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Psychopathy, Addictions, Interpersonal Violence and Antisocial Behavior, a mixed relationship

Psicopatía, adicciones, violencia interpersonal y conducta antisocial, una relación mixta

Gerardo Flórez*, **

*Unidad de Conductas Adictivas, Complejo Hospitalario Universitario de Ourense, España
**Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, España

Addictions and interpersonal violence are mayor public health challenges strongly linked to each other. Obviously, addictions can increase the risk of interpersonal violence directly through intoxication, funding of drug use or being part of an ilegal, then violent, drug market. Nonetheleast, the following shared risks at the individual level for both problems have also been described as significative (Yu et al., 2012): suffering from an internalizing disorder, having a mayor mental health disorder, being male, being young, having poor education and school performance, being aggressive and having personality disturbances that include impulsivity, sensation seeking and lack of executive control.

Internalizing symptoms, aggression, impulsivity, sensation seeking and lack of executive control are common symptoms for Personality Disorders (PD) (Skodol et al., 2005), an heterogenous group of disorders with a general population prevalence that ranges from 4% to 13% (Yu et al., 2012). Therefore, it is no big surprise that a clear association between PD and violence has been found (Yu et al., 2012), with a 3.0 Odds Ratio (OR) (Confidence Interval (CI): 2.6 to 3.5). A greater association has been reported for Antisocial Personality Disorder (ASPD), with a 12.8 OR (CI: 7.4 to 14) (Yu et al., 2012), a similar risk to those who are addicted to alcohol or drugs. So that to prevent a violent act seven ASPD subjects have to be detain (Yu et al., 2012). ASPD individuals also have a greater re-offending risk (Yu et al., 2012).

ASPD seems to be important to understand interpersonal violence and to try to prevent it, but, what is ASPD? For DSM it is "a pervasive patterns of disregard for, and violation of, the rights of others that begins in childhood or early adolescence and continues into adulthood" (Lynam and Vachon, 2012). So ASPD is about being antisocial, and being antisocial is what makes that someone receives an ASPD diagnosis. This is not very helpful. It is the same as saying that someone is ill because he has fever, and that he has fever because he is ill. True, but its reductionism gets us nowhere in search for solutions. A more specific aproach is needed. DSM establishes that three or more of the following signs and symptoms are needed to assure the ASPD diagnosis: failure to conform to social norms, reckless disregard for safety of self or others, consistent irresponsibility, deceitfulness, impulsivity, irritability and aggressiveness, and lack of remorse. The first four are the needed signs to affirm that an individual shows "a pervasive patterns of disregard for, and violation of, the rights of others….."; the final three are the symptoms needed to put an individual into such pattern. As we have previous-

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Send correspondence to:
Unidad de Conductas Adictivas, Hospital Santa María Nai, Complejo Hospitalario Universitario de Ourense, Ramón Puga 52-56, 32005, Ourense
E-mail: gerardo.florez.menendez@sergas.es.

ly mentioned impulsivity, irritability and aggressiveness are also shared risks for addictions and interpersonal violence. But what about lack of remorse?

Lack of remorse has been described as one of the central symptoms that clinicians and researchers need to be aware of when looking for psychopathy, another type of PD close and generally confused with ASPD and antisocial behavior (Cooke and Michie, 2001). This confusion is quite understandable as psychopathy is not included in diagnostic manuals such as DSM or ICD, and even more important, because both disorders share some features. Psychopathy has been described as a pattern of: (1) callous and unemotional (CU) affects reflecting a deficient affective experience, (2) a grandiose and arrogant interpersonal style, and (3) a pervasive impulsive behavior (Cooke and Michie, 2001; Hare et al., 2000). If we do compare both patterns we can easily established that impulsivity is a common feature for both disorders. This common feature makes both disorders part of the externalizing syndrome, and even explains why there is a genetic overlap between both of them (Larsson et al., 2007). So, impulsivity is the key to define that someone has an externalizing disorder, but not all externalizers have antisocial behavior, or ASPD, or psychopathy. No, impulsivity is the common ground, necessary but not sufficient. At least one of two other factors are needed(Larsson et al., 2007): an environment that promotes antisocial behavior and / or being CU, which is clearly related to lack of remorse. Before turning the discussion towards these factor lets consider the nature and biological basis of impulsivity.

In the first paragraph impulsivity, sensation seeking and lack of executive control were defined as personality disturbances that were related at the same time to addictions and interpersonal violence. Like in the case of ASDP and psychopathy there is also confussion between these terms. Sensation or novelty seeking is a construct characterised by the pursuit of novelty even at the risk of increase harm (Mujica-Parodi et al., 2014), dopaminergic pathways in the drive and motivational brain circuits modulate this strongly biological and heritable behavior. This behavior has it benefits and its risks specially if we consider high novelty seekers, externalizers, with a tendency to look for positive emotional reward versus low novelty seekers, internalizers, with a tendency to avoid negative emotional punishment. An equilibrium isneeded for evolutionary purposes between the two. Neither of them is a priori pathological in an individual if behavioral flexibility is present. In the case of novelty seeking, this flexibility is lost, when there is lack of executive control, and in this case impulsivity appears. From this point of view, the distinction between the "brave", they feel fear and overcome it organizing their behavior to react to danger, the "coward", they feel fear and retreat because they think that they are not capable of mananing danger, and the "reckless", thay do not feel fear so they ignore danger, is clear (Mujica-Parodi et al., 2014).

Non-pathological sensation seekers do have the brains to be aware of the risk, to control the fear that emerges because of that risk, and to organice behavior that allows them to achieve their goal. Pathological sensation seekers, impulsive people, might also achieve the goal, but they lack the brains to see danger and feel fear, so they do not organice their behavior, they simply pursue the goal. Now, which brain circuits are needed to be "brave" and not "reckless"?, the ones that give executive control (Mujica-Parodi et al., 2014). It is important to remember that we are not currently discussing about antisocial but impulsive behavior whose consequences can be pro or anti-social. Research has constantly shown that brain Prefrontal regions and the Amygdala are the essential structures for executive control. The Amygdala, a complex subcortical area that regulates conditioned non concious learning based on emotional and physiological clues, makes an automatic understanding of the fear that is being felt, and sends the information to the OrbitoFrontalCortex (OFC) were the fear is related to the danger and with the help of the rest of the Prefrontal cortex a structured behavioral answer will be arranged to overcome the fear, control the danger and achieve the goal (Mujica-Parodi et al., 2014).

Anger, with or without fear, is another emotion that can trigger impulsive or reactive aggression. In this case a hyper-responsive Amygdala reacts to anger that comes with automatic aggresive behavior destinated to eliminate or supress the present environment stimulus that has been automatically perceived to be the source of the threat or frustration. Prefrontal regions, such as the OFC and the Anterior Cingulate Cortex (ACC), lack enough executive control to inhibit the agressive behavior (Rosell and Siever, 2015; Siever, 2008).

Neuroimaging research has proved that Prefrontal cortical thinning and reduced functioning is correlated with impulsivity (Mujica-Parodi et al., 2014) and with antisocial individuals (Yang and Raine, 2009). In a 43 studies meta-analysis increased antisocial behavior was associated with structural and functional impairment in the right OFC (an area that helps in the inhibition of non planned behaviors that are considered to be inadequate so that behavior can be calibrate to social cues, whose rewards and punishments are not so inmediate as the emotional driven ones), right ACC (an area that helps in the processing of emotions in order to control the behaviors that those emotions bring with them) and left DorsoLateral Prefrontal Cortex (DLPC) (an area that helps in cognitive flexibility achievement) (Yang and Raine, 2009). In short, when sensation seeking goes wrong because of lack of executive control people become impulsive and the risk of impulsive aggression and violence, reactive and non-planned, increases, it does not matter with which diagnosis the individual has been labeled (Blair and Lee, 2013). Drug abuse and addictions is another consequence of that impulsivity, and this is why impulsivity is a

common risk factor for both problems. Once that someone who is impulsive is abusing drugs or alcohol the risk of being violent and agressive in an antisocial way increases (Romero-Martínez & Moya-Albiol, 2015). Obviously, impulsive people can be antisocial before abusing addictive substances, if the environment, family or social, were they grow up promotes antisocial behavior, due to socio economic deprivation and / or a criminal way of live; or if they are CU and they lack remorse.

As we have previously mentioned being callous and unemotional is one of the three dimensions of psychopahty. Where does this dimension comes from? Once again the Amygdala and the Prefrontal Cortex are invoked, but in a different fashion. The Amygdala not only is involved in the processing on internal emotions but also of others emotional expressions, specially fear, pain and sadness, signs of distress (Blair, 2008). As an area for automatic stimulus reinforcing learning it is easy to understand that others emotional expressions are also going to be used to learn threatening / punishing and rewarding associations (Blair, 2008). The VentroMedial Prefrontal Cortex (VMPC) its another Prefrontral executive control area, related to emotional regulation through the representation on value information (Blair, 2008). Psychopathic children, which means that they are high on CU traits, show similar emotional attention- related impairments as patients with Amygdala lesions (Blair, 2008), with a reduced response to fearfull ,painfull and sad expressions (facial expressions, vocal tones and body gestures) and impairment in the stimulus reinforcement learning conditioned by those espressions. Without receiving from the Amygdala the correct emotional reinforcing information, weaker functional connectivity between the two areas has been found (Herpers et al., 2012), the VMPC can not represent it for correct decision making. Psychopathic children lack a basic skill for socialization, something that can be learn but not teach, as it is conditioned learning. Basically, that fear, pain and sadness in those that surround them is aversive and has to be avoided like other negative stimulus. Without this crucial emotional information the VMPC can not help other Prefrontal áreas in social correct decision making. Psychopathic children and adults do not show emotional empathy, they do have cognitive empathy knowing what fear,pain and sadness means and what is right and wrong (Blair et al., 2006), but when fear, pain and sadness appears arround them they feel no distress, so that there is no emotional urge to help others overcome their fear, pain and sadness, there are no empathic behaviors and they keep on trying to achieve their goal (Blair, 2008; Blair and Mitchell, 2009). This emotional blindness can be considered as an attentional deficit (Blair and Mitchell, 2009; Newman et al., 2010), relevant bottom-up emotional information for correct socialization is ignored and because of this correct moral and social decision making is impaired (Blair et al., 2006), psychopaths only consider top-down information that moves them towards achieving their goals (Blair and Mitchell, 2009). Basically, care and justice based norms are ignored by psychopaths (Blair et al., 2013). Thereby, the problem starts as an emotional déficit, or weaker affective priming, that interferes with moral judgement (Young and Koenigs, 2007), so that these individuals are seen by others as CU, without empathy and attachment, lacking guilt and remorse, showing shallow affect and superficial interpersonal relationships. This is why psychopathy is the only mental disorder where the risk of instrumental aggression is increased, this type of violence is purposeful and goal directed and can be planned and executed without autonomic activation. Psychopathic individuals lack all the emotional and moral brakes that stop normal people from performing the instrumentral violence that comes to their minds. This does not mean that the risk for reactive aggresion is not increased in psychopaths, actually it is, they can also be impulsive as they can be "reckless",angry and frustrated (Blair, 2008). Another issue has to be considered in relation to violence and psychopathy, not only they show a reduced emotional response to expressions of fear, pain and sadness in others, but also to threat ones (Blair et al., 2013). In situations of interpersonal threat they show less Cortisol response, high Testosterone levels, and less physiological arousal (Herpers et al., 2012). Once again their reinforcement-based decision making is impaired, they show less distress to the emotional negative value of being injured by others, which turns then more violent and agressive.

