 836 participants. All data are available at the Open Science Framework (https://osf.io/p2967/).

Results

Descriptive Statistics and Correlational Analysis

Table 1 shows the descriptive statistics and correlation coefficients between all study variables. Generally, the dimensions of DM were negatively associated with PIU and SU at T1 and T2. Specifically, Acting with Awareness and Non-judging were negatively associated with both PIU and SU at both timepoints, while Describing was negatively associated only with PIU at T1. PIU and SU were positively associated with each other at both timepoints.

Predictive Model

The predictive model via path analysis displayed excellent fit indices $c^2(36, N = 836) = 1085.063$, RMSEA = .052 (90% CI [.034–.072]), SRMR = .02, NNFI = .92, CFI = .98. The model explained 42% of the variance of PIU at T2, and 50% of the variance of SU at T2.

Figure 1 displays the significant and marginally significant longitudinal paths of the model. The autoregressive paths for PIU and SU were statistically significant, indicating the high stability of both variables over time. Regarding predictive paths from T1 DM dimensions to measures of addictive behaviors at T2, Acting with Awareness predicted lower SU, and Non-judging marginally predicted lower PIU; however, Describing predicted an increase in both PIU and SU. Furthermore, an interaction term between Acting with Awareness and Observing predicted changes in PIU.

Figure 2 shows the form of this interaction for adolescents that scored low (z = −1) and high (z = 1) on the Acting with Awareness and Observing dimensions. The predictive association between T1 Observing and T2 PIU was negative when Acting with awareness was high. Finally, an interaction term between Describing and Observing marginally predicted changes in PIU. Figure 3 shows the form of this interaction for adolescents that scored low (z = −1) and high (z = 1) on these dimensions. The findings indicated that Observing could predict less PIU only when Describing was low.

Discussion

The present study longitudinally evaluated the role that the differentiated facets of DM have in protecting against PIU and SU. Likewise, taking into account the maladaptive role of the Observing facet in the face of numerous problems, the interactions between Observing and the other facets of DM were evaluated to predict changes in PIU and SU.

Cross-sectional results, in accordance with previous studies (e.g., Kircaburun et al., 2019; Robinson et al., 2014), indicated negative associations between most of the DM facets (i.e., Acting with Awareness, Non-judging, and Describing) and both SU and PIU. At the longitudinal

Table 1. *Correlations coefficients between variables and descriptive statistics*.

	1	2	3	4	5	6	7	8	9	10
1. T1 PIU										
2. T1 SU	.15**									
3. T1 O	.04	.04								
4. T1 D	−.10**	−.03	.22**							
5. T1 AA	−.37**	−.25**	−.10**	.25**						
6. T1 NJ	−.34**	−.10**	−.27**	.17**	.40**					
7. T1 NR	−.02	.04	.41**	.37**	−.04	−.10**				
8. T2 PIU	.63**	.16**	.02	−.03	−.27**	−.27**	−.01			
9. T2 SU	.13**	.65**	.05	.03	−.21**	−.09*	.02	.16**		
10. Age	.30**	.52**	.07*	−.02	−.34**	−.19**	.02	.30**	.44**	
Mean	1.90	0.32	2.81	3.16	3.50	3.67	2.71	1.90	0.30	14.65
SD	0.91	0.47	0.74	0.67	0.75	0.82	0.65	0.87	0.49	1.74

Note. T1 = Time 1; T2 = Time 2; PIU = Problematic Internet use; SU = Substance use; O = Observing; D = Describing; AA = Acting with awareness; NJ = Non-judging; NR = Non-reacting. * p ‹ .05. ** p ‹ .01.

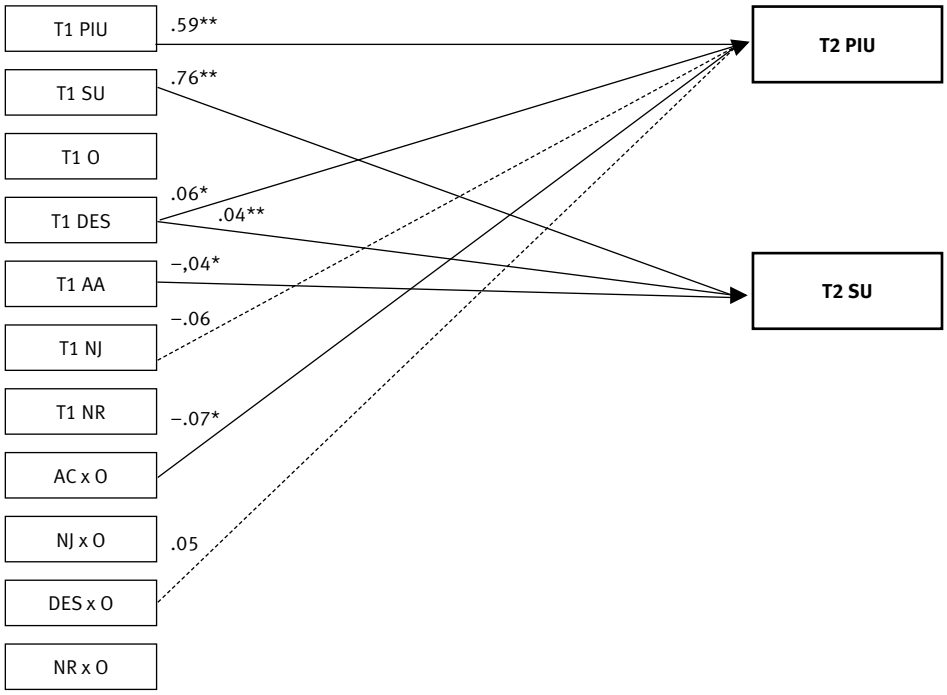

Figure 1. Statistically significant longitudinal paths of the general model.

Note. T1 = Time 1; T2 = Time 2; PIU = Problematic Internet use; SU = Substance use; AA = Acting with Awareness; NJ = Non-judging; NR = Non-reacting; DES = Describing; O = Observing. Values provided are standardized coefficients. *p ‹ .05. **p ‹ .01. ***p ‹ .001. The broken lines represent marginally significant paths (p = .07).

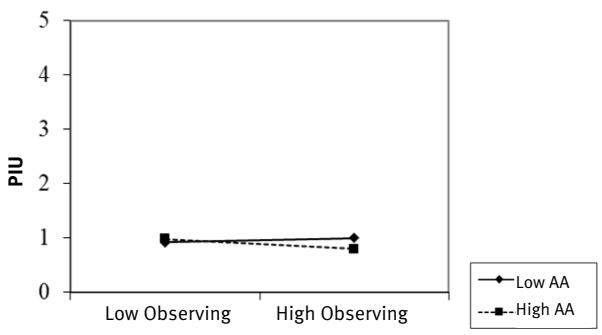

Figure 2. Interaction between Acting with Awareness and Observing for PIU.

Note. PIU = Problematic Internet use; AA = Acting with Awareness.

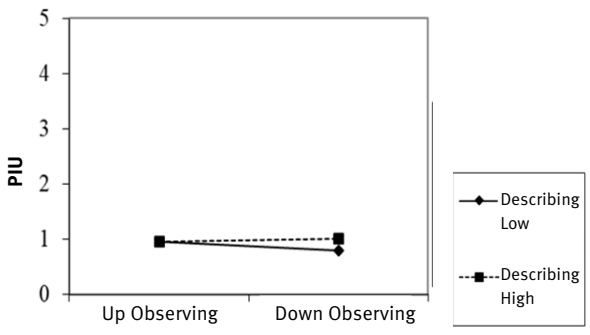

Figure 3. Interaction between Describing and Observing for PIU.

Note. PIU = Problematic Internet use.

level, the Acting with Awareness predicted lower SU levels and Non-judging marginally predicted lower PIU levels over time, which was consistent with the results of previous studies (e.g., Calvete et al., 2017a; Robinson et al., 2014). It has been suggested that adolescents who are more able to not judge their internal experiences and who can act conscientiously may be more likely to accept their negative emotions and realize when they are not behaving in a healthy manner (Sala et al., 2020). Therefore, they may be less likely to attempt to alleviate their emotional distress through SU or PIU than other adolescents.

Contrary to previous studies (e.g., Bowen & Enkema, 2014; Calvete et al., 2017a), Describing predicted increased levels of both PIU and SU. Furthermore, Describing appeared to have a maladaptive role for PIU, especially in combination with high levels of Observing. There are several tentative explanations for these findings. It has been suggested that describing and labeling in words what one feels, if not done properly, may lead to less participation in health-promoting behaviors (Sala et al., 2020). Additionally, it may be that adolescents who observe and describe their emotions the most are those who experience the most negative emotions, and the association between negative emotions and addictive behaviors (Kassel et al., 2007) could therefore explain this result.

In the present study, Observing was not found to be significantly predictor of either SU or PIU. This finding was in line with the results obtained in a meta-analysis conducted by Karyadi et al. (2014), which indicated Observing could not predict SU; however, it contrasted the results obtained by Calvete et al. (2017a), who found that Observing played an adaptive role in relation to PIU. This difference could be because Calvete et al. (2017a) only examined direct paths between DM facets and PIU, while the current study included the interaction terms between Observing and the other facets. In fact, the present results are consistent with previous literature that highlights that this facet can be beneficial in interaction with other DM facets (Desrosiers et al., 2014; Eisenlohr-Moul et al., 2012). In this study, Observing was beneficial against PIU when combined with high levels of Acting with Awareness. Numerous studies have shown how the Observing facet is more adaptive in samples of meditators (e.g., Baer et al., 2006; 2008), which indicates that they may be more able than others to act with awareness, not judge internal experiences, and not react impulsively. Thus, it appears that Observing can protect adolescents from PIU only when they also have the ability to act with awareness. In fact, these results are consistent with the idea that those who score high on Observing should try to develop the Acting with Awareness facet (Sala et al., 2020).

Limitations and Future Research

The present study has some limitations. First, all evaluations were conducted using self-report measures. Future research could include other sources of information, such as peer or/and parental reports. Second, Non-reacting and SU measures showed low reliability, which may be conditioning the results obtained with respect to these variables. In the case of SU, the low consistency may be because the use of one particular substance does not have to be associated with the use of other substances. Third, although this study included a large sample of adolescents, the age range was wide. It would be interesting for future studies to evaluate whether the findings of the present study are maintained or differ in different age ranges. Finally, despite this being a longitudinal study, future studies could include more timepoints or a longer interval between measurements, to observe whether the results are maintained over time.

Despite its limitations, this study also has several strengths, such as its longitudinal design. To our knowledge, most extant research in this area has been cross-sectional; therefore, it is important to perform studies that allow for the evaluation of how the facets of DM protect against SU and PIU over time. Furthermore, this study was conducted with a large sample of adolescents. Considering that many addictive behaviors that persist in adulthood begin in adolescence, it is important to have more research that allows us to determine protective factors for adolescents against increasingly frequent problems, such as PIU and SU.

Conclusion

This study indicates that not all the facets of DM are beneficial against PIU and SU in adolescents. Specifically, it appears that the Non-judging and Acting with Awareness facets may play relevant roles for adolescents when facing these problems. Furthermore, Acting with Awareness seems to protect those adolescents with high levels of Observing. Regarding Describing, it would be interesting for future studies to analyze in detail the role of this facet in combination with other variables, such as levels of stress and emotional distress.

Overall, the findings of this study may provide useful information for the development of new mindfulness-based interventions aimed at preventing addictive behaviors in adolescents. The techniques aimed at improving the different dimensions of DM should depend on the addictive behavior to be prevented. Thus, if the results of this study are confirmed by other studies, interventions aimed at reducing SU could include techniques to enhance the ability to acting with awareness, whereas those aimed at reducing PIU should enhance the ability of adolescents to not judge their internal experiences.

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Conflict of interests

Declarations of interest: none.

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Consensus document on asthma and smoking of the Regional Asthma Forum of SEPAR

Documento de consenso sobre asma y tabaquismo del Foro Autonómico de Asma de la SEPAR

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Abstract

The prevalence of active smoking in adults with asthma is similar in the total population. Smoking is associated with worse clinical control of the disease, a rapid reduction of lung function and a variable response to corticoids. Tobacco consumption negatively affects the quality of life of asthmatic patients as well as increasing the number of medical visits and hospital admissions due to exacerbations. Moreover, smoking entails a higher risk of developing lung cancer, cardiovascular comorbidities and death in asthmatic patients. Nevertheless, current asthma guidelines do not include specific recommendations on the management of smoking asthmatic patients and the treatment of the smoking habit in this subpopulation. For this reason, a narrative review of the literature was carried out for consensus using a nominal group methodology developed throughout 2019 to extract practical recommendations that would allow the diagnosis and treatment of asthma in smokers, as well as the treatment of smoking in asthmatics, to be improved. The conclusions and recommendations were validated at the SEPAR national congress of the same year. Among the most relevant, the need to address smoking in people with asthma through health advice, pharmacological treatment and behavioral therapy was emphasized, as this is a factor that negatively impacts the symptoms, prognosis and response to asthma treatment. In smokers with suspected asthma, the presence of emphysema and the differential diagnosis of other diseases should be evaluated and the impact of smoking on the result of diagnostic tests should be considered. It is also concluded that smoking reduces the response to treatment with inhaled corticosteroids, which is why combined therapy with bronchodilators is recommended.

Keywords: Asthma; smoking; treatment; consensus; recommendations.

Resumen

La prevalencia de tabaquismo activo en adultos con asma es similar a la de la población general. El tabaquismo se asocia con un peor control clínico de la enfermedad, una disminución acelerada de la función pulmonar y una respuesta irregular a la terapia con glucocorticoides. El consumo de tabaco impacta negativamente en la calidad de vida de los pacientes asmáticos y provoca un incremento en el número de visitas y de hospitalizaciones por exacerbaciones. Además, el tabaquismo aumenta el riesgo de cáncer de pulmón, comorbilidades cardiovasculares y muerte en pacientes asmáticos. A pesar de todo ello, las guías actuales del manejo del asma no incluyen recomendaciones específicas para el manejo de los pacientes asmáticos fumadores. Por este motivo, se procedió a una revisión narrativa de la literatura para un consenso mediante metodología de grupo nominal desarrollada a lo largo del año 2019 para extraer recomendaciones prácticas que permitieran mejorar el diagnóstico y el tratamiento del asma en fumadores, así como el tratamiento del tabaquismo en asmáticos. Las conclusiones y recomendaciones fueron validadas en el congreso nacional de la SEPAR del mismo año. Entre las más relevantes, se incidió en la necesidad de abordar el tabaquismo en las personas con asma mediante consejo sanitario, tratamiento farmacológico y terapia conductual, al ser un factor que impacta negativamente en la sintomatología, el pronóstico y la respuesta al tratamiento del asma. En el fumador con sospecha de asma, se debe evaluar la presencia de enfisema y el diagnóstico diferencial de otras enfermedades y considerar el impacto del tabaquismo en el resultado de las pruebas diagnósticas. También se concluye que el hábito tabáquico reduce la respuesta al tratamiento con corticoides inhalados, por lo que se recomienda terapia combinada con broncodilatadores.

Palabras clave: Asma; tabaquismo; tratamiento; consenso; recomendaciones.

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Smoking is as prevalent in adults with asthma as it is in the general population (Cerveri et al., 2012). Furthermore, it has been estimated that around half of adult asthmatics are smokers or ex-smokers (Thomson, Chaudhuri & Livingston, 2004).

Smoking has significant negative effects on clinical symptoms, prognosis, and response to asthma treatment (Polosa & Thomson, 2013). Likewise, it is associated with more severe asthma and a worse response to glucocorticoid treatment (Polosa et al., 2013). In the most severe cases, it contributes to chronic airflow obstruction, leading to the development of chronic obstructive pulmonary disease (COPD), and is associated with a clinical profile called asthma-COPD overlap (ACO) (Gelb, Christenson & Nadel, 2016).

Moreover, it has been observed that active smokers, especially women or those patients with allergic rhinitis, have a higher risk of developing asthma, which is why smoking could contribute to the pathogenesis of the disease. In addition, it has been shown that smoking cessation reduces symptoms and improves lung function. However, asthmatic patients have a low rate of smoking cessation, which points to the need to improve strategies aimed at treating smoking in these patients (Cerveri et al., 2012).

Current asthma management guidelines do not include specific recommendations for managing asthmatic patients who smoke. For this reason, the Asthma Forum (FORASMA) of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) decided to review the available literature to develop this management consensus with the FORASMA panel.

Method

A Coordinating Committee (CC) was formed, comprising three experts (FJA, MBA and JSCM), to supervise the quality and suitability of the consensus processes and methodology (Supplementary Material). A Recommendations Development Group (RDG) was also set up, with seven experts (EPE, JLGR, JGS, FJC, PJRP, JARM and CAJR), whose main function was to review and synthesize the available evidence for the manuscript and formulate conclusions (C) and recommendations (R). To validate the C and R formulated, a Recommendations Validation Group (RVG) was set up with 54 experts from different societies of pulmonology specialists in the autonomous communities of Spain.

A non-systematic literature search was carried out in PubMed and Scopus databases, limited to articles from the last 10 years in English or Spanish dealing with the thematic blocks to be covered in this study: the impact of smoking on the development and clinical treatment of asthma, the impact of smoking status on differential diagnosis and interpretation of diagnostic tests, prognosis and follow-up; and the treatment of asthma in smokers and of smoking in asthmatics. To this end, the base keywords were tobacco, smoking and/or asthma, combined with other terms and their synonyms to refine searches (diagnosis, treatment/therapy, prognosis, smoking cessation, inhaled toxic substances, cannabis, passive smoking, e-cigarette etc.) The search results were reviewed and discussed by the RDG in order to identify the most relevant evidence regarding the management of asthma in smokers. Based on this review and the discussion conclusions, the RDG prepared some C and Rs to be evaluated in a face-to-face meeting of the 2019 Asthma Forum of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), which constituted the RVG. The recommendations were discussed in person, and RVG members expressed the extent to which they agreed or disagreed on a 1-4 scale (1 strongly disagree, 4 strongly agree). In the first round, all the Cs and Rs drawn up by the RDG were evaluated, the results were aggregated and the vote percentages of responses 1 and 2 (disagreement) and of 3 and 4 (agreement) were calculated. R and Cs with more than 70% agreement were considered consensual, while those scoring between 35% and 70% of agreement and those with 35% or below were considered doubtful or incompatible, respectively, and were discussed in a later review. Additional recommendations proposed by the panellists were collected. The modified and additional proposals were voted by the RVG in a second round using an online televoting system.

Finally, the CC and the RDG drafted the manuscript, which was submitted to successive reviews by the same group until final approval by all signatories.

Smoking as a risk factor for developing asthma

The effect of smoking on the etiology of asthma in adults continues to be a matter of debate (Bakakos, Kostikas & Loukides, 2016). In most longitudinal studies, smoking is a risk factor for asthma development (relative risk from 1.4 to 3.0) (Coogan et al., 2015; Godtfredsen, Lange, Prescott, Osler & Vestbo, 2001; Lundback, Ronmark, Jonsson, Larsson & Sandstrom, 2001; Pallasaho et al., 2011; Plaschke et al., 2000; Toren, Olin, Hellgren & Hermansson, 2002; Vignoud et al., 2011). However, some studies do not report this association (Anto et al., 2010; Ekerljung et al., 2008; Huovinen, Kaprio & Koskenvuo, 2003; Toren et al., 2011).

Link to sex

Other studies limit this relationship to the female sex, with a higher incidence of asthma observed in women who smoke (Nakamura et al., 2009; Piipari, Jaakkola, Jaakkola & Jaakkola, 2004). However, there are studies with contradictory evidence. On the one hand, it was shown that in the Canadian population, women who smoked had

a 70% higher prevalence of asthma than non-smokers, and that the link between smoking and asthma was stronger in women under 25 years of age and those with higher smoking intensity (Chen, Dales, Krewski & Breithaupt, 1999). Conversely, in Japan a relationship between smoking and the onset of asthma was observed only in men (Nakamura et al., 2009). The annual report of the United States Department of Public Health (Department of Health and Human Services, 2014) concludes that there is sufficient evidence to infer a causal relationship between smoking and asthma exacerbations in adults, but not between active smoking and the incidence of asthma.