Research on CU trait has shown the following: the trait is dimensional rather than categorical (Blair and Lee, 2013), like with novelty seeking flexible levels of empathic contagion are usefull from an evolutive perspective, specially for men who have more dominance evolutive behaviors and might need to be agressive and violent on more occasions during their lives compare to women; it can be reliably assessed as from childhood (Herpers et al., 2012); affected children are more aggressive and pervasive (Herpers et al., 2012); genetic factors contribute importantly to its expression (40-78% of the trait variance is attributable to genetic influences), while antisocial behavior seems to be more environmentally driven (Herpers et al., 2012; Larsson et al., 2006; Larsson et al., 2007; Viding and McCrory, 2012); unlike antisocial behavior with age the trait becomes more stable and is associated with more conduct problems and violent behaviors (Herpers et al., 2012; Herpers et al., 2014; Lynam et al., 2007), so that this trait can be considered a basic tendency whereas antisocial behavior is more an adaptation to environmental factors (Cooke and Michie, 2001).

An important remark has to be made about the relationship of being CU, receiving a psychopathy diagnosis and being antisocial. As psychopathy is a diagnosis used in forensic settings that have a direct relationship with the criminal justice system, most, if not all, of adults labeled psychopaths will show a combination of antisocial behavior

and CU traits. They need the last to meet the criteria for psychopathy, but also the first to be assessed by a forensic officer who makes the diagnosis (Viding and McCrory, 2012). Does this mean that CU traits always comes with AB? Not necessary (Benning et al., 2003). We might find individuals with CU traits, that are not impulsive and do not take or abuse drugs, who have found an ecological – social niche where they can express their CU behavior without being interviewed by forensic staff (for instance, the loan shark Mr. Scrooge from Dickens` A Christmas Carol novel). Research on children also shows that they have CU traits before being labelled as antisocial (Viding and McCrory, 2012). In this way, impulsivity and drug abuse make CU individuals show more AB that will lead them to commit crime, generally with more violence than other criminals, that will throw them into a forensic assessment were they will receive the psychopath label.

As previously noted Lack of Remorse, an ASPD symptom, and CU trait, a psychopathic dimension, can be interpreted as being the same. Well, we can stablish that someone who is CU surely lacks remorse. But not all individuals that score high on lack of remorse do have a CU trait and should be consider psychopaths. Good assessment is needed to determine if someone shows a lack of remorse because he or she shows no emotional empathy, clearly psychopathic, or if it is something enviromentally driven and the individual can show emotional empathy to someone, which is more antisocial (Cooke and Michie, 2001; Hare et al., 2000; Sellbom et al., 2015).

What relationship has research found between psychopathy and substance use? Research using the Psychopathic Checklist List revised (PCL-R), a forensic tool for diagnosing psychopathy has answered this question (Hare et al., 2000). The PCL-R can be divided into two factors, (1) Interpersonal and affective, (2) impulsive and antisocial lifestyle (Hare et al., 2000; Storey et al., 2015). Well replicated studies report that alcohol and drug addiction and PCL-R total scores show a moderate to low correlation (Hemphill et al., 1994), being stronger for non alcohol drug addiction. But they also show that factor 2 is more correlated with drug and alcohol addiction than factor 1 (Hemphill et al., 1994). This correlation is also present when other variables such as number of substances tried, age at first alcohol intoxication and number of charges or convictions for drug related crime are considered (Hemphill et al., 1994). So substance use and abuse in psychopathic people is more related with being "reckless" than with being CU, also a common factor por interpersonal violence. This difference, as some research suggests, migh be more intense in psychopathic women, where factor 1 could even be protective against substance abuse (Schulz et al., 2015).

As a conclusion a risk on interpersonal violence asessment checklist is given for clinicians working at Addiction Treatment Units (see Table 1).

Table 1. *Checklist for assessment of risk on interpersonal violence at Addiction Treatment Units.*

- Patient is young.
- Patient is male.
- Patient shows low educational achievement.
- Patient is a sensation seeker.
- Patient suffers from a mental health disorder.
- Patient suffers from a personality didorder.
- Patient is "reckless", impulsive and lacks executive control, intoxicated or not; detecting this behavior when there is no intoxication is more relevant.
- Patient gets easily irritated, angry or frustrated, intoxicated or not; detecting this behavior when there is no intoxication is more relevant.
- Patient comes from, and lives in a criminal environment.
- Patient funds alcohol or drug use through violent acts.
- Patient uses to the point of intoxication substances that increase impulsivity and irritability such as alcohol or cocaine.
- Patient shows a stable callous and unemotional trait.

Not all these signs and symptoms predict the same risk level, but we can assume that the more a patient shows the higher the risk is. Only the last one is clearly related to instrumental violence, although funding alcohol and drug use through violent acts could also be. The rest are associated with reactive violence. So, if an intoxicated young male, with a previous history of impulsive behaviors and violent criminal convictions, comes into your office and in a highly irritated fashion demands you to fund his alcohol and drug use, you should probably take actions to guarantee your personal safety, specially if you know that this particular patient shows a stable CU trait.

Clinicians with an interest in gaining more knowledge in these topics should try to receive trainimg in the assesssment of psychopathy, with tools such as the Comprehensive Assessment of Psychopathic Personality (CAPP) or the PCL-R, and in risk assessment training, with tools such as the Historical Clinical Risk Management (HCR-20 V3).

Conflict of interest

The author declares that he does not have any conflict of interests.

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Adolescents and Dual Diagnosis in a Psychiatric Emergency Service

Adolescentes y Diagnóstico Dual en el Servicio de Urgencias Psiquiátricas

José Luis Matali*, Oscar Andión**, Marta Pardo*, Raquel Iniesta***, Eduard Serrano*, Luis San*

*Adolescent Drug Unit. Child and Adolescent Psychiatric and Psychology Department. Parc Sanitari Sant Joan de Déu, Barcelona (España). CIBERSAM; **Psychiatry Department. Hospital Universitari Vall d'Hebron. Barcelona (Spain). CIBERSAM; ***Methodology and Statistic Service. Sant Joan de Deu Foundation. Barcelona (Spain). CIBERSAM.

Abstract

In recent years, both the prevalence of drug use and related child and adolescent psychiatric emergencies have risen sharply. There are few studies about the impact on child and adolescent emergency services. This study has a twofold aim. The first is to describe the prevalence of substance use disorders, mental disorders and dual diagnosis (substance use problems plus mental disorder) in adolescents in psychiatric emergency service. The second is to analyze clinical and healthcare differences between patients with dual diagnosis and patients with a mental disorder without substance use disorder.

We retrospectively reviewed 4012 discharge forms for emergencies treated at the psychiatric emergency department during the period 2007-2009. We obtained a sample of 1795 visits. This sample was divided into two groups: the dual diagnosis group (n = 477) and the psychiatric disorder group (n = 1318).

The dual diagnosis group accounted for 26.5% of psychiatric emergencies analyzed. Compared to the psychiatric disorder group, the dual diagnosis group had significantly more conduct disorders, social problems, involuntariness in the visit, less hospital admissions and less connection with the healthcare network.

Adolescents with a dual diagnosis account for a high percentage of visits at child and adolescent psychiatric emergency services. This patient group requires specialized care both at emergency services and in specific units. Accordingly, these units should play a triple role when handling dual diagnosis: detection, brief treatment and referral to a specialised unit.

Keywords: Adolescent, Substance use, Dual disorder, Emergency Department..

Resumen

En los últimos años, la prevalencia del consumo de drogas y las urgencias psiquiátricas relacionadas han incrementado notablemente en los adolescentes. Pocos estudios han examinado el impacto en los servicios de urgencias psiquiátricos infantojuveniles.

Este estudio tiene un doble objetivo. Primero, describir la prevalencia del consumo de sustancias y de otros trastornos mentales comórbidos en una muestra de adolescentes que consultan a un servicio de urgencias psiquiátricas. Segundo, analizar las diferencias clínicas y asistenciales entre el grupo de pacientes con patología dual (comorbilidad de trastorno mental y trastorno por uso de sustancias) y el grupo de pacientes con trastorno mental sin consumo.

Se revisaron 4012 historias de adolescentes que acudieron a un servicio de urgencias de psiquiatría durante los años 2007-2009, obteniéndose una muestra de 1795 visitas. La muestra se dividió en dos grupos: el grupo de patología dual (n = 477) y el grupo de patología psiquiátrica (n = 1318).

El grupo con patología dual representó el 26,5% de las urgencias analizadas. En comparación con el grupo de pacientes psiquiátricos, presentaba significativamente más trastornos de conducta, patología social, involuntariedad en las visitas, más ingresos y menor vinculación a la red asistencial.

Los adolescentes con una patología dual generan un elevado impacto en los Servicios de Urgencia psiquiátricos infantojuveniles. Este grupo requiere de una atención especializada tanto en los servicios de urgencias como en unidades específicas. En consecuencia, los servicios de urgencias deben cumplir una triple función en el abordaje de pacientes con patología dual: la detección, la intervención breve y la derivación a unidades especializadas.

Palabras clave: Adolescente, Uso de sustancias, Trastorno dual, Servicio de Urgencias.

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Send correspondence to:
Jose L. Matalí. Hospital Sant Joan de Déu. Carrer Sant Rosa s/n. 08950 - Esplugues (Barcelona). Spain.
Phone: +34-93-280.40.00. Fax: +34-93-600.94.54.
Correo electrónico: jmatali@hsjdbcn.org

Surveys on substance use in the school-aged population conducted in the recent years show an increase in the prevalence of drug use (Observatorio Español sobre Drogas, 2013) and in the psychiatric emergencies related to it (Mahajan et al., 2009; Soto et al., 2009; Nogué et al., 2014), although the exacts reasons are not known (Goldstein & Horwitz, 2006). In this regard, it has been observed that psychoactive substance use is one of the most common reasons for visiting a child and adolescent emergency service, with cannabis and alcohol as the substances most often related to these visits (Chun et al., 2010; Sindelar-Manning, Lewander, Chun, Barnett, & Spirito, 2008). Others prevalent diagnoses observed in this population has been depressive disorders, conduct disorders, anxiety disorders and self-harm attempts (Dorfman, Trokel, Lincoln, & Mehta, 2010; Goldstein, Frosch, Davarya, & Leaf, 2007; Goldstein & Horwitz, 2006; Grupp-Phelan et al., 2009; Mahajan et al., 2009; Soto et al., 2009). Furthermore, adolescents who use psychoactive substances have a high degree of comorbidity with other mental disorders (Roberts, Roberts, & Xing, 2007), being the presence of an externalizing disorder plus substance use as the most common comorbidity (Chi, Sterling, & Weisner, 2006). This condition in adolescents was associated with poorer treatment outcomes, higher costs, recidivism, higher relapse rates, and poorer access to both medical and psychiatric services (Whitmore & Riggs, 2006).

Typical characteristics of adolescence, such as little planning, curiosity or desire to fit in among others, may predispose theirs to the substance use. Moreover, adolescent users are not normally aware of the seriousness of use and tend to normalize substance use or minimize its consequences (Matalí Costa et al., 2009); which could be minimized the reported prevalence of dual disorders. Taking in consideration the above mentioned characteristics of adolescence, the concern about the increase of prevalence, the complexity and difficulty in detecting dual diagnosis (Roberts et al., 2007), child and adolescent psychiatric emergency services provide an opportunity to detect and steer this problem. (Sanz Marcos et al., 2009).

Therefore, child and adolescent psychiatric emergency services could play a key part in managing adolescent dual diagnosis patients by fulfilling three functions. First, by detecting changes in drugs consumption tendency before other healthcare services do it. As has been extended recognized, change in consumption patterns may constitute an early indicator of the health consequences of substance use (Chung, Colby, O'Leary, Barnett, & Monti, 2003). Second, they allow for "in situ" treatment to be conducted. These early intervention has shown to reduce future conduct problems and has shown to decrease the amount and frequency of drug use (Spirito et al., 2004) . Third, child and adolescent psychiatric emergency services can serve to facilitate access to specialized healthcare units in those no treating cases (Velasco Arnaiz et al., 2010).

As mentioned previously, the child and adolescent psychiatric emergency services could help to detect and treat adolescent with dual diagnosis with both problems drug consumption and mental disorders. However, few studies have been conducted to analysis the clinical and healthcare implications of dual diagnosis adolescents who consult in child and adolescent psychiatric emergency services. Consequently, this study has the following aims: first of all, to describe the prevalence of substance use disorders and their comorbidity with other mental disorders in a sample of adolescents treated in a child and adolescent psychiatric emergency service; second, to study whether there are differences in the clinical profile and the healthcare management between the dual diagnosis patients and patients treated for another psychiatric disorder. Finally, we were interesting in study if any of the studied variables could detect those patients who presented a higher severity and those new cases.

Method

Participants

To conduct this study, we reviewed the discharge forms for emergency patients treated in the child and adolescent (1-18 years old) psychiatric emergency service of Child and Adolescents University Hospital from 2007 to 2009. The discharge forms were reviewed by two professionals in the Addictive Behavior Unit of the Child and Adolescent Psychiatry and Psychology Department of this hospital.

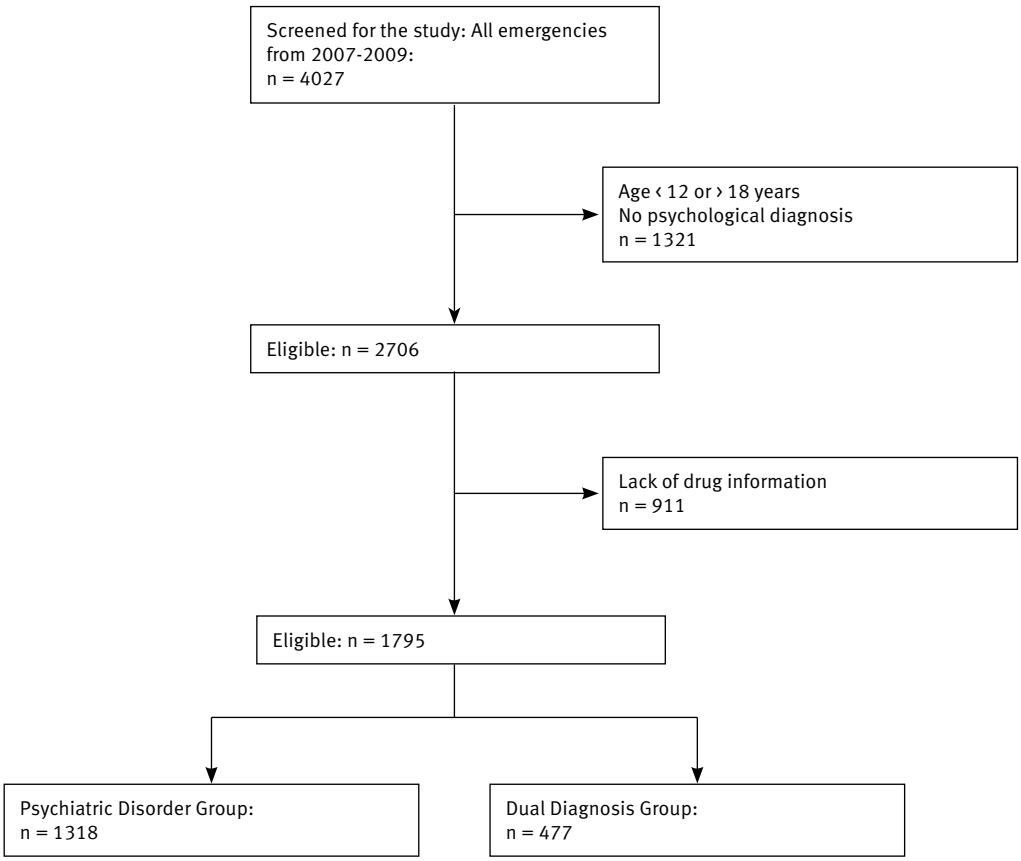
Instruments and procedure

We recorded the following variables for each emergency: age, sex, reason for the visit, time of the visit, family history of psychiatric disorders and the psychiatric diagnosis. We also noted whether or not the visit was voluntary, defined as whether the patient came to the emergency room by choice or by ambulance. We recorded whether the patient, at the time of the visit, was being treated at a mental health unit (outpatient center, hospital or privately), if he/she was at a youth center, if a toxicological screening was performed during the emergency (and if so, for which substances),

Based on the recorded data, other variables were defined. A new case was defined as a patient who at the time of the emergency visit was not undergoing treatment at a mental health unit, and upon discharge was referred to a healthcare unit. Youth center case was defined as a patient who was living at a residential state-certified i.e., who was separated from his/her family and whose legal guardian was the state, and in these cases we understand that exist a social problems. A critical case was defined as a patient who, following an assessment in the emergency service, was admitted to a psychiatric unit.

To obtain the study sample, we screened the entire sample (see Fig. 1) of psychiatric emergency visits made during the period 2007-2009 (n = 4027). From these, we excluded pa-

Fig.1. *Algorithm to Conduct Study*



tients who did not have a psychiatric diagnosis and patients under 12 years old (1321 patients). We chose this cutoff age taking in consideration the minimum age of onset of drug use in the Spanish population and the fact that the age of onset of drug use tends to be earlier in a clinical population than in the general population (Observatorio Español sobre Drogas, 2013). Likewise, and given the aim of the study, we excluded from the sample those patients in which a substance use clinical evaluation and urine test screening had not been conducted or were not recorded (911 patients). We hence obtained a final sample of 1795 patients. The dual diagnosis group (DDG) was defined as patients who at the time of the emergency had a psychiatric disorder and substances use disorder diagnosed by the psychiatrist on call (who made the clinical interview with parents and patient) and had a positive urine test for drug screening. The psychiatric disorder group (PDG) was defined as patients who at the time of the emergency only had one psychiatric disorder. Dual diagnosis group consisting of 477 patients; and psychiatric disorder group consisting of 1318.

Statistical analysis

The main study variables were compared between groups (DDG vs PDG) using the chi-square test or Fisher's exact test depending on the criteria met to apply these tests. Because it was an exploratory study, significance levels of the univariate analysis were not adjusted using the sequential Bonferroni test (Bender & Lange, 2001). However, Bonferroni correction was used to determine which variables (p-value of 0,05/25; $p < 0.002$) were entered into a multivariate logistic regression model in order to study predictors of severity and the detection of new cases. We used the step-forward method to explore the introduction of variables in the two models presented.

Results

In the total psychiatric patients sample (n = 1795), 43.7% (n = 784) were boys and 56.3% (n = 1011) were girls, and the average age was 15.4 years (SD = 1.6). Principally, patients visited the emergency department from 5:00 pm to 11:59 pm (43.5%, n = 782); from 9:00 am to 4:59 pm (42.1%, n = 757), and the lower frequency was observed from midnight to 8:00 am (14.4%, n = 257).