Some studies indicate that ex-smokers also have an increased risk of asthma, determined at 1.34 in men and 2.38 in women (Piipari et al., 2004). However, this data is not supported by other studies (Polosa et al., 2014).

Relationship with atopy and rhinitis

The association between smoking and asthma can be modified by the presence of atopy. In the European Community Public Health Survey (European Community Respiratory Health Survey [ECRHS]) (Anto et al., 2010), the frequency of asthma in atopic adults was higher among smokers compared to non-smokers (odds ratio [OR]: 1.45; 95% confidence interval at 95% [95% CI]: 0.81-2.61), while the opposite trend was observed for non-atopic patients (OR: 0.67; 95% CI: 0.40-1.15). However, in a Swedish study (Plaschke et al., 2000), while the probability of asthma onset increased among atopic smokers (OR: 1.8; 95% CI: 0.8-4.2) compared to non-smokers, this was even higher among non-atopic compared to atopic patients (OR: 5.7; 95% CI: 1.7-19.2). Furthermore, an increased risk of asthma was observed among smokers with allergic rhinitis in a cohort of Italian patients (Polosa et al., 2008).

Passive smoking and asthma in children and adolescents

Passive smoking is a risk factor for developing asthma in children (Gilliland et al., 2006; Kalliola et al., 2013). A systematic review and meta-analysis of 76 studies showed that the risk of asthma in children exposed to pre- or postnatal smoking increased from 21% to 85% (Burke et al., 2012). Smoking during pregnancy can thus clearly increase the risk of asthma in offspring (Gilliland, Li & Peters, 2001; Neuman et al., 2012), and it is striking that approximately 50% of pregnant women do not quit smoking during this period (Schneider, Huy, Schutz & Diehl, 2010). Two large longitudinal studies with follow-ups of 14 and 20 years, respectively, have demonstrated the relationship between asthma and prenatal exposure to tobacco toxins (Grabenhenrich et al., 2014; Hollams, de Klerk, Holt & Sly, 2014). Furthermore, it has been shown that 41% of asthmatic children in Spain are passive smokers in their family environment, thus worsening their baseline situation and increasing the frequency of asthmatic attacks involving hospitalization (Lopez Blazquez, Perez Moreno, Vigil Vazquez & Rodriguez Fernandez, 2018).

Finally, smoking increases the risk of asthma among adolescents, especially in those without atopy and in those exposed to maternal smoking during pregnancy (Chen et al., 1999). Adolescents smoking more than 300 cigarettes/year have a much higher risk of developing asthma (OR 3.9; 95% CI: 1.7-8.5) than non-smokers (Gilliland et al., 2006).

Table 1 summarizes the clinical and functional effects of smoking in asthma, while Table 2 summarizes the conclusions and recommendations agreed on with reference to all of the above.

Table 1. *Summary of the clinical and functional effects of smoking in asthma. Modified from (Polosa et al., 2013).*

Adverse effects of smoking on asthma	Detailed effects
Increased prevalence of asthma	High prevalence, especially in women who smoke compared to non-smokers (especially those under 25 years of age). The relationship between smoking and gender is more evident in heavy smokers compared light or non-smokers (dose-effect relationship).
Incidence of asthma	Smoking is a strong predictor of the development of new cases of asthma in adult allergic patients (allergic rhinitis) with a clear dose-response effect to tobacco exposure.
Increased morbidity and mortality	Smoking asthmatics are at high risk of more severe symptoms, more exacerbations and poorer quality of life, as well as an increase in severe asthma attacks and high mortality.
Increased severity of asthma	Smoking and smoking duration are closely linked, in a dose-dependent way, to the severity level of asthma. The closest association with severity has been observed in smokers of >20 packs/year.
Uncontrolled asthma	The relationship between smoking and poor asthma control has been described in population studies and in controlled studies.
Faster decline in lung function	Lung function decline is faster in smoking asthmatics than non-smokers with asthma, although some negative studies exist.
Persistence of airflow obstruction	A proportion of smokers with asthma develop AFO.
Glucocorticoid insensitivity	Smoking asthmatics are less sensitive to the beneficial effect of glucocorticoids in relation to respiratory symptoms and lung function, regardless of the route of administration.

Table 2. *Conclusions and recommendations on smoking as a risk factor for developing asthma.*

• Smoking should be addressed in asthmatics as it can condition clinical symptoms, prognosis and response to asthma treatment.
• Smoking, especially in women, is a risk factor for developing asthma and is correlated with cumulative tobacco use.
• Patients with allergic rhinitis who smoke are at increased risk of developing bronchial asthma.
• Smoking during pregnancy increases the risk of asthma for the child, so prevention and treatment are essential.
• Passive smoking increases the risk of asthma in children and adolescents and increases severity if already present.

Diagnosis, prognosis and monitoring of asthma in smokers

Current asthma management guidelines do not include specific treatment recommendations for smoking asthmatic patients. It is therefore necessary to improve understanding of the particularities of asthma in smoking patients, as well as what constitutes the most effective treatment for these patients.

How smoking affects the diagnosis of asthma and ACO

Measuring lung function, especially obstruction reversibility, serves to confirm the diagnosis of asthma (Executive Committee of GEMA 5.0). This test has high specificity, but low sensitivity, so a negative result requires further testing. However, in a compatible clinical setting, a positive result mostly ensures a diagnosis of asthma.

In smokers, the possibility of obtaining a bronchodilator response may be hampered by tobacco use. This response is sometimes assessed after treatment with high-dose inhaled corticosteroids. Here, it has been observed that treatment with 1000 µg of fluticasone propionate daily for 3 weeks in asthmatic active cigarette smokers did not produce significant changes in the morning peak expiratory flow (PEF), the mean value of forced expiratory volume in the first second (FEV_1) and PC20 after methacholine challenge (Chalmers et al., 2002). Regarding the bronchodilator response after treatment with oral steroids, a randomized, placebo-controlled, crossover study assessed active smokers, ex-smokers and never-smoker asthmatics after taking prednisolone (40 mg daily) or placebo for 2 weeks. Never-smoker patients showed a significant improvement in FEV_1 (237 ml) and morning PEF (36.8 L/min). With smokers and ex-smokers, there were no significant changes in any of the symptom control scores, while prednisolone treatment only led to an improvement in morning and evening PEF (29.1 and 52.36 L/min, respectively) (Chaudhuri et al., 2003).

Usefulness of FENO in the diagnosis of asthma in smokers

Various authors have suggested that fraction of exhaled nitric oxide (FeNO) values could serve as a sensitive and specific diagnostic tool. Recently, the combination of FEV_1 and FeNO results has been described as providing high sensitivity and specificity for the diagnosis of asthma (Giovannelli et al., 2016). High FeNO values would thus be highly compatible with asthma diagnosis, especially in patients with airway obstruction.

However, there is some controversy about the reference values for FeNO in smoking patients. The cut-off point has been set at 50 parts per billion (ppb) in adults (Dweik et al., 2011). According to the Spanish Guide for Asthma Management (GEMA) (Comité Ejecutivo de GEMA 5.0), the FeNO value is especially sensitive and specific for the diagnosis of asthma in non-smoking patients not using inhaled glucocorticoids (IGC), particularly if associated with reduced FEV_1. However, a normal FeNO value does not exclude the diagnosis of asthma, especially in non-atopic people.

In most studies it has been observed that FeNO values are lower in active smokers than in non-smoking asthmatics (Giovannelli et al., 2016). The 30% lower cut-off value for smokers is associated with a specificity of 90% (22 vs. 31 ppb) and a sensitivity of 90% (7 vs. 10 ppb) (Malinovschi, Backer, Harving & Porsbjerg, 2012). However, this may apply to allergic asthmatic patients, but not to those without atopy (Rouhos et al., 2010). FeNO levels can discriminate the diagnosis of asthma in allergic vs. non-atopic, but only in non-smoking patients (Giovannelli et al., 2016).

A reduction in FeNO has been observed in asthmatics, passive and active smokers (Jacinto, Malinovschi, Janson, Fonseca & Alving, 2017), so passive smoking should also be considered when using FeNO as a diagnostic criterion for asthma (Nadif et al., 2010). Values may be associated with a sputum eosinophil count of ≥3%, although the IGC dose, and the patient's smoking level and atopy must be taken into account. In a retrospective study (Schleich et al., 2010), FeNO values discriminating and predicting sputum eosinophilia of >3% were ≥41 ppb. Sensitivity was 65% and specificity 79%, and there was a trend towards a lower threshold in smokers (27 ppb) compared to non-smokers. Finally, in COPD patients, FeNO values are able to discriminate between different types of patients (Alcázar-Navarrete, Romero-Palacios, Ruiz-Sancho & Ruiz-Rodríguez, 2016) and are associated with the presence of eosinophils in sputum (Chou et al., 2014), characteristically found in ACO. In a cross-sectional study carried out in Spain, FeNO levels were high in patients defined as ACO, with a cut-off point of 20 ppb for the diagnosis of ACO (Alcázar-Navarrete et al., 2016). Therefore, we conclude that FeNO can be a useful marker for detecting ACO in COPD patients, thus adding a clinical value to the determination of eosinophils in peripheral blood.

Inflammatory profile in smoking asthmatics

Smoking asthmatics have fewer eosinophils and a greater number of mast cells in the submucosa of the airway wall. They also present greater remodelling of the airways, with increased epithelial thickness and goblet cell hyperplasia. However, the mechanisms by which smoking modifies airway inflammation are currently unknown. Similarly, the mechanism underlying the decreased response to glucocorticoids is not known (Fattahi et al., 2011).

A strong association has been described between eosinophil levels and the risk of hospitalization in patients without a history of smoking (hazard ratio [HR]: 2.16; 95% CI: 1.27-3.68; p = 0.005)] but not in active smokers (HR: 1.00; 95% CI: 0.49-2.04; p = 0.997) (Kerkhof et al., 2018). An analysis of data from the National Health and Nutrition Examination Survey (NHANES) (N = 3162 patients with asthma and eosinophilia between 6 and 64 years of age) found that higher eosinophil values were linked to a greater number of asthma exacerbations in children but not adults (Tran, Khatry, Ke, Ward & Gossage, 2014). Smoking is believed to play a role in these results as more than half of these adults said they were smokers or ex-smokers. Therefore, smoking appears to exert a suppressive effect on eosinophilic inflammation (van der Vaart, Postma, Timens & ten Hacken, 2004).