The 34.3% (n = 616) of the sample reported the presence of a family history of psychiatric disorders and that 64.2% (n = 1152) of patients were in treatment at the time of their emergency visit; primarily at child and adolescent men-

Table 1. *Patient Characteristics, Clinical Profiles and Flow in Dual Diagnosis Group (DDG) and Psychiatric Disorder Group (PDG)*

	DDG	PDG	P
Gender	% (n)	% (n)	
Male	50,9 (243)	41 (541)	‹0,001**
Female	49,1 (234)	59 (777)	
Family History of Psychiatric Disorders	% (n)	% (n)	
Yes	27,5 (131)	36,7 (484)	‹0,001**
Age	% (n)	% (n)	
12-14 years	25,8 (123)	43,0 (567)	‹0,001**
15-16 years	45,5 (217)	39,6 522)	
17-18 years	28,7 (137)	17,4 (229)	
Time of Visit	% (n)	% (n)	
0:00 - 8:59 am	19,3 (92)	12,5 (165)	0,001**
9:00 am – 4:59 pm	41,1 (196)	42,6 (561)	
5:00 pm – 11:59 pm	39,6 (189)	44,9 (592)	
Diagnosis	% (n)	% (n)	
Conduct Disorder	43,8 (209)	30,4 (400)	‹0,001**
Psychotic Disorder	10,3 (49)	7,7 (191)	0,82
Affective Disorder	14,3 (68)	24,9 (328)	‹0,001**
Anxiety Disorder	10,3 (49)	21,5 (283)	‹0,001**
Adjustment Disorder	2,7 (13)	5,4 (71)	0,016
Autism Disorder	0 (0)	2,7 (35)	‹0,001**
Pharmacological Treatment	% (n)	% (n)	
Antipsychotics	23,3 (111)	17,5 (231)	0,008
Anxiolytics	15,1 (72)	28,2 (371)	‹0,001**
Antidepressants	5 (24)	11,2 (148)	‹0,001**
Other	3,4 (16)	6 (79)	0,031
Arrival at Hospital	% (n)	% (n)	
Ambulance (serious case)	47,8 (228)	38,7 (510)	‹0,001**
On own	34,2 (163)	47,3 (623)	
Other	5,7 (27)	1,5 (20)	
In Prior Treatment	% (n)	% (n)	
Child and Adolescent Mental Health Center	38,2 (182)	47,1 (621)	0,001**
Hospital	7,5 (36)	9,4 (124)	0,26
Private	7,8 (37)	7,3 (96)	0,76
Youth Center	6,5 (31)	1,9 (25)	‹0,001**
Referral	% (n)	% (n)	
Admitted	37,9 (181)	28,4 (374)	‹0,001**
Child and Adolescent Mental Health Center	38,4 (183)	44,6 (588)	0,020
Specific Program	9,6 (46)	9,6 (127)	1
Youth Center	2,5 (12)	0,5 (7)	0,001**
Number of Emergencies	% (n)	% (n)	
Has come once	44,4 (212)	44,5 (587)	0,914
Has come twice	20,4 (97)	19,5 (257)	
Has come more than twice	35,2 (168)	36 (474)	
New Case	% (n)	% (n)	
New case	35,4 (169)	29,6 (390)	0,021

tal health centers (44.8%, n = 804). In terms of diagnosis, 33.9% (n = 609) had conduct disorder, 22% (n = 396) had affective disorder and 18.5% (n = 333) had anxiety disorder. We also observed that 44.5% of the patients (n = 799) had gone to the emergency room once before, 19.7% (n = 354) twice before and 35.8% (n = 642) more than twice before.

The analysis of the Information about referral upon discharge indicated that 93.4% (n = 1684) of all the patients were referred to some type of psychiatric care. Of these, 43% (n = 772) were referred to a child and adolescent mental health center, 30.9% (n = 555) were admitted to a psychiatric unit, 11.3% (n = 203) were sent for an emergency outpatient visit, 9.6% (n = 173) were referred to specific hospital programs, and 11.4% (n = 204) were other referrals.

As expected, conduct disorders [39.9% (306), p = 0.001] and psychotic disorders [10.3% (81), p = 0.05] and pervasive development disorder [3,6 (28), p = 0.001] were significantly more prevalent in boys than girls, (see Table 1), while affective disorders [24.3% (246), p = 0.001], adjustment disorders [5.7% (58), p = 0.01], anxiety disorders [20.4% (206), p = 0.02] were significantly more common in girls. Along these lines, we observed that boys used more cannabis [25.0% (196) vs. 19.3% (195), p = 0.004] and more inhalants [5.1% (40) vs. (0.4) (4), p < 0.001] than girls. However, there were no gender differences in prior treatment, in referral upon discharge, or in the time of the visit (p > 0.10).

Dual diagnosis Group (DDG, n = 477)

Dual diagnosis group accounted for 26.5% (477) of psychiatric emergencies studied (see Figure 1). Principally, patients in this group were in the range of 15-16 year age range (45.5%) with a mean of 15.4 years old (SD = 1.6). There was more girls in treatment at child and adolescent mental health centers than boys [42.2%, (n = 101) vs. 33.3% (n = 81); p = 0.003]. Moreover, principally a higher frequency of girls was observed at the range of 12-14 year range [32.9%, (n = 77) vs. 18.9 %, (n = 46); p > 0.001], and there were more boys in the 15-16 year range [52.7%, (n = 128) vs. 30%, (n = 89); p < 0.001], while no differences were observed in the 17-18 range.

The reported most frequent drug used by dual diagnosis patients (prior month) was cannabis 82% (n = 391), followed by alcohol 20.1% (n = 96), cocaine 16.8% (n = 80), inhalants 9.2% (n = 44), ecstasy 4.4% (n = 21), benzodiazepines 4 % (n = 19), ketamine 2.3% (n = 11), and heroine 0.4% (n = 2). Between gender differences didn't show significant differences in the type of substance, except for inhalants, which were more commonly used by boys [16.5%, (n = 40) vs. 1.7%, (n = 4); p < 0.001].

The most common comorbid mental disorder in the DDG was conduct disorders (43.8%, n = 209), followed by affective disorders (14.3%, n = 68), psychotic disorders (10.3%, n = 49) and anxiety disorders (10.3%, n = 49). Only a higher rate of personality disorders [4.1%, (n = 10) vs. 8.5%, (n = 20); p = 0.05], and eating disorders [0.4%, (n = 1) vs. 3.4%, (n = 8); p = 0.02] were found for girls.

Over half of the patients in the dual diagnosis group (59.9 %, n = 286) were being treated at some sort of mental health unit (whether hospital or outpatient) and the most prevalent health resource was a child and adolescent mental health center (38.2%, n = 182). A total of 47.8% (n = 228) of patients were critical cases. Patients were principally referred on discharge to a hospitalization unit 37.9% (n = 182) and only 9.6% (n = 46) were referred to specialized addiction treatment units.

One hundred sixty nine patients (35.4%) were not in treatment at the time of the emergency visit. Since these cases were referred to a healthcare unit on discharge, they are considered new cases for the healthcare network.

Psychiatric Disorder Group (PDG, n = 1318)

The Psychiatric Disorder Group accounted for 73.5% (1318) of all psychiatric emergencies studied (see Figure 1). There was an average age of 15.3 years (SD = 1.6) in this group, with the 12-14 year age range (43.0% n = 567) as the most prevalent, and a greater frequency of girls (59.0%, n = 777). There was more girls in treatment at child and adolescent mental health centers than boys [42.2%, (n = 101) vs. 33.3% (n = 81); p = 0.003]. Moreover, principally a higher frequency of girls was observed at the range of 12-14 year range [32.9%, (n = 77) vs. 18.9%, (n = 46); p > 0.001], and there were more boys in the 15-16 year range ([52.7%, (n = 128) vs. 30%, (n = 89); p < 0.001], while no differences were observed in the 17-18 range.

As in the dual diagnoses group, the most prevalent disorder in the psychiatric group was conduct disorders (30.3%), followed by affective disorders (24.9%), anxiety disorders (21.5%), eating disorders (7.9%) and psychotic disorders (7.7%).

At the time of the emergency visit, the 65.3% (n = 861) of patients in were in treatment at some sort of mental health unit (whether hospital or outpatient), being the most common a child and adolescent mental health center (47.1%, n = 621). A total of 38.7% (n = 510) of patients were critical cases. Of all the patients, 83.1% (n = 1096) were referred to a healthcare unit following the emergency visit, including 28.4% (n = 364) who were admitted to a psychiatric unit. A total of 390 new cases were detected in the psychiatric disorder group, accounting for 29.6% of all patients treated.

Comparison between Groups:

In the group comparisons (see Table 2), we observed a higher frequency of girls in the PDG [59% (n = 777) vs 49.1% (n = 234), p ≤ 0.001]. Patients in PDG were principally at 12-14 year age range (p ≤ 0.001), while patients at DDG were older (17-18 year age range, p ≤ 0.001) than those at the PDG.

A higher frequency of conduct disorders was observed in the DDG [43.8% (n = 209) vs 30.4% (n = 400), p ≤ 0.001],

Tabla 2. *Diferencias de sexo en la muestra íntegra (n=1795)*

	Male	Female	P
Group	% (n)	% (n)	
Psychiatric Disorder Group	41 (538)	59 (775)	0,001**
Dual Diagnosis Group	50,8 (245)	49,2 (237)	
Diagnosis	% (n)	% (n)	
Conduct Disorder	39,9 (306)	30 (303)	0,001
Psychotic Disorder	10,3 (81)	6,8 (69)	0,05
Affective Disorder	19,2 (150)	24,3 (246)	0,001
Anxiety Disorder	16,2 (127)	20,4 (206)	0,024
Adjustment Disorder	3,3 (26)	5,7 (58)	0,018
Pervasive Development Disorder	3,6 (28)	0,7 (7)	0,001
Substances	% (n)	% (n)	
Cannabis	25 (196)	19,3 (195)	0,004
Alcohol	5,2 (41)	5,4 (55)	0,9
Inhalants	5,1 (40)	0,4 (4)	0,001
Cocaine	4,7 (37)	4,3 (43)	0,06
Ecstasy	1,8 (14)	0,7 (7)	0,045
Benzodiazepines	1,7 (13)	0,6 (6)	0,03
Ketamine	1 (8)	0,3 (3)	0,67

while affective disorders ($p \leq 0.001$), anxiety disorders ($p \leq 0.001$) and autism spectrum disorders ($p \leq 0.001$) were more frequent observed in PDG (see table 2).

Patients in PDG had a previous connection with treatment in child and adolescent mental health centers more frequently than DDG patients [47.1% (n = 621) vs 38.2% (n = 182), p=0.001], whereas there was a lower frequency of adolescents living in youth centers in the PDG than in the DDG [1.9% (n = 25) vs 6.5% (n = 31), $p < 0.001$]. Moreover, patients in PDG compared with patients in DDG more often arrived to hospital voluntary [47.3% (n = 623) vs 34.2% (n = 163), $p < 0.001$], were admitted less frequently [28.4% (n = 374) vs 37.9 (n = 181), $p < 0.001$] and there were a lower number of new cases [29.6 % (n = 390) vs 35.4% (n = 169), p = 0.021] (see Table 2).

Regressions analysis for severity and new cases:

Finally, the logistic regressions analyses realized to study predictors of severity and the detection of new cases showed that, cases defined as critical (patients who after being examined in the emergency room were admitted to a psychiatric unit) were significantly younger (OR = 0.933), had more frequently been treated at a child and adolescent mental health center (OR = 1.335), more often lived in youth centers (OR = 1.840), and had more frequent dual diagnosis (OR = 1.574) compared to non-critical cases. New cases were principally predicted by the variables self-harm behavior and comorbid condictions, with an odds ratio of 1.37 and 1.48, respectively (see Table 3).

Discussion

This study describes the prevalence of dual diagnosis between substance use and mental disorders among adolescents treated in a psychiatric emergency service, and it compares the clinical and healthcare characteristics between a dual diagnosis group (DDG) and a group of patients with a single psychiatric disorder (PDG). The results show that dual diagnosis has a high prevalence in psychiatric emergency service. Dual diagnosis patients were found to be a group of critical patients with a high presence of externalizing disorders and social problems, and many of them were not connected with any sort of mental health service. This situation makes them a group that should receive specialized care in emergency services and in subsequent treatment.

Regarding the age of onset of substance use, the data obtained are consistent with the results of longitudinal studies that report that girls show higher use in early adolescence while boys show higher use in later ages (Chen & Jacobson, 2012). Moreover, taking into account that an early age of onset of use is associated with a worse prognosis of developing a substance use disorder (Behrendt, Wittchen, Höfler, Lieb, & Beesdo, 2009), special attention must be paid to the group of young adolescents with mental disorders and especially to young girls.

The results, as in other studies conducted in other countries (Chun et al., 2010; Chung et al., 2003; Sindelar-Manning et al., 2008; Stolle, Sack, & Thomasius, 2009) show that, alcohol and cannabis are the most frequently detected substances in child and adolescent emergency services. However, although studies in general population indicate that use patterns have tended to become more uniform (Observatorio Español sobre Drogas, 2013) our results indicate that in clinical population boys, use and visit healthcare units more frequently for illegal drugs (Matalí Costa et al., 2012).

In our study no gender differences in healthcare management were observed. Although, no studies have analyzed this topic in adolescents samples, traditionally has been

Table 3. *Logistic Regression to Inpatient Flowchart and New Patients*

	P	OR	C.I. 95%
Inpatient Flowchart			
Age	0,001	0,933	(0,924-0,943)
Child and Adolescent Mental Health Center	0,005	1,335	(1,091-1,634)
Youth Center	0,030	1,840	(1,061-3,190)
Dual Diagnosis Group	0,001	1,574	(1,256-1,974)
New Patients			
Dual Diagnosis Group	0,001	1,488	(1,184-1,871)
Conduct Disorder	0,001	0,506	(0,401-0,639)
Psychotic Disorder	0,001	0,439	(0,289-0,668)
Self-harm	0,024	1,372	(1,043-1,804)

considered that adults patients have difficulties in accessing substance use treatment programs, especially among women (Tuchman, 2010). This difference may be due to the characteristics of the sample (Tuchman, 2010) and could be indicating that substance use in adolescent patients is managing differently that in adults patients.

As expected, we found that the most frequent presentation in the dual diagnosis group was the presence of an externalizing disorder and cannabis substance use (Díaz et al., 2011). Moreover, in this group a higher frequency of involuntary visit (arrive by ambulance) and higher rate of admit to inpatient unit was observed compared with psychiatry group. These results could be indicating that dual patients requires the use of many resources in order to manage them, indicating the importance of detect the presence and the prevention of substances use in externalizing disorder patients. In the same line, the studies with adult population with dual diagnosis seen at an emergency service (Martín-Santos, 2006) detect a high prevalence of conduct problems and social pathology (Arias Constantí et al., 2010; Christodulu, Lichenstein, Weist, Shafer, & Simone, 2002), highlighting the need for early detection in order to avoid the present of worse consequence in adulthood (Larm, Hodgins, Larsson, Samuelson, & Tengström, 2008).

Like other studies, our results identified the following items as predictors of going to emergency services: dual diagnosis, involuntariness, age, comorbidity with conduct disorders, the presence of violent behavior, and being under the guardianship of the state (Christodulu et al., 2002; Curran et al., 2008; Martín-Santos, 2006). Our study also showed that a visit to the emergency room of a dual diagnosis patient is associated with greater severity and with an opportunity to connect the patient to the mental healthcare network.

In this study, dual diagnosis patients accounted for 26.5% psychiatric emergencies analyzed, which highlights the importance of emergency services in detecting dual diagnosis adolescents. These results are particularly important when taking into account that adolescent users have little contact with general healthcare units (Van Hook et al., 2007). Moreover, many adolescents with a mental disorder are neither diagnosed nor in treatment (Mahajan et al., 2009). It shows the importance of conducting a thorough toxicological screening in adolescents who visit emergency services in order to avoid missing the opportunity to detect them. In fact, in our study, the 22.6% of the total sample were discarded by lack of information about substance abuse, become an important limitation in our study to generalize our data, and make it necessary to interpret the results with caution. Other limitations, as mentioned above, are the difficulty in making a reliable diagnosis in an emergency context and acute symptoms. Another limitation is the retrospective study methodology used because the lack of follow-up on recorded cases makes it impossible to describe how many adolescents who have been referred to a specific outpatient treatment are connected to the healthcare network. Nevertheless, we believe that the results presented in this study are important, as they show the reality of child and adolescent emergency services. In conclusion, our results indicated the need to conduct specific care procedures for dual diagnosis adolescents in order to improve detection and subsequent referral to a specific resource.

Conflict of interest

The authors declare that they do not have any conflict of interests.

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Mortality due to acute adverse drug reactions in Galicia: 1997-2011

Mortalidad por reacción aguda tras consumo de drogas en Galicia: 1997-2011

Domingo Miguel-Arias*; César Pereiro Gómez**; Ana Mª Bermejo Barrera***; Benito López de Abajo Rodríguez****; María Sobrido Prieto*****.

*Psiquiatra. Servicio de Psiquiatría. Complexo Hospitalario Universitario A Coruña (CHUAC). SERGAS. (Psychiatrist. Psychiatry Service. University Hospital Complex, A Coruña). **Psiquiatra. Unidad Asistencial de Drogodependencias (ACLAD). (Psychiatrist. Drug Dependency Assistance Unit) A Coruña. *** Servicio de Toxicología del Instituto de Medicina Legal de la Universidad de Santiago de Compostela. (Toxicology Service of the Institute of Legal Medicine, University of Santiago de Compostela). ****Médico Forense. Instituto de Medicina Legal de Galicia (IMELGA). Santiago de Compostela (Forensic Doctor, Institute of Legal Medicine of Galicia (IMELGA), Santiago de Compostela). *****Servicio de Biblioteca. Complexo Hospitalario Universitario A Coruña (CHUAC). SERGAS. (Library Service. University Hospital Complex, A Coruña)

Abstract

The aim of this research is to study all people who died in the Autonomous Community of Galicia from acute death after drug consumption (ADR) in which there was judicial intervention during the period from 1997 to 2011, according to inclusion and exclusion criteria established by the National Drug Plan for the entire national territory. Sociodemographic and clinical characteristics of deceased subjects were studied, in order to identify key risk factors and/or vulnerable populations.

A total of 805 deaths were recorded. The distribution by provinces and municipalities corresponds to the areas of greatest population, incidence of consumption and proximity to the coast. The average age of these patients was 34.34 years, with a gradual increase over years. Most of them were male (91.2%) and single (47.7). 43.5% of the deceased habitually used the parenteral route of administration and 36.4% had positive HIV serology. The most frequently-detected substances corresponded to opiates (heroin: 61.3%, methadone: 35.6%), followed by cocaine (53.7%), although the most common pattern was that of poly-consumption. ADR mortality figures remain relatively stable throughout the study period. The predominant pattern is that of males, opiates and a long history of consumption.

Keywords: Drug overdose; drug-induced deaths; mortality; epidemiology.

Resumen

Se estudian todos los sujetos fallecidos en Galicia por reacción aguda tras consumo de drogas (RAD) en los que existe intervención judicial a lo largo del periodo 1997-2011, según los criterios establecidos por el Plan Nacional sobre Drogas para todo el territorio nacional. Se recogieron y analizaron variables sociodemográficas, clínicas y toxicológicas de cada uno de los casos. El objetivo fundamental es tratar de determinar los principales factores de riesgo y/o perfil de las poblaciones vulnerables, así como sugerir medidas preventivas. En total se registran 805 fallecimientos. La edad media de los fallecidos fue de 34,34 años, con un aumento progresivo a lo largo de los años. La mayoría eran varones (91,2%) y solteros (47,7%). El 43,5% de los fallecidos utilizaban la vía de administración parenteral y un 36,4% presentaban serología positiva frente al VIH. Las sustancias detectadas con más frecuencia correspondían a opiáceos (heroína: 61,3%, metadona: 35,6%), seguidos de cocaína (53,7 %), aunque el patrón más habitual era el policonsumo. Las cifras de mortalidad por RAD se mantienen relativamente estables a lo largo del periodo de estudio. El patrón predominante es el de varones, consumidores de opiáceos y con larga historia de consumo.

Palabras clave: Sobredosis de drogas; muertes inducidas por drogas; epidemiología; mortalidad

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Send correspondence to:
Domingo Miguel Arias. Servicio de Psiquiatría. CHUAC. C/ As Xubias, s/n. 15006. A Coruña.
e-mail: Domingo.Miguel.Arias@sergas.es

Drug consumption is associated with a marked increase in morbidity and mortality rates which can range between 10 and 20 times those of non-consumers (Bargagli, Hickman, Davoli, Perucci, & Schifano, 2006; EMCDDA, 2013), and is related to different circumstances, among which stand out death by acute reaction after consumption, suicide, accidents, traumatisms, physical assaults etc. (Vicente, Giraudon, Matias, Hedrich, & Wiessing, 2009; Degenhardt, 2011; Mathers, Degenhardt, Bucello, Lemon, Wiessing, & Hickman, 2013; Waal & Gossop, 2014; Razvodovsky, 2014). It is estimated that in 2010 there were between 99,000 and 252,000 deaths worldwide related to the consumption of illicit drugs, which would represent between 0.5 and 1.3% of all deaths of persons between the ages of 15 and 64.