Furthermore, non-smoking asthmatics with high levels of eosinophils have been shown to have a higher risk of suffering new exacerbations. A study by (Kerkhof et al., 2018) monitoring 2,613 asthmatics found that those patients with high levels of eosinophils ($\geq 0.35 \times 10^9$ cells/L) had a higher risk of new exacerbations, especially if they were non-smokers or ex-smokers (HR: 1.84; 95% CI: 1.20-2.80; p = 0.005) but not if they were active smokers (HR: 0.88; CI95%: 0.44-1.76; p = 0.73).

Prognosis and follow-up

Smoking has been associated with increased severity of asthma, poorer quality of life, accelerated loss of lung function, and poorer response to corticosteroid treatment. Likewise, asthmatics who smoke need emergency services and hospitalization more frequently.

A study with 760 severe asthmatics, both smokers and non-smokers (Thomson et al., 2013), showed that active smokers had lower scores on the asthma control questionnaire (ACQ) compared with non-smokers, in addition to a greater number of medical visits and use of emergency services in the previous year. Additionally, smokers had worse scores on the EuroQol scale and higher scores on the HAD scale (Hospital Anxiety and Depression Scale), revealing a higher degree of emotional stress.

Current evidence confirms that active smokers with asthma have more severe symptoms and worse control of the disease than patients with asthma who have never smoked (McCoy et al., 2006; Pedersen et al., 2007; Polosa et al., 2011; Schatz, Zeiger, Vollmer, Mosen & Cook, 2006; Siroux, Pin, Oryszczyn, Le Moual & Kauffmann, 2000; Thomson et al., 2013; Westerhof et al., 2014). In addition, it has been observed that ex-smokers also have worse control of the disease in comparison to never-smokers (Pedersen et al., 2007).

Additionally, both active and passive smoking increase hospital admissions rates and worsen the quality of life of asthmatics (Sippel, Pedula, Vollmer, Buist & Osborne, 1999). Moreover, the death rate is higher among active smokers with asthma than among never-smokers (Marquette et al., 1992).

Lung function in smokers

Bronchial asthma can cause faster loss of lung function, although loss is much more rapid in asthmatic smokers compared to non-asthmatics and non-smoking asthmatics (Apostol et al., 2002; Grol et al., 1999; Hancox, Gray, Poulton & Sears, 2016). Moreover, in terms of decreased FEV_1, the combination of active smoking and asthma has a synergistic (Lange, Parner, Vestbo, Schnohr & Jensen, 1998) or additive effect (James et al., 2005). It has been shown that smoking reduces FEV_1 by a ratio of 69 ml per 100/year in smokers and by 1.5% of the FEV_1/FVC ratio (forced vital capacity) ratio in asthmatic patients diagnosed de novo (Jaakkola et al., 2019). Finally, an annual decrease in FEV_1 of 58 ml was noted in actively smoking asthmatics compared to 33 ml in those who did not smoke (Lange, Colak, Ingebrigtsen, Vestbo & Marott, 2016).

It is estimated that approximately 20% of patients with asthma or COPD have ACO. To assess the effect of lung function loss in ACO patients, in addition to the risk of exacerbations and mortality, the authors of the Copenhagen City Heart Study conducted a subsequent study with the same cohort of patients (Lange et al., 2016). Results showed that patients with ACO and late-onset asthma experienced a drop in FEV_1 of 49.6 ml/year, significantly higher than that of patients with early-onset asthma ACO or patients with COPD (39.5 ml/year) or healthy non-smoking patients. The authors concluded that patients with ACO have a worse prognosis, although this depended on the age of asthma diagnosis, with a worse prognosis for those aged over 40 years when diagnosed. This implies the need for close monitoring of such patients in order to prevent rapid deterioration of lung function and exacerbations. A study by (Tommola et al., 2016) which analyzed the lung function of recently diagnosed asthmatic smokers and non-smokers, observed that those with a cumulative consumption of >10 p/a (packs/year) had an accelerated loss of lung function.

Clinical control of asthma and morbidity and mortality in smokers

With regard to clinical control, smoking has been associated with poor long-term asthma control. The

Seinäjoki Adult Asthma Study (SAAS) (Tuomisto et al., 2016) followed patients with a recent diagnosis of late-onset asthma (N = 203) over a period of 12 years. During this time, it was found that 34% of the patients were controlled, 36% partially controlled, and 30% poorly controlled. The percentage of active smokers was higher in the partial (60.8%) and poor control (61.7%) groups than in the group of controlled patients (36.2%). Poor asthma control was linked to male sex, older age, high doses of IGC or combination with a long-acting beta-agonist (LABA), and history of smoking. Each increase of 10 packs/year increased the risk of worse asthma control (OR: 1.82; 95% CI: 1.06-3.12; p = 0.03). Another study with 200 patients and a two-year follow-up showed that smoking >10 p/a was the most important independent predictor of asthma severity (Loymans et al., 2016).

A prospective analysis in the Copenhagen General Population Study (Colak, Afzal, Nordestgaard & Lange, 2015) showed that 6% of all the individuals studied (N = 94,079) had asthma (2,304 non-smokers, 2,467 ex-smokers, and 920 active smokers). The HR for asthma exacerbations in asthmatics was 11 (95% CI: 5.8–22.0) for non-smokers, 13 (95% CI: 6.2–29.0) for ex-smokers and 18 (95% CI: 8.2–39.0) for active smokers. It should be noted that the risk of lung cancer, cardiovascular comorbidities and death only increased in smokers with asthma. It was thus shown that smoking is the main factor in poor prognoses for asthmatics, which is why it has been included in a predictive model of exacerbations (Loymans et al., 2016).

Smoking and use of resources in asthmatic patients

Additionally, smoking predicts a greater frequency in the use of emergency services and an increase in mortality in patients with a history of exacerbation who have required mechanical ventilation (Marquette et al., 1992). A study of 344 asthmatics (Kauppi, Kupiainen, Lindqvist, Haahtela & Laitinen, 2014) showed that the risk of needing ER visits was higher in smokers (HR: 3.9) or ex-smokers (HR 1.8) compared to non-smokers. In a multivariate analysis, the independent risk factors were active smoking (HR 3.6), poorer health-related quality of life (HRQoL) (HR 2.5), and FEV_1 <65% (HR 2.2).

Prognosis of ACO

Mortality and exacerbation frequency in ACO patients have been assessed and compared with those of patients with asthma and airflow obstruction and patients with COPD (Kurashima et al., 2017). Patients with asthma and airflow obstruction had a better prognosis than patients with ACO or COPD, with the prognosis of ACO patients being better than those with COPD. A population study (Diaz-Guzman, Khosravi & Mannino, 2011) with 15,203 individuals recorded asthma with COPD in 357 subjects (2.7%), COPD in 815 (5.3%), and asthma in 709 (5.3%). The presence of both asthma and COPD was associated with greater airway obstruction as well as greater risk of mortality (HR = 1.83) throughout the study follow-up.

Taking into account all previous evidence, the RVG agreed on the conclusions and recommendations shown in Table 3 with regard to the diagnosis, prognosis and follow-up of asthma in smokers.

Treatment of asthma in smokers and ex-smokers

Challenges in the treatment of asthma in smokers and ex-smokers

The main problem for smoking asthmatics is the reduced response to IGC treatment, leading to poor control of asthma symptoms (Thomson, 2018). In fact, it has been proposed that the effect of IGC treatment in smoking asthmatics be assessed considering multiple indicators, since the observation of a single clinical result may suggest that the treatment is not effective (Hayes, Nuss, Tseng & Moody-Thomas, 2015).

Table 3. *Conclusions and recommendations on the diagnosis, prognosis, and follow-up of asthma in patients who smoke.*

- Smoking favours the loss of lung function in asthmatics, especially if the cumulative consumption is over 10 p/a and if asthma is diagnosed after the age of 40 years.
- In all smoking asthmatics with severe and not totally reversible obstruction, it is recommended that the presence of emphysema is assessed by means of a carbon monoxide diffusion capacity test (DLCO) and alpha-1-antitrypsin serum levels are determined (Comité Ejecutivo de GEMA 5.0).
- In smoking asthmatics with severe and not totally reversible obstruction, computerized axial tomography (CAT) should be performed so that other diseases that can simulate asthma are ruled out (tumours, bronchiolitis, bronchiectasis, syndrome Churg-Strauss, etc.) (Chung et al., 2014; Comité Ejecutivo de GEMA 5.0).
- In the diagnosis of asthma, it should be taken into account that FeNO (exhaled nitric oxide test) values can be up to 30% lower in smokers than in non-smokers.
- In the diagnosis of asthma, it should be remembered that exposure to air polluted by tobacco smoke (passive smoking) is also associated with lower FeNO values.
- In the diagnosis of asthma, it should be taken into account that patients who smoke present an alteration of the inflammatory profile in blood and sputum, with a lower proportion of eosinophils and indications of neutrophilic inflammation.
- Smoking asthmatics have poorer clinical control of the disease, greater risk of exacerbations, cardiovascular diseases and higher mortality.
- Patients with asthma, airflow obstruction and a history of smoking >10 p/a (patients considered ACO) have higher mortality and risk of exacerbations than patients with asthma and airflow obstruction, but with cumulative consumption <10 p/a.

The inflammatory mechanisms involved in treatment response are currently unclear, but smoking is known to induce a rise in CD8 cells and neutrophils, which could alter the response to treatment. The main mechanism proposed for this reduced response is the decrease in the activity of the enzymatic system of histone deacetylase 2 (HDAC2). The efficacy of various HDAC2 enhancers, including low-dose theophylline, is therefore being studied for the treatment of smoking asthmatics. Anti-inflammatory therapies, including phosphodiesterase 4 (PDE4) inhibitors and p38 mitogen-activated protein kinase (MAPK) inhibitors (Spears, Cameron, Chaudhuri & Thomson, 2010; Thomson, 2018), are also being developed.