In Europe, it is estimated that between 10,000 and 20,000 consumers of opiates die every year, with overdose being the most frequent cause (between a third and a half of the total, which implies in the region of 7,000 to 8,000 deaths per year) (Waal et al, 2014; EMCDD, 2011), and despite prevention campaigns and therapeutic programs that are carried out with the aim of reducing the risks in the most vulnerable groups, mortality owing to acute reactions after the consumption of drugs remains stable and is even increasing in certain countries (Giraudon, Vicente, Matías, Mounteney, & Griffiths, 2012).

Mortality owing to acute reaction after drug consumption therefore constitutes the principal cause of death among drug addicts. Its ethiopathogenesis (Pereiro, Bermejo, & López, 2005) may be extremely varied (overdose, anaphylactic reaction, adulterants, poly-consumption) and it is frequently difficult to determine the exact cause of death. Toxicological determinations (both qualitative and quantitative) play a fundamental role (Martínez, 2014) in the diagnosis, although the difficulty in establishing the lethal dose of each substance must be borne in mind, since the fatal outcome in each specific case is also related to individual circumstances that are not easily objectifiable (tolerance, physical condition, previous illnesses etc.).

On an epidemiological level, determining the cause of death owing to an acute reaction to drugs is one of the principal indicators of the level of consumption among the population, which is fundamental when it comes to putting in place assistance and prevention strategies for drug addiction. At the same time, it allows us to be aware of risk factors and especially vulnerable populations with the aim of drawing up specific measures aimed at those groups.

Materials and methods

This is an observational, descriptive, longitudinal and prospective study. The sample group is made up of all the deaths that occurred in the Autonomous Community of Galicia between 1997 and 2011 (including both of those years), where there was judicial intervention and in which acute drug reaction (ADR) was the suspected cause. The same criteria of inclusion and exclusion established at a national level by the State System for Information on Drug Addiction (Sistema Estatal de Información en Toxicomanías) and specified on the Individual Registry Sheet of Death by Acute Reaction to Psychoactive Substances, drawn up by the National Drugs Plan for the whole of the Spanish State, were considered and the variables gathered are included in Table 1.

In Galicia, all cases of death by ADR were detected and notified by the forensic doctor when a death of this type was suspected. The action of the forensic doctor followed a protocol which is obligatory in all cases of death with judicial connotations, although with special reference to deaths presumably related to drug use, including the removal of the body, the autopsy on the drug addict and the collection of bodily fluids (vitreous humor, urine, bile and blood). These samples were later sent, together with all the information regarding the case, to the Toxicology Service of the Institute of Legal Medicine at the University of Santiago de Compostela, where different toxicological tests were carried out and the Mortality Indicator of the Autonomous Community was drawn up.

The toxicological techniques used included enzymoimmunoassay and fluoromoimmunoassay (Engvall, 1971; Rubinstein, & Ullman, 1971; Spector, 1970), thin-layer chromatography of gases and liquids (Davidow & Quame, 1968; Blass, 1974) and mass spectrometry (Bermejo, Fernández, & Tabernero, 1998; Fernández, Bermejo, & Tabernero, 2004; Álvarez, Tabernero, López,, & Fernández, 2007; Pietracci, Álvarez, Cabarcos, Balduini, & Tabernero, 2013; Di Palma, Álvarez, Cabarcos, Bacchielli, & Tabernero, 2009).

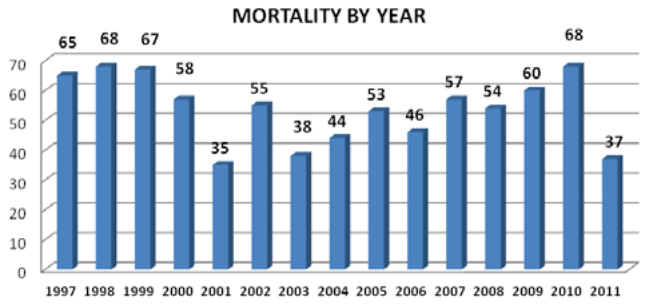
Table 1. *Collected variables*

Administrative data
Name, Surnames, ID Document Nº
Forensic Report Nº, Toxicological Report Nº, Preliminary Proceedings Nº
Institution collecting information, Courtroom (Nº, Province, Municipality)
Sociodemographic data
Death (Date, Province, Municipality)
Sex, Marital status, Age, Birth (Date, place), Nationality
Residence (Province, Municipality)
Clinical data
Death criteria RASUPSI (recent drug use, autopsy, forensic diagnosis)
Body found in..., signs of suicide
Signs of venipuncture (needle use), aggravated previous pathology, HIV
Toxicological data
Type of biological sample
Substances detected
Quantitative result

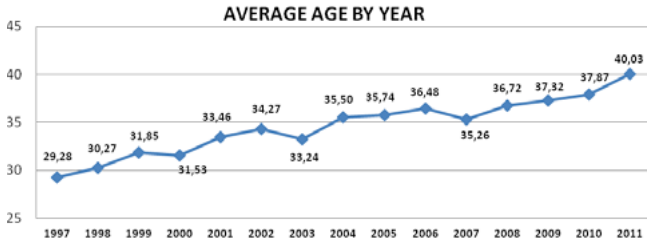
For the statistical analysis the SPSS 17.0 software package for Windows was used. A descriptive study of the different variables was made (frequency tables for qualitative variables and central tendency measures and measures of dispersion for the quantitative variables). The association between different variables was made by means of contingency tables and median comparison, attributing statistical significance to values of $p<0.05$.

Results

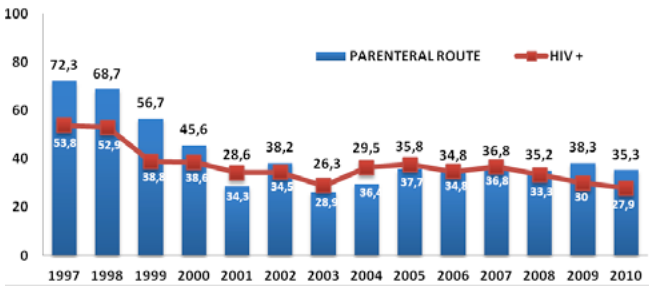
Over the 15 years of the study period (1997-2011) a total of 805 deaths by ADR were registered in Galicia in accordance with the aforementioned criteria. This represents an accumulated mortality rate for the whole period of 29.1 deaths per 100,000 inhabitants, which means an average annual rate of 1.94 per 100,000 (with the highest value being 1998, with 2.49 per 100,000 and the lowest being 2001, with 1.28 per 100,000).



Graph 1. Nº of ADR deaths per year



Graph 2. Evolution of the average age (in years) by year



Graph 3. Use of intravenous injection (parenteral route of administration) (%) and HIV infection (%) by year

Tabla 2. *ADR Mortality by provinces*

	Total	%	Mortality rate
A Coruña	366	45,5%	29,5/100.000 hab.
Pontevedra	302	37,5%	31,6/100.000 hab.
Lugo	75	9,3%	21,7/100.000 hab.
Ourense	62	7,7%	19/100.000 hab.

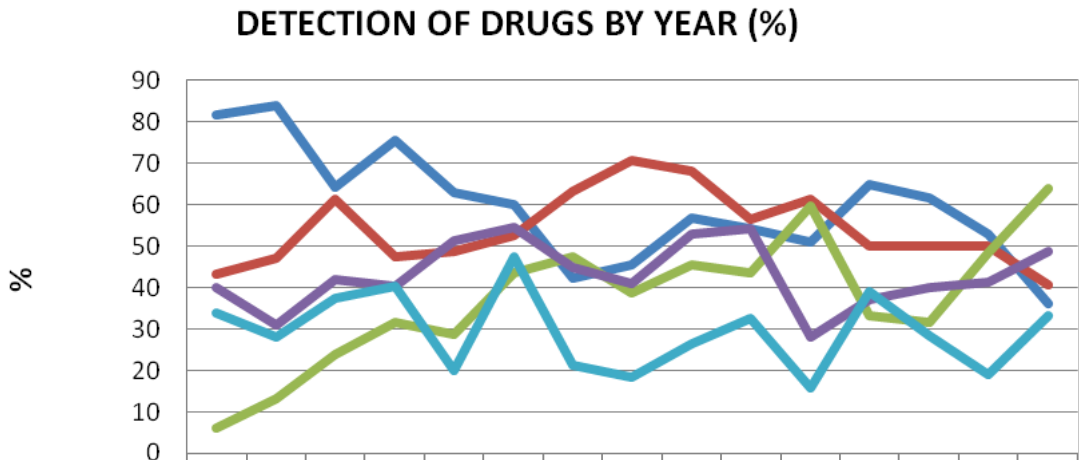
The total number of deaths by ARD remained relatively stable in Galicia throughout the period studied (Graphic 1), except for a couple of years in which there seems to be a noticeable drop (2001 and 2003), and also 2011 (possibly owing to the data entered in the registry being skewed).

Within the sample group males predominate (n=734), representing 91.2% of the sample with there being no significant variation in the males/females percentage over the years of the study. The average age of the dead was 34.34 (34.8 for women and 34.3 for men), with an interval ranging from 17 to 56 years of age, and a 30-year mode. A progressive increase in age can be observed over the years of the study, rising from 29.28 in 2007 to 40.03 in 2011 (Graphic 2). Regarding the marital status (a variable that began to be registered in 2007, for which reason these data are limited to the period from 2007 to 2011), there is a predominance of unmarried persons (47.7%), followed by those who were separated or divorced (26.1%), married (25.3%) and, lastly widows/widowers (0.8%). It can also be observed that among the males the unmarried predominate (49.5%), while among the females it is married women who predominate (43.5%).

Regarding geographical location, the province in which the greatest number of deaths was registered (Table 2) was A Coruña, followed by Pontevedra, Lugo and, lastly, Ourense. Among the municipalities with the highest number of deaths are, in first place Vigo, the largest city in Galicia (n=123), followed by A Coruña (n=100), Pontevedra (n=65), Santiago de Compostela (n=60), Ferrol (n=43), Ourense (n=42), Ribeira (n=38), Lugo (n=30), Betanzos (n=22), Cangas (n=14) and Villagarcía (n=14).

Some 43.5% of the deceased were injecting drug users (IDUs). During the first years of the study a marked decrease in this way of administering drugs can be observed, dropping from 72.3% in 1997 to 28.6% in 2001. From that year onwards, the figures remained stable between 30 and 40% (Graphic 3). Signs of recent venipuncture (less than a week old) were found on 34.1% of the subjects who died between 2007 and 2011 (before that this was not registered), with a slightly higher, but statistically insignificant, percentage in males.