The RVG reached complete consensus on the recommendations related to this section, as shown in Table 4.

Influence of smoking on the response to inhaled corticosteroids

Multiple studies have compared the different IGC treatments in smoking and ex-smoking asthmatics. The OLiVIA study stands out, comparing treatments with extrafine and non-extrafine particle IGC in asthmatic smokers. However, no differences were observed in terms of efficacy and safety for these treatments (Cox et al., 2017).

Lastly, tobacco smoke has been shown to increase viral replication (Feldman & Anderson, 2013), and while inhaled glucocorticoids protect against rhinovirus-induced airway inflammation, they do not do so against viral replication (Bochkov et al., 2013), which could partly explain the poor response to treatment among smokers.

Influence of smoking on the response to bronchodilators (combination of corticosteroids and bronchodilators)

It is believed that smoking asthmatics may respond similarly to patients with chronic obstructive pulmonary disease (COPD). As a result, some studies have considered the possibility of using anticholinergic agents for the treatment of these patients (Ahmad & Singh, 2010).

Treatment of smoking in asthmatic smokers

There is evidence indicating that asthmatics need a different approach to the treatment of smoking than other smokers. Around 25% of asthmatics are smokers, but between 8 and 35% of them deny this in the interview with the health professional. The interview with asthmatics on smoking should therefore always be biochemically validated (through co-oximetry or the determination of cotinine in biological fluids) (de Granda-Orive et al., 2001). It should also be noted that although most are aware of the need to quit smoking, it is often difficult for them to do so (Perret, Bonevski, McDonald & Abramson, 2016; Saba, Dan, Bittoun & Saini, 2014), and the therapeutic intervention must therefore be adjusted to their characteristics. Some data suggest that people with asthma start smoking at an earlier age (Avallone et al., 2013). In addition, although attempts to quit smoking may be more frequent in smokers with asthma, they are shorter in duration than in non-asthmatics (Vozoris & Stanbrook, 2011).

The motivation to quit will be different for an asthmatic than for a healthy smoker or one without asthma and will be influenced by age, educational level and fear of exacerbations (Tankut, Mowls & McCaffree, 2015). Some studies have shown that asthmatics have a higher level of anxiety and this can lead to a greater risk of exacerbations (McLeish, Farris, Johnson, Bernstein & Zvolensky, 2015). It has also been observed that withdrawal symptoms in asthmatics are longer and more intense, which may imply a greater risk of relapse. Moreover, asthmatic women have been observed to have a higher degree of nicotinic dependence than women without the pathology (Vozoris et al., 2011). Thus, longer and more specific treatments, with a higher level of intensity, are recommended (McLeish, Farris, Johnson, Bernstein & Zvolensky, 2016).

Current recommendations advocate specific and intensive interventions that make the relationship between smoking and worse clinical outcomes, the greater number of attacks and exacerbations and worsening lung function clear to the patient. The concept of keeping lung age as low as possible by quitting smoking should also be introduced (Perret et al., 2016).

Smoking cessation treatment should be offered to all smokers who are able and willing to quit.

The combination of psychological counselling and pharmacological treatment offer the best approach to the treatment of smoking in asthmatic smokers (Cahill, Stevens, Perera & Lancaster, 2013; Guichenez, Underner & Perriot, 2019; Jimenez-Ruiz et al., 2015; Perret et al., 2016; Rigotti, 2013). Both areas are outlined below from a practical perspective.

Table 4. *Conclusions and recommendations for the treatment of asthma in smokers.*

- Smoking asthmatics have a worse response to inhaled corticosteroid treatment.
- For smoking asthmatics, combination therapy (inhaled corticosteroids + bronchodilators) is more effective in reducing symptoms than therapy based solely on inhaled corticosteroids.
- Smoking asthmatic patients benefit from anticholinergic treatment to a greater extent than non-smoking asthmatics.

General aspects of counselling

The advice given to asthmatic smokers should include the following aspects (Jimenez-Ruiz et al., 2015):

1. An explanation of the close link between smoking and asthma should be provided with empathy and an understanding of the patient's attitude to the subject. The health professional must clearly explain to the smoker that quitting smoking is the most effective health measure to control the pathological process.
2. Smokers should be shown the need to find a day (D-day) on which to start. It is highly recommended that they choose a day which is expected to be calm, with few high-risk situations and on which the subject is willing to make a serious effort not to smoke at all.
3. The smoker must identify those daily life situations which they most closely associate with smoking, thereby helping to avoid them from D-day on. If they are unavoidable, the smoker should think about developing alternative behaviours to smoking in such circumstances.
4. Smokers should be informed of the different withdrawal symptoms that they may suffer as a result of the smoking cessation process. Informing them that symptoms last approximately 8-12 weeks and that they are intense and numerous during the first 4-6 weeks is essential in this regard. The use of pharmacological treatment is key to controlling withdrawal symptoms and helps avoid relapses and ensure success in the attempt to quit (Leone et al., 2020).

Psychological approach

The combination of several techniques is recommended for this group of smokers in order to address the different factors maintaining smoking behaviour. Both behavioural and cognitive-behavioural techniques can be used (Becoña, 2004; Fernández Castillo & Esteban de la Rosa, 2017; Lancaster & Stead, 2017; Perret et al., 2016).

- The behavioural model suggests several coping techniques: a) stimulating control, which consists of breaking the association between external stimuli and smoking behaviour to facilitate cessation; b) systematic desensitization, through which patients are exposed to situations of "risk", from least to greatest difficulty for them; and c) reinforcement of abstinence behaviour and patients learning to congratulate and reward themselves. To this end, it is important not to reinforce behaviours indiscriminately, but only those that help maintain abstinence. Food should be avoided as reinforcement (Becoña, 2004; Fernández Castillo et al., 2017; Lancaster et al., 2017; Perret et al., 2016).
- The cognitive-behavioural model also has several coping techniques: a) cognitive restructuring, which helps the patient to identify erroneous ideas regarding smoking; b) finding a thought process that can prevent those automatic and recurring thoughts preceding smoking behaviour; c) distraction techniques, the main aim of which is to train subjects to distract themselves from thoughts and feelings linked to the urge to smoke; d) self-instructions, through which patients can try to reduce distress by guiding the dialogue towards overcoming difficulties; e) self-control training, through which subjects learn to reduce activation at a physiological and cognitive level; f) imagination techniques, which allow patients to modify thoughts using their imagination (this can be achieved by substituting a negative image); and g) problem solving, through which patients learn to solve problems in ways that reduce the probability of resorting to smoking as a coping strategy (Becoña, 2004; Fernández Castillo et al., 2017; Lancaster et al., 2017; Perret et al., 2016).

Pharmacological approach

Controlled studies analyzing the efficacy and safety of the use of different drugs for smoking cessation in asthmatic smokers are very scarce. However, three studies are worth highlighting (Lancaster et al., 2017; Perret et al., 2016; Tonnesen et al., 2005) whose main conclusion is that, in addition to psychological counselling, asthmatics who want to quit smoking should receive drug treatment, and that this should extend for over three months. In addition, no safety problems have been detected with the use of these drugs in asthmatic smokers (Lancaster et al., 2017; Perret et al., 2016; Tonnesen et al., 2005). Three types of drug treatments can be applied to treat smoking in asthmatic smokers: Nicotine replacement therapy (NRT), bupropion and varenicline. Some tips in this regard include:

1. For NRT, gum, tablets, mouth spray and nicotine patches can be prescribed, which are the treatments available in Spain. It is highly recommended that patches, a prolonged form of nicotine administration, be combined with gum, tablets or mouth spray as a temporary form of administration. Using both types of treatment helps smokers to better control withdrawal symptoms. Moreover, in terms of drug interactions, NRT does not conflict with bronchodilator drugs or inhaled steroids used by asthmatic patients.
2. Bupropion should be prescribed at a dose of 150 mg every 12 hours for a period of 12 weeks (Fiore et al., 2008; Gratziou et al., 2014; Jimenez-Ruiz et al., 2015). It should be taken into account that this is a drug which is metabolized by the liver, through the P450 enzyme system, and that this fact may be associated with important interactions with other medications occasionally used by some asthmatics: drugs that affect CYP2B6, drugs metabolized by CYP2D6, and

enzyme inducers/inhibitors (Tonstad et al., 2006). Finally, it should be remembered that bupropion produces adverse effects more frequently than NRT or varenicline. The most common include insomnia, headaches, and dry mouth (Tonstad et al., 2006). It should be used with caution in clinical situations when the seizure threshold is reduced since the production of seizures is another of the adverse effects that can appear in 0.1% of subjects using this medication. All these data favour the use of bupropion only as a second-choice drug for smoking cessation in asthmatics.

3. Varenicline should be used at standard doses and for a period of 12 weeks (Fiore et al., 2008; Gratziou et al., 2014; Jimenez-Ruiz et al., 2015; Westergaard et al., 2014). However, the only clinical trial that has been carried out using this medication in asthmatic subjects found that abstinence rates dropped off very significantly after three months of follow-up (Westergaard et al., 2014). Even in the open and follow-up study by Gratziou et al., abstinence rates were found to decrease upon termination of drug treatment. These data suggest that the use of varenicline in asthmatic smokers should be prolonged up to six months of follow-up. Indeed, a randomized, placebo-controlled clinical trial involving smokers without associated pathology showed that prolonging treatment with varenicline until six months of follow-up is more effective than using this drug for only twelve weeks (Tonstad et al., 2006).

Follow-up in the treatment of smoking

Follow-up plays a fundamental role in the treatment of smoking in asthmatics. It is essential that follow-up consultations be scheduled with the main aim of assessing the progress of the quitting process and of controlling both the subject's correct application of all psychological techniques and adherence to the different pharmacological treatments prescribed to quit smoking. Scheduling a follow-up regimen is recommended as of D-Day, starting after the first week and continuing in the second, fourth, eighth, twelfth, sixteenth and twenty-fourth weeks. At all points, it will be necessary to perform a psychological intervention appropriate to the respective moment in the quitting process. The few studies that have analyzed the efficacy of smoking treatments in asthmatics indicate that those subjects who adhered to an intensive treatment program, that is, those who combined psychological and pharmacological treatment, obtained the best results (Fiore et al., 2008; Gratziou et al., 2014; Westergaard, Porsbjerg & Backer, 2015).