Regarding HIV serostatus, this was positive in 36.5% of the sample, negative in 58.4% and unknown in 5.1%. The analysis by gender shows very similar results in both groups, with a slightly higher prevalence among females (40.3%) than among males (38.3%). If we observe the evolution over the years (Graph 3), we see a downward trend in HIV



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
MORPHINE	81,5	83,8	64,2	75,4	62,9	60	42,1	45,5	56,6	54,3	50,9	64,8	61,7	52,9	36,1
COCAINE	43,1	47,1	61,2	47,4	48,6	52,7	63,2	70,5	67,9	56,5	61,4	50	50	50	40,5
METHADONE	6,2	13,2	23,9	31,6	28,6	43,6	47,4	38,6	45,3	43,5	59,6	33,3	31,7	48,5	63,9
BENZODIAZ	40	30,9	41,8	40,4	51,4	54,5	44,7	40,9	52,8	54,3	28,1	37	40	41,2	48,6
ALCOHOL	33,8	27,9	37,3	40,4	20	47,3	21,1	18,2	26,4	32,6	15,8	38,9	28,3	19,1	33,3

Graph 4. Variation in the type of substances detected by year

seropositivity, going from more than half of the sample in the early years (1997-1998) to lower than a third in the later years (2009-2010). There seems to be a clearly observable parallelism between the reduction if the use of syringes and HIV seropositivity.

In more than half of all cases, the dead body was found in the home (n=461, 57.1%), followed by those who were found in the street (n=190, 23.5%), penitentiary facilities (n=42, 5.2%), hotels or guesthouses (n=33, 4.1%), hospital (n=31, 3.9%) and public establishments (n=23, 2.9%), while 25 persons (3.3%) came from unspecified places. Being found in the street was much more common among males (24.8% as opposed to 9.9% in the case of females), as was the case with public establishments (3% as opposed to 1.4%), which could be related to a greater level of marginalization and/or "street living" of males.

From 2007 onwards, evidence that the death could have been self-induced or even a case of suicide began to be registered. This evidence was only found in 9% of cases, while in the great majority there were no data found that pointed in that direction. A greater prevalence is observed among females, 18.8% as opposed to 8% in the case of males, but this difference is not statistically significant owing basically to the small size of the sample in the case of females.

The distribution of deaths over the days of the week shows that the greatest number happened on Sundays (32.1%), followed by Saturdays (17.3%), Tuesdays (13.8%), Fridays (13%), Thursdays (12.3%), Wednesdays (9.9%), while only a small percentage occur on Mondays (1.8%). Therefore, the greater part was concentrated around the weekends, meaning almost half of all cases (49.4%) occurred between Saturdays and Sundays.

The substance (or combination of substances) found with the greatest frequency were opiates. Within this group morphine (a heroin metabolite) which was detected in 61.3% of cases, appeared in first place, followed by methadone (35.6%), and codeine (27.6%). In second place was cocaine, whose presence was detected in 53.7% of cases, followed by the benzodiazepines which were found in 42.4%. Alcohol consumption was determined in almost a third (29.9%) of subjects, and lastly, cannabis appeared in samples from 17.9% of the deceased persons. Over the years of the study, variations may be observed regarding the type of substances found (Graphic 4). Thus, although the opiates are the substances that were most detected throughout the period of the study, there was a progressive decline of the implication of heroin in ARD deaths, going from being found in 81.5% of the deaths in 1997 to 36.1% in the last year studied (2011). On the other hand, methadone appeared with greater frequency as the years passed, going from 6.2% in 1997 to 63.9% in 2011. Cocaine increased noticeably from the early years, going from 43.1% in 1997 to 70.5% in 2004, after which there was a steady decline to 40.1% in 2011. The benzodiazepines remained at relatively stable levels of between 30 and 50% throughout, reaching their highest level in 2002 (54.4%) and their lowest in 2007 (28.1%), but with no clear tendency that can be shown over the years. Lastly, alcohol also showed an irregular pattern between its highest value, reached in 2002 (47.3%), and its minimum, corresponding to 2007 (15.8%).

Without any doubt, poly-consumption was the most prevalent pattern and the combination of substances was the most habitual situation, with only one substance being detected in just 114 subjects (13.2% of cases), while in 361 ca-

ses (44.8%) there were two, in 240 cases (29.95) there were three, in 77 cases (9.6%) there were four, in twelve subjects (1.5%) there were five and in one case (0.1%) there were six. As far as gender is concerned, poly-consumption patterns did not show noticeable differences, although in males the highest percentage showed two substances (46%), while in females that figure corresponded to the finding of three (41.8%). Poly-consumption became more consolidated over the years. Thus, the cases in which only one substance was found went from 21.5% in 1997 to 8.1% in 2011. On the other hand, the percentage of subjects in whom three substances were detected rose from 26.2% in 2007 to 29.7% in 2011, those in which four were detected rose from 1.5% in 2007 to 18.9% in 2011, while five substances were not detected in any case in the earlier years but in the last five years that number settled at around 5%.

It is important to point out that a total of 42 deceased persons came from penitentiary centers, (5.2% of the sample). Of them, 90.5% were males with an average age of 34.95, which is in line with the general sample. The presence of HIV-positive serology was of 42.9%, higher than the median of the sample. Regarding the drugs detected in this sub-population, in order of prevalence they were: methadone (60.0%), benzodiazepines (66.7%), morphine (46.6%), cocaine (28.6%), cannabis (20.8%), codeine (16.7%) and alcohol (2.4%).

Discussion

Our study shows, in the same way as various works reviewed (Degenhardt, 2011; UNODC, 2012; Giraudon et al, 2012; Gjersing et al, 2013), that ADR constitutes one of the principal causes of death among drug addicts. At the same time, and despite the different policies aimed at reducing harm among drug users, mortality remains relatively stable, as in other countries (Giraudon et al., 2012). In any case, we are dealing with figures that are smaller than those collected in our catchment area between 1992 and 1997 (Pereiro, 2003; Pereiro, 1999), and those corresponding to other regions and neighboring countries (Bargagli, 2006; EMCDDA, 2011; Gjersing, 2013; DGPND, 2012). We consider this fact to be related to the implementing of harm reduction strategies and the widespread use in our region of maintenance programs with agonists.

It is important to point out that the data for 2011 are less reliable as they show both a noticeable reduction in the number of deaths registered as well as having fewer data, and those being of poorer quality. This could be related to the lack of funding for the program on the part of the National and Autonomous Drug Plans owing to budgetary cut-backs affecting government spending, themselves a result of the current economic crisis.

The deaths affected the relatively young population especially (an average age of 34.3). However, the average age in our sample was notably higher than that found in our Autonomous Community over the period from 1992 to 1997 (28.8) (Pereiro, 2003; Pereiro, 1999), and rose over the years of our study. These figures are in line with those found at a national level in this country and in other neighboring countries (DGPND, 2012). For that reason, it is clear that we can consider the ADR mortality rate shows a greater prevalence among persons with a long history of drug use, and that "experience", far from being a factor of protection, as might be supposed a priori, seems rather to be associated with greater vulnerability.

Regarding gender, males clearly predominated, with figures that remained similar over the years of the study. The progressive increase in the prevalence of substance use among females does not seem to be reflected in the figures for ADR deaths, probably because the consumption of legal drugs predominated among them, but they also continued to be far below the males in terms of illegal drugs, particularly opiates which, as we have already stated, were the main substance involved in those deaths. Other factors that might explain the greater risk of death by overdose among males, as some authors indicate, may have to do with greater levels of social marginalization and isolation (Darke, Degenhardt, & Mattick, 2007), as well as greater alcohol consumption among them (Bird & Robertson, 2011).

The majority of deceased persons who died were unmarried (47.7%), a figure that is well below that captured at national level, of around 60% (DGPND, 2012), and in second place were those who were separated or divorced. That is to say, the great majority of our sample is made up of persons who either did not live with a partner in a stable union, or whose union had broken down. Although the average age of the sample is, as we have stated, relatively young, these data are probably connected to the general psychosocial deterioration of the drug using population and its serious repercussions in their immediate circles (Darke, 2007), which makes cohabitation with anyone beyond their family of origin difficult.

As for the geographical distribution of the deaths in our Autonomous Community, in general it correlated with the areas of greatest consumption, which usually corresponds to the cities, the areas of greatest population density and the proximity to the coast (this last fact is probably related to the greater purchasing power of young people there, and the fact that those places are entry and distribution points for illegal drugs in this country).

The fact that only 43.5% of the dead were intravenous users is worthy of note, as well as the fact that those on whom signs of needle use in a period of less than a week before their death were detected was also relatively low (34.1%), showing a slight downward tendency over the period in which these data were registered (2007-2011), which seems to point to a progressive diminishing of the use of syringes as a means of administering drugs by users

in this region. These figures are in line with those found at national level (DGPND, 2012), although in this case the values are slightly higher, sitting at around 35 to 50%. This fact should also alert us to the serious risk of overdose when using other means of administration (a circumstance that many drug addicts are not always aware of and which they often play down), particularly when several substances are consumed at the same time, as was the case in most of the subjects in our sample, meaning therefore that preventive strategies must be extended to the non-IDU population who, as we have just pointed out, are at high risk of death by ADR.

HIV-positive serology accounted for 36.5% of cases. In any case, the presence of HIV seropositivity was higher than that detected in drug-dependent patients who seek treatment, for which reason there is an association of HIV with overdosing, as other studies show (Green, McGowan, Yokell, Pouget, & Rich, 2012). This association seems to be related to other circumstances that have already been mentioned, fundamentally the age (relatively high), the prolonged period of use, a greater use of intravenous administration, as well as general deterioration (both organic and psychosocial) derived from the lifestyle of drug addicts, apart from HIV infection itself (Wang et al., 2005). However, it should also be pointed out that this percentage dropped from year to year, going from the 53.8% detected at the beginning of our study (1997), to almost half (27.9%) in 2010. This drop seems to be related to the reduced use of intravenous administration (the principal cause of infection among drug addicts) (DGPND, 2012), together with the extension of maintenance programs with agonists, harm-reducing programs, safe-sex workshops etc. and other strategies aimed at preventing infection among this group.