Inhaled Toxic Substances

Many studies show a link between marijuana use and increased respiratory symptoms, although more studies are needed to establish the long-term risks of marijuana use (Hancox, Shin, Gray, Poulton & Sears, 2015).

In a study assessing the association between cannabis use and respiratory symptoms (N = 1037 young adults), it was found that frequent use was associated with the presence of morning cough (OR: 1.97; p <0.001), sputum production (OR: 2.31; p <0.001) and wheezing (OR: 1.55; p <0.001). In addition, reducing or stopping use was linked to a fall in the prevalence of all three (Taylor, Poulton, Moffitt, Ramankutty & Sears, 2000). In another study, analyzing the relationship between cannabis use and respiratory symptoms and lung function in young adults (91 cannabis users [9.7%] and 264 [28.1%] tobacco users), it was observed that the respiratory symptoms associated with cannabis dependence, after controlling for tobacco use, were: wheezing, exercise-induced respiratory distress, waking at night with chest pressure, and sputum production in the morning (Chatkin, Zani-Silva, Ferreira & Zamel, 2019).

In addition, the results of a population survey with 2,602 young adults showed that the probability of a cannabis user needing asthma drugs was 1.71 (95% CI: 1.06-2.77; p = 0.028) compared to non-cannabis users. According to the authors, this suggests that cannabis use is a risk factor for bronchial asthma or for the use of asthma medication, even when other risk factors are taken into account (Bramness & von Soest, 2019).

Finally, with regard to other substances, the evidence shows that the inhalation of cocaine or heroin is associated with an increase in asthma symptoms and a reduction in lung function. In addition, using crack, snorting cocaine or heroin, or smoking heroin have been reported to increase the risk of needing emergency services and hospitalization for asthma (Self, Shah, March & Sands, 2017). Another review shows that the proportion of heroin users is higher in asthmatics and that the prevalence of asthma and bronchial hyperresponsiveness is higher among heroin users. A positive association between heroin abuse and asthma exacerbations has also been shown (Underner, Perriot, Peiffer & Jaafari, 2017). Finally, one study compared the readmission rate for exacerbations in patients with current and past illicit drug use versus current tobacco users or ex-smokers. Results showed the rate of hospital admissions due to exacerbations to be higher in patients currently using or having used illicit drugs compared to tobacco smokers and ex-smokers (1.00 versus 0.22/0.26; p <0.001) (Yadavilli et al., 2014).

Finally, in a recent systematic review analyzing over 1,500 studies on the health effects of cannabis, Campeny et al. concluded that its habitual use is related not only to problems of a psychiatric nature but also to respiratory, cardiovascular and gastrointestinal problems (Campeny et al., 2020).

Use of electronic cigarettes

Regarding electronic cigarettes or new ENDS (Electronic Nicotine Delivery Systems), there is currently no scientific

evidence favouring their use as an aid to smoking cessation for smoking asthmatics (Chatkin & Dullius, 2016). Some studies have introduced the possibility of using e-cigarettes as a possible alternative, with the idea of "harm reduction" (Polosa et al., 2014). However, a recent longitudinal study conducted in the United States has concluded that e-cigarette use is in itself a risk factor for the development of respiratory disease (COPD, chronic bronchitis, emphysema, or asthma), with an adjusted OR for tobacco consumption and clinical and demographic characteristics of 1.34 (95% CI: 1.23-1.46) for former and 1.32 (95% CI: 1.17-1.49) for active electronic cigarette smokers. In addition, this study concluded that smoking both electronic and standard (combustible) cigarettes increased the risk associated with each one separately of suffering one of the respiratory diseases studied up to an OR of 3.3, compared to an individual never smoker or e-cigarette user (Bhatta & Glantz, 2020).

It is worth noting the increased use of electronic cigarettes in recent years, especially in the younger population. The composition of the aerosol generated by these devices includes numerous compounds (glycerine, propylene glycol, nicotine, flavouring agents, etc.) in addition to toxic compounds such as formaldehyde, acetaldehyde or metallic nanoparticles. The use of e-cigarettes has been associated with respiratory tract irritation, hypersecretion of mucus, or an inflammatory response (Bozier et al., 2020) as well as with the development of asthma (Osei et al., 2019). All the above increases respiratory symptoms and changes in respiratory function in e-cigarette users (Thirion-Romero, Perez-Padilla, Zabert & Barrientos-Gutierrez, 2019; Wang, Ho, Leung & Lam, 2016), in particular asthmatics (Hickman & Jaspers, 2020). A further important aspect is the surge in cases of acute lung damage associated with the use of electronic cigarettes or EVALI (E-cigarette or Vaping Product Use-Associated Lung Injury), with more than 2,000 cases and 42 deaths. The average age of those affected was 24 years (Centers for Disease Control and Prevention, 2020).

A recent study used a questionnaire with the aim of assessing the association between e-cigarette use and symptoms of chronic bronchitis in adolescents (N = 2,086). Most noteworthy among the results is the fact that the risk of suffering from bronchial symptoms in patients who had used electronic cigarettes in the past was almost two times higher than in patients who had never used them (OR: 1.85; 95% CI: 1.37-2.49) and 2.02 times higher (95% CI: 1.42-2.88) among current users. In addition, this risk remained high for subjects who had used electronic cigarettes in the past (OR: 1.70; 95% CI: 1.11-2.59) (McConnell et al., 2017) after adjusting for confounding factors, including tobacco use. Another survey, with 35,904 high school students, found that the risk of asthma for those who currently used electronic cigarettes compared to those who had never used them was 2.36 (95% CI: 1.89- 2.94). It should be noted that the adjusted risk of asthma among current smokers was 2.74 (95% CI: 1.30-5.78) (Cho & Paik, 2016).

Furthermore, it should be taken into account that the use of electronic cigarettes could increase the risk of initiating tobacco use. One study assessed the link between e-cigarette use and susceptibility to tobacco use and asthma attacks in adolescents (N = 36,085). Results showed an association between the ever or past 30-day use of e-cigarettes with increased susceptibility to tobacco use among participants with asthma who had never tried tobacco before (N = 2,410; prior use, AOR = 3.96; 95% CI: 1.49-10.56; past 30-day use, AOR = 422.10, 95% CI = 50.29-> 999.99). Additionally, e-cigarette use in the past 30 days was associated with having at least one asthma attack in the previous 12 months among participants with asthma (N = 5,865, p <0.01) (Choi & Bernat, 2016). A review of the literature indicates that adolescent patients with asthma use e-cigarettes more frequently (12.4%) than non-asthmatics (10.2%). In addition, asthmatic patients often express positive ideas about tobacco-related products, especially e-cigarettes (Clapp & Jaspers, 2017).

The consensus recommendations regarding aspects of treating smoking in asthmatics are shown in Table 5.

Table 5. *Recommendations regarding aspects of the treatment of smoking in asthmatics.*

- The therapeutic approach to smoking in asthmatics should be more intensive than the treatment of smokers without asthma.
- The motivational interview for smoking cessation should stress the cause-effect link between smoking and increased lung age and greater risk of exacerbations.
- The most effective strategy for the treatment of smoking in asthmatics includes health advice to stop smoking together with pharmacological treatment (replacement therapy with nicotine, varenicline, bupropion).
- Cannabis abuse is associated with increased respiratory symptoms such as cough, sputum production or wheezing, regardless of the diagnosis of asthma and smoking.
- Abusing cannabis, smoked in the form of marijuana or hashish, increases the risk of developing bronchial asthma.
- Abusing inhaled cocaine and heroin is associated with an increased risk of bronchial hyperresponsiveness, asthma exacerbations, and emergency room visits for asthma.
- There is no scientific evidence to support the use of electronic cigarettes or new devices (*Electronic Nicotine Delivery Systems* [ENDS]) in the treatment of smoking in asthmatics.
- In adolescent asthmatics, the use of electronic cigarettes is associated with an increase in respiratory symptoms, even in those not smoking conventional cigarettes.
- The use of electronic cigarettes among adolescent asthmatics increases the possibility of becoming smokers or initiating tobacco use.

Discussion

This document details the recommendations for the diagnosis and treatment of smokers with asthma as agreed by pulmonologists treating asthma and smoking-related pathologies. The main conclusions of the working group and panellists in relation to the available evidence include the need when diagnosing asthma to take into account the effects of smoking, and it is recommended that the presence of emphysema as well as the exclusion of other diseases be assessed. Moreover, a combined therapy of inhaled corticosteroids with bronchodilators is recommended in the treatment of asthma in smokers, and the importance of smoking cessation should be stressed. The therapeutic approach to smoking in asthmatics must be adapted to the characteristics and motivations of these patients, making behavioural therapy combined with pharmacological treatment necessary.

The conclusions and recommendations of this consensus were quantitatively validated with the participation of a large panel of pulmonologists from all over Spain. However, the use of an approach involving a narrative review of the literature can be seen as a limitation. Although the RDG reviewed and debated the collected evidence, a systematic method involving exhaustive analysis of the literature or of the quality of the evidence was not employed.

This consensus document can be useful at a practical level, addressing fundamental aspects in the diagnosis, prognosis and treatment of smokers with asthma, and highlights the importance of including the use of tobacco and inhaled toxins in asthma management guidelines of asthma.

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Conflict of interests

FJAG declares that in the last three years he has received fees for consultancy work and giving conferences or grants to attend congresses and scientific meetings by ALK, Astra-Zeneca, Bial, Boehringer-Ingelheim, Chiesi, GSK, Menarini, Mundi-pharma, Novartis, Orion and TEVA.

MBA declares receiving fees for participating in training activities by Astra-Zeneca, GSK, Teva, Novartis, Chiesi, Zambon, as well as financial support to attend congresses and meetings.

JSCM has received fees for lectures, participation in clinical studies, and publications from: AstraZéneca, Boehringer, Ferrer, GSK, Menarini, Novartis, Pfizer, Rovi and Teva

EPE has received fees for participating in training activities from TEVA, Novartis, Pfizer, Dr. Esteve, Ferrer, Rovi and Boehringer, as well as financial support to attend conferences and meetings.

JLGR has received fees for participating as a speaker in meetings sponsored by Astra-Zeneca, Novartis, GSK, Boehringer-Ingelheim, Chiesi, ALK, Teva, Menarini, Rovi, Grifols and Esteve; and for advisory activities for Novartis, GSK, Astra-Zeneca, Teva, Boehringer-Ingelheim, Grifols, ALK and Esteve.

JGSC declares that in the past three years he has received fees for speaking at meetings sponsored by Astra-Zeneca, Boehringer, Novartis, and as a consultant from Astra-Zeneca, GSK, Chiesi, Novartis and Bial. He has received financial support from Boehringer, Menarini and Novartis to attend conferences and received grants for research projects from Novartis, GSK and Boehringer.

FJCG has received fees for conferences, grants for research, as a consultant and to support conference attendance from various pharmaceutical companies, such as GlaxoSmithKline, Chiesi, Boehringer Ingelheim, Mundipharma, Menarini, Pfizer, Novartis, Esteve, Teva Pharmaceutical, Ferrer, Rovi, Roche, Astra Zeneca, Bial, Actelion, Alter, CSL Behring, Faes Farma and Gebro Pharma.

PJRP declares that in the last three years he has received fees for consultancy work and giving lectures, or grants to attend scientific conferences and meetings from ALK, Chiesi, GSK, Menarini and Novartis.

JARM has received fees for conferences, grants for research, as a consultant and to support conference attendance from various pharmaceutical companies, such as GlaxoSmithKline, Chiesi, Boehringer Ingelheim, Mundipharma, Menarini, Pfizer, Novartis, Esteve, Teva Pharmaceutical, Ferrer, Rovi, Astra Zeneca, Bial, Faes Farma and Gebro Pharma.

CAJR has received fees for participating in training activities from Pfizer and Johnson & Johnson, as well as financial aid to attend conferences and meetings.

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Impact evaluation of European strategy on Spanish National Plan on Drugs and the role of civil society

Evaluación del impacto de la estrategia europea de adicciones en el Plan Nacional Sobre Drogas español según la sociedad civil

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The European Drug Strategy (2013-2020) addressed the issues of illicit drugs, new psychoactive substances, the legal sale of alcohol, tobacco and medicines with addictive potential, and behavioural addictions, promoting coordination between EU member states and within individual national action plans (European Monitoring Centre for Drug Dependency and Addiction, 2017). Coordination is a way of ensuring that actions and policies are as reasonable and efficient as possible (O'Gorman, Quigley, Zobel & Moore, 2014); it provides an action framework to prevent potential duplication; it leverages and pools efforts; it reduces people's care and treatment timelines (EMCDDA, 2017); it saves and maximises the use of resources (financial and human) and promotes significant levels of involvement for each of the organisations forming part of the Spanish National Plan on Drugs (PNSD, 2020). The strategic objectives of the national strategy include encouraging and promoting meaningful participation and engagement of civil society (scientific and professional associations, NGOs, social partners, neighbourhood associations and others), for the purpose of which these organisations were invited to join the Spanish Council on Drug and Other Addictions.

The interest of Civil Society Organisations (CSOs) in participating in policies on drugs and other addictive behaviours has been expressed in national and international forums (O'Gorman et al., 2014). To this end, CSOs have proposed the participation of drug user organisations in national forums as well as international committees (Ernesto, 2017).

Commissioned by the *Civil Society Forum on Drugs*, a study was carried out to analyse the impact of the European Drugs Strategy (2013-2020) on the Spanish action plan on drugs, especially the role of CSOs in this impact, taking into account the perceived strengths and improvement proposals of CSOs. The study used a qualitative methodology (Flick, 2018) with an action research approach (Creswell & Creswell, 2017). The instrument used for the analysis was a focus group as a primary source and a review of articles, reports and various studies as a secondary source. As a working strategy, participatory method research was proposed. The *Consolidated Criteria for Reporting Qualitative Research,* COREQ, report was used during the data gathering procedure (Tong, Sainsbury & Craig, 2007).

A discussion group technique was adopted using a panel of experts on addiction interventions. A group of individuals significantly involved in the subject were selected, all of them considered key contributors at the international level (Tiburcio & Kressel, 2011). The selection criteria were: being a member of a non-governmental organization; with influence in the national and international network; being active locally, nationally and internationally; having proven

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knowledge of the aspect in question (addiction intervention policies); and with at least 10 years' experience in the evolution of the problem.

Certain themes recurred in the discussion group, as in any type of meeting involving Spanish CSOs: funding, the coordination between public administrations and NGOs, the gap between plans and strategies and the realities of organizations in their day-to-day work, and the great distance from research to intervention (Belackova, Ritter, Shanaham, & Hughes, 2016). The need for institutional channels of communication between CSOs and the administration was expressed on several occasions. The formal structure of the Council allows the active participation of CSOs, but, as confirmed in the focus group, there is a gap between the proposed and real participation of NGOs in this forum, which has not maintained the original frequency of meetings and output. There is a very clear need for the Spanish Council on Drug and Other Addictions to act as a useful tool for connecting Spanish policies with the commitment of CSOs. Furthermore, CSOs propose that the inclusion of drug user organizations is necessary in formal forums to ensure the voice of those affected is heard. In conclusion, while it is true that the European Action Plan addresses relevant and essential issues and proposes a series of actions for change and improvement, in reality the theory has not been turned into practice but remains at an abstract level, especially in terms of harm reduction (Belackova et al., 2016). Likewise, the current focus of the debate on fighting drug use is still on intervention in the supply of drugs rather than in the demand for drugs, although it is the latter which would represent an advance in managing drug use, according to several studies (Korf, O'Gorman & Werse, 2017).

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Conflict of interests

The authors declare no potential conflict of interest in relation to this article.

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Desde el año 2012 sólo se admite la normativa APA.

Ante la preparación de un artículo de cara a su publicación se deben revisar y aplicar las normas extensas, que pueden ser consultadas en www.adicciones.es

Adicciones está editada por Socidrogalcohol, Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y otras Toxicomanías. Adicciones publica artículos originales sobre el tratamiento, la prevención, estudios básicos y descriptivos en el campo de las adicciones de cualquier tipo, procedentes de distintas disciplinas (medicina, psicología, investigación básica, investigación social, etc.). Todos los artículos son seleccionados después de pasar un proceso de revisión anónimo hecho por expertos en cada tema. Adicciones publica 4 números al año. Adicciones tiene las secciones de editorial, artículos originales, informes breves, artículos de revisión y cartas al director. La revista se publica en español, aunque admite artículos en inglés. Cuando publica un artículo en inglés, puede exigir su traducción también al español, pero no es la norma.

Papel. La revista Adicciones está impresa en papel estucado fabricado con pastas libres de cloro (TCF).

Conflictos de intereses. La política de la revista es que en todos los artículos y editoriales conste expresamente la existencia o no de conflicto de intereses en el apartado correspondiente. Todos los conflictos de interés son importantes, pero especial cuidado hay que poner en el caso de haber recibido para el estudio financiación de la industria farmacéutica, alcoholera, tabaquera, etc. La revista Adicciones sigue en este tema las recomendaciones de ISAJE (International Society of Addiction Journals Editors). Tener conflicto de intereses no significa no poder publicar el artículo. En caso de duda sobre esta cuestión se debe contactar con el editor.

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Preparación de manuscritos. Los autores deben seguir exclusivamente para la presentación de sus manuscritos las Normas de Publicación de la American Psychological Association (6ª edición, 2010; http://www.apastyle.org). Las excepciones a esta regla son mínimas y dependen sólo de las diferencias que puede haber en el uso del español y del inglés. Por ejemplo, los ingleses utilizan en la bibliografía el signo '&' antes del último autor, mientras que en español dicho signo se corresponde exactamente con la 'y' (por tanto los artículos en español utilizarán solo la 'y'); otra diferencia puede ser en los títulos de los artículos, puesto que en inglés se pone en mayúscula la primera letra de muchas de las palabras, mientras que en español sólo ponemos la primera…

NO existe un límite exacto de palabras para los trabajos que se presenten. Pero deberá cuidarse mucho que toda la información que se incluya sea estrictamente la necesaria.

Es importante que los artículos sean interesantes para la comunidad científica del campo de las adicciones. Se evitarán trabajos que se refieran a realidades muy concretas –a menos que precisamente en ello resida su interés-, o que sean básicamente descriptivos –a menos, nuevamente, que se trate de algo novedoso.

Artículos originales. Serán preferentemente trabajos de investigación clínicos o experimentales sobre el campo de las drogodependencias o las adicciones. Pero también pueden ser aceptados trabajos teóricos o de otro tipo.

Informes breves. En esta sección se considerarán los trabajos de investigación que por sus características especiales (series con número reducido de observaciones, casos clínicos, trabajos de investigación con objetivos y resultados muy concretos, estudios epidemiológicos descriptivos, primeros resultados de un estudio amplio, etc.) pueden ser publicados de forma abreviada y rápida.

Artículos de revisión. Presentarán la actualización de un tema de forma rigurosa y exhaustiva. Deberán regirse normalmente por metodologías sistematizadas. El contenido del artículo podrá llevar los apartados necesarios para la mejor comprensión de los lectores. En su parte final debe aparecer un apartado de discusión o conclusiones. La extensión preferiblemente no debería superar las 5.000 palabras, pero siempre que esté justificado, se admitirían revisiones más largas.

Cartas al Director. Tendrán normalmente un máximo de 800 palabras, 10 referencias y una tabla o figura. Pueden consistir en una presentación breve sobre algo novedoso, una investigación original, o la contestación o matización a un artículo publicado en la revista. Cuando sea éste el caso la carta tendrá que recibirse dentro de las 6 semanas subsiguientes a la publicación del artículo en el número de la revista

PRESENTACIÓN DE LOS TRABAJOS

Envío electrónico. La forma más rápida y preferente de enviar artículos para su revisión editorial es a través de www.adicciones.es. Allí encontrará todas las instrucciones a seguir y la forma de adjuntar el original. Todo el seguimiento del proceso de revisión y editorial se realizará a través de la web (a través de la plataforma de RECYT). Ésta es la única forma prevista para envío de artículos (pero si tiene alguna duda puede comunicarse con secretaria@adicciones.es). Será muy útil para facilitar el proceso de revisión que en el momento del envío del artículo proporcione a través de la misma plataforma información sobre por lo menos dos posibles revisores para su artículo (nombre, institución y correo electrónico). Estos revisores deberán ser expertos en el tema y no estar ligados a la investigación que se desarrolla en el trabajo presentado. Tampoco podrán pertenecer al actual Comité de Redacción o Editorial. La revista se reserva la decisión de utilizar o no dichos revisores propuestos. El editor señalará además normalmente otros revisores. Recordar que el proceso de revisión es anónimo para los autores. Caso de que no fuese posible por alguna razón o tuviese algún problema con el envío del artículo a través de la web, le agradeceremos que se ponga en contacto con secretaria@adicciones.es o al teléfono (+34) 971727434 o a Editor de Adicciones. Rambla, 15, 2ª, 3ª. 07003 Palma de Mallorca.

ESTRUCTURA DE LOS TRABAJOS ENVIADOS A LA REVISTA

Todas las hojas deberán ir numeradas correlativamente en la parte superior derecha. Cada parte del manuscrito empezará una página en el siguiente orden:

1. En la *primera página* del artículo se indicarán, en el orden que aquí se cita, los siguientes datos:

- Título del artículo, en minúsculas (en castellano e inglés) excepto la letra inicial.
- Nombre de los autores completo (no sólo iniciales), y uno o dos apellidos del/los autor/es (p. ej.: Miguel García o Miguel García Rodríguez o bien Miguel García-Rodríguez, teniendo en cuenta que la forma que hayan utilizado los autores es la que se enviará a las bases de datos) en minúsculas, excepto la letra inicial. Los distintos autores vendrán separados por punto y coma. Detrás del apellido de cada autor, sin espacio intermedio y en superíndice, deberá ir un asterisco de llamada (1 asterisco para el primero, 2 para el segundo, etc.). Estos asteriscos son necesarios para indicar en el siguiente punto la institución donde se ha realizado el trabajo.
- Precedidos por un asterisco o los que fuesen necesarios –según el punto anterior– se indicarán el nombre/s del centro/s donde se ha realizado el trabajo o donde trabajan los autores.

Al final de la primera página (no como 'nota al pie') se colocará este texto: "Enviar correspondencia a: ...", indicando el nombre, la dirección postal, correo electrónico u otra información mediante la cual el autor elegido podrá ser contactado. Este será

el autor al cual la secretaría se dirigirá durante el proceso de revisión, a menos que se acuerde mutuamente otra solución.

2. La *segunda hoja* del artículo incluirá un resumen del trabajo presentado, tanto en español como en inglés. Dicho resumen tendrá alrededor de 250 palabras. Siguiendo las normas de publicación internacional ya citadas, el resumen debe especificar los objetivos del estudio o investigación; la metodología fundamental utilizada; los principales resultados; y las conclusiones más importantes y/o novedosas. El resumen debe redactarse en uno o varios párrafos siguiendo las normas de publicación de la APA, sin atender a las divisiones de antecedentes, método, etc.

Después del resumen se incluirá un listado de alrededor de 5 Palabras clave en español y luego en inglés (Key words) en minúsculas y separadas por comas que, a ser posible, se adapten a las normalmente utilizadas en los índices al uso (ej., Index Medicus, Psychological Abstracts, Índice Médico Español).

3. La *tercera hoja* dará inicio al texto del artículo. Se recomienda la redacción del texto en impersonal. Conviene dividir claramente los trabajos en apartados, siguiendo, siempre que sea posible por las características del estudio, el esquema general siguiente: Introducción (no obstante la palabra introducción no se pondrá, pues se da por supuesta), Método, Resultados, Discusión, Reconocimientos, Conflicto de intereses y Referencias.

Introducción. Será breve y deberá proporcionar sólo la explicación necesaria para que el lector pueda comprender el texto que sigue a continuación. No debe contener tablas ni figuras, a menos que sean imprescindibles para la comprensión del texto. Debe incluir un último párrafo en el que se exponga de forma clara el o los objetivos del trabajo. Siempre que se pretenda publicar una observación muy infrecuente, debe precisarse en el texto el método de pesquisa bibliográfica, las palabras claves empleadas, los años de cobertura y la fecha de actualización.

Métodos. Se describirá claramente la metodología empleada (selección de la muestra, como se recogieron los datos, instrumentos de recogida de datos o de evaluación, temporalización,… Se deben identificar los métodos, instrumentos de evaluación, tratamientos, fármacos utilizados, aparatos, sistema de evaluación, pruebas estadísticas si son novedosas, métodos nuevos, etc. Debe especificarse el tipo de estudio (descriptivo, epidemiológico, experimental, ensayo clínico, etc.), sistema de asignación de los sujetos a grupos, aleatorización, etc. Cuando haya un protocolo debe citarse. Cuando los experimentos son realizados con animales o el ensayo es experimental en humanos debe especificarse explícitamente que se han seguido las normas éticas deontológicas, de investigación y que se han cumplido los convenios internacionales de experimentación animal o humana. Debe especificarse el tipo de análisis estadístico que se va a utilizar, describirlo cuando éste sea nuevo o poco conocido, e indicar el paquete estadístico que se va a utilizar. Se valorará positivamente si se ha conseguido la aprobación del estudio por algún comité ético o se podrá exigir cuando el estudio realizado lo requiera.

Resultados. Los resultados deben presentarse en una secuencia lógica en el texto, tablas y figuras. Utilice sólo aquellas tablas y figuras estrictamente necesarias, que expresen claramente los resultados del estudio. No duplique los datos en tablas y figuras. No repita en el texto todos los datos de las tablas y figuras, sólo los más importantes. Enfatice y resuma sólo las observaciones más importantes. Adicciones adopta el sistema convencional del 5% como valor para la significación estadística y no acepta tener en cuenta las tendencias para valores menores.

Los ensayos clínicos aleatorizados deben adecuarse a las guías CONSORT (www.consort-statement.org) y los estudios con diseños no experimentales a las guías TREND (www.trend-statement.org/asp/trend.asp) para la mayor claridad de los lectores y revisores del trabajo. Igualmente, se presentarán los estadísticos del tamaño del efecto.

Discusión. Enfatizará los aspectos nuevos e importantes del estudio y las conclusiones que se derivan del mismo. No repita en detalle los resultados que ha presentado en la sección anterior ni en la introducción. Destaque lo más importante y controvertido y relacionelo con otros estudios relevantes sobre el tema. No haga suposiciones si no se ven apoyadas por los datos. Cuando sea apropiado pueden incluirse recomendaciones. Indique las implicaciones de sus hallazgos y sus limitaciones (estas preferiblemente formarán un párrafo al final del artículo).

Reconocimientos. Este apartado se situará al final del texto del artículo y justo antes del apartado de Referencias. Cuando se considere necesario se citará a las personas, centros o entidades que hayan colaborado o apoyado la realización del trabajo. Pueden incluirse todas aquellas personas que hayan ayudado en la preparación del artículo, pero no con la intensidad requerida para ser considerados autores. Si el trabajo ha sido financiado se indicará la entidad financiadora.

Conflicto de intereses. Todos los artículos, editoriales, comentarios, opiniones, reseñas de libros y cartas que se publican en la revista estarán acompañados por una declaración sobre los posibles o reales conflictos de interés o una declaración de que los autores no tienen conflictos de intereses que declarar.

Referencias. Seguirán de forma estricta las normas de la American Psychological Association [American Psychological Association (2010). Publication Manual of the American Psychological Association (6th ed.). Washington, DC. http://www.apastyle.org

Tablas y figuras. Irán al final del texto, numeradas, y cada una en una página distinta, siguiendo el diseño propio de la APA.

EL PROCESO DE REVISIÓN DEL MANUSCRITO

Los artículos son enviados a la revista a través de la www.adicciones.es. Los autores reciben al enviar el artículo unas claves para poder entrar en la web y revisar la situación de su artículo. No obstante el editor de la revista enviará un mensaje cuando tenga una decisión tomada o quiera preguntar alguna cuestión. Una vez recibido el manuscrito en la Redacción de la Revista Adicciones empezará el proceso de revisión.

El Editor, normalmente consultando con los editores asociados, puede desestimar de entrada un artículo que entienda que claramente no reúne la calidad suficiente o no entra dentro de las prioridades de la revista. El editor puede rechazar de entrada aquellos artículos que no cumplan estrictamente dicha normativa, sin pasarlo a revisión.

Los manuscritos serán enviados por el Editor o los Editores Asociados a dos o más expertos en el tema (revisores), que harán los comentarios pertinentes sobre el mismo y que requerirán aquellos cambios que estimen necesarios; también pueden dar su opinión sobre la aceptación o rechazo del artículo. La última decisión, basada en el informe de los revisores, o del editor asociado que se hubiese responsabilizado de la revisión, será tomada por el Editor de la revista, que podrá consultar además a los Editores asociados. En todo el proceso de revisión se mantendrá el principio de confidencialidad por parte de los revisores hacia el trabajo que revisan, así como la confidencialidad de los nombres de los revisores entre ellos o ante los autores del manuscrito.

El resultado de la revisión del manuscrito será enviado al autor de correspondencia que viene en el artículo indicándole su aceptación, rechazo o la necesidad de someterse a una nueva revisión una vez tenidos en cuenta los comentarios de los revisores o del editor. El autor, si es el caso, deberá hacer los cambios señalados –cuando esté de acuerdo con ellos–, enviando:

- Una copia del manuscrito revisado.
- Otro documento en donde se exponga de forma detallada las principales modificaciones efectuadas, así como sus propios comentarios sobre los principales aspectos de la revisión, con los que obviamente puede estar en desacuerdo.

Una vez aceptado el artículo, se enviará a los autores las pruebas de imprenta para que las corrijan. Los autores son totalmente responsables de la versión final que se publique. Los autores pueden hacer el uso que crean pertinente para la difusión del artículo, siempre que quede clara toda la información necesaria acerca de la revista donde ha sido publicado.

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