As to the place of death, the most frequent location was the home (57.1%), followed by the street, although in a much lower percentage (23.5%). These two places were also the most frequent in the period from 1992 to 1997 (Pereiro, 2003; Pereiro, 1999), although at that time the percentage of deaths at home was significantly lower (39.2%), and that of deaths in the street was higher than in our study (30.2%), which denotes lower levels of marginalization in the period covered by our study. At a national level too, a higher percentage of deaths at home can be observed over the years, going from 54.5% in 2003 to 64.3% in 2010 (DGPND, 2012).

The fact that a greater percentage of ADR deaths occurred at home and/or in the subject's immediate circles could make it easier for family and friends to request help. In this sense, implementing preventive programs aimed at training them to recognize the symptoms of overdose, give first aid and request medical assistance where overdose is suspected (Siegler, Tuazon, Bradley O'Brien, & Paone, 2013).

Lastly, the significant percentage of subjects who die of ADR in penitentiary centers (45, 5.2% of the total) should be mentioned, as it would fully justify the existence of therapeutic and risk reduction programs in these institutions with a high population of drug addicts. Studies carried out in other countries also indicate high numbers of deaths by overdose in prisons. Identifying the profile of these subjects and of the inmates who have been witnesses to cases of overdose could help to identify the target population as well as the developing of preventive policies in these institutions (Albizu-García, Hernández-Viver, Feal, & Rodríguez-Orengo, 2009; Kinner, Milloy, Wood, Qi, Zhang, & Kerr, 2012; Moore, Winter, Indig, Greenberg, & Kinner, 2013).

Signs of suicide were detected in a relatively small number of cases, although in the case of females, the percentage was considerably higher than in males, in line with data found in other studies (Cottler, Campbell, Krishna, Cunningham-Williams, & Abdallah, 2005). Of course, we are dealing here with completed suicides, so the percentage of attempts with no fatal outcome is assumed to be much higher. However, as we have already pointed out, it is not usually easy to determine whether a death by overdose was intentional or accidental (Britton, Bohnert, Wines, & Conner, 2012), so only those cases in which there was clear evidence of the intention of the subject to take his or her own life were registered as such.

As for the day of the week on which most ADR deaths occur, the weekend appears to be clearly associated, as it was when almost half of the deaths occurred, with Sundays being the day of greatest prevalence. These figures were significantly higher than those for the period from 1992 to 1997, although in that period too there was a greater frequency of weekend deaths (Pereiro, 2003; Pereiro, 1999). We believe that the tendency to engage in poly-consumption at weekends, particularly the association of CNS depressants, could explain this increase.

Regarding toxicological determinations, the most habitual situation was the detection of two or more drugs in the majority of subjects studied, while only in a small proportion was just one substance found. This is a faithful reflection of the poly-consumption that the majority of drug addicts engage in and is in line with other studies on ADR (Vicente, 2009; EMCDDA, 2011; Gjersing, 2013; DGPND, 2012), with a clear upward tendency of poly-consumption with the passing of the years over our period of study.

The most frequently-found substances were opiates and, in particular, heroin. However, a significant downward trend can be observed vis-à-vis the figures obtained for the period from 1992-1997 within our Community itself, which in that sample was as high as 84.4% (Pereiro, 2003; Pereiro, 1999), and over the years of our study. These data are in line with the drop in the consumption of heroin which was detected both in population surveys (DGPND, 2012) and among the drug addicts who seek treatment.

Within the opiates group, in second place was methadone which was found in 35.7% of the deceased. This figure was much higher than that found in the period from 1992 to

1997, which was of 8.3% (Pereiro, 2003; Pereiro, 1999). This tendency became very clear over the course of our study, in which a progressive increase of the detection of this substance can be observed. Only in 13 cases (4.5%) was methadone detected as the sole substance, while in all other cases other associated substances appeared, for which even though it may be considered as a contributor to the toxic effect of other CNS depressants, its role as the principal and/or only cause of death does not appear to be particularly relevant. It was not registered whether the patient was having methadone maintenance treatment or if the drug had been acquired on the illegal market, but the increase in the detection of this substance does reflect a greater dissemination and access of drug addict patients to these programs which without doubt do contribute to improvements in the general health and quality of life of this group, and can therefore be considered as an indicator of the quality of assistance provided. Although on first sight a certain causal responsibility in mortality could be attributed to it (and without any doubt, in combination with other CNS depressants it does contribute to the fatal outcome), the truth is that all studies point to the important role of methadone maintenance programs in the reduction of risk of ADR death (Brugal, Domingo-Salvany, Puig, Barrio, García de Olalla, & de la Fuente, 2005; Clausen, Anchersen, & Waal, 2008; Schwartz et al, 2013; Sherman, Han, Welsh, Chaulk, & Serio-Chapman, 2013; Strang, Hall, Hickman, & Bird, 2010).

Cocaine was, after the opiates, the second most frequently detected substance in ADR victims, with significant gender differences. This figure is much higher than in the period from 1992 to 1997, when it was only 22.2% (Pereiro, 2003; Pereiro, 1999). Regarding the evolution of this parameter over the period of our study, there was a notable increase in the early years, followed a period of stabilization and a certain drop later, which reflects the evolution of the consumption of this substance in recent years as detected in general population surveys (DGPND, 2012), as well as in treatment indicators.

The combination of alcohol (detected in approximately a third of the deceased) with other CNS depressants (opiates, benzodiazepines, etc.) is especially dangerous, as it enhances their effects and, therefore, increases the risk of overdose. The average concentration of alcohol was of 1,122±0,666 gr/L, levels which were practically the same as those detected in the period from 1992 to 1997, in which they were 1.115±0.843 g/L (Pereiro, 1999). In any case, these levels are too far below the lethal dose (Minian & Bontiette, 1989; Jones, 2003; Darke, Duflou, Torok, & Prolov, 2013; Darke, Duflou, Torok, & Prolov, 2013b) for it to be considered as a principal cause of death, although it does seem to have an important role as a contributor of the same, when combined with other depressants.

Benzodiazepines were detected in an important percentage of cases (42.4%), a figure that is significantly higher than those found in other neighboring countries such as the United Kingdom where it was in the region of 30% (EMCDDA, 2011, Bird, 2011), but much lower than those detected by Gjersing (2013) among the deceased in Oslo, Norway, where the figure rose to 68%. On the other hand, we cannot establish a clear tendency over the period of our study, as even though there were years with a notable increase (54.5% in 2002), there were no relevant differences to be observed between the early years and the later ones. Nevertheless, the figures were notably higher than those from 1992 to 1997, in which the percentage of subjects among whom this substance was detected was of 27.5% (Pereiro, 1999).

The presence of cannabis began to be determined from 2007 onwards, for which reason we have no previous data. However, the percentage of detection (17.9%) in our sample does not seem excessively high, bearing in mind how widespread its consumption is. While it is true that, according to the profile of our sample population of ADR deaths (advanced age, long-term consumers of opiates, psychosocial deterioration…), the consumption of cannabis would very much occupy a second place, unlike in younger populations of consumers. On the other hand, the concentrations of this substance that were detected were not especially high, if we compare them with those of other studies that have been published (Karch, 2006; Hartung, Ritz-Timme, & Daldrup, 2014).

Conclusions

ARD is one of the principal causes of mortality among drug addicts, and in recent years it has not been possible to diminish its incidence despite the multiple strategies developed to reduce harm among this population and the change in consumption patterns (reduction in the use of opiates, and of intravenous drug use etc.). Males show much higher death rates than females, which is not exclusively attributable to greater levels of drug use among them, since the percentages by gender are much higher than those detected in population surveys and among drug addicts who seek treatment. The average age of the deceased, relatively high, which is going up year on year, means that deaths are not usually happening among new or inexperienced users, but rather among those with a long-term experience of consumption. More than half of all deaths were concentrated around the weekend, with Saturdays and Sundays being the days of the week with greatest prevalence, which could be related to the consumption of associated substances at those times. Regarding the place in which the dead body was found (and supposedly where death had occurred), it seems to be primarily the subject's own home, with a slight, and increasing, tendency for this to happen there, and in the street, where there is a slight downward tendency (both data sets seem to indicate a reduction in the marginalization of these subjects). But possibly the most striking fact is the continuous increase of those who die in penitentiary institu-

tions. Among these patients, as in the drug-dependent population in general, there was a reduction in intravenous use, as in the presence of HIV-seropositivity. The most frequently detected substances among the deceased in this group continued to be the opiates, especially heroin, but increasingly less, with, on the contrary, an increased presence of methadone, which indicates higher levels of accessibility to this substance and a greater level of penetration of maintenance programs using opiate agonists among the drug-dependent patients. After some years with a marked increase in cocaine amongst ADR victims, it seems that in the later years of our study this tendency was reversing. Other substances, such as alcohol or benzodiazepines remained relatively stable, with certain fluctuations from one year to another, but with no clear tendency over the study period. In the great majority of subjects, the presence of two or more substances was determined, which makes it difficult to establish a clear link between the concentrations detected of each of them and the causal attribution of the death. On the other hand, the most usual pattern of poly-consumption is reflected and had already been detected in other indicators (population surveys, treatment etc.).

Therefore, the group that is principally at risk is made up of male drug addicts with a dependency on opiates, who have been previously consuming for some years, and who usually combine several substances, particularly CNS depressants. Many of them are candidates for, or are already enrolled in maintenance programs with opiate agonists. It is on them, and their immediate circles, where strategies that allow them to avoid situations of risk should be focused, and in case of suffering an overdose, identify the signs and symptoms, give first aid and alert the health services with the aim of preventing a fatal outcome.

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Conflict of interests:

The authors state that there are no conflicts of interest to declare.

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Cannabinoid hyperemesis syndrome. A report of six new cases and a summary of previous reports

Síndrome de hiperemesis cannabinoide. Reporte de seis nuevos casos clínicos y resumen de casos previos publicados

Carla Contreras Narváez*, Montserrat Mola Gilbert*, Enric Batlle de Santiago*, Jordi Bigas Farreres**, Eloy Giné Serven*, Josep Cañete Crespillo*

* Department of Mental Health and Addictions, Mataró Hospital; ** Emergency Department, Mataró Hospital.

Abstract

Cannabinoid hyperemesis syndrome (CHS) is a medical condition which was identified for the first time in 2004 and affects chronic users of cannabis. It is characterized by cyclic episodes of uncontrollable vomiting as well as compulsive bathing in hot water. The episodes have a duration of two to four days. The vomiting is recognizable by a lack of response to regular antiemetic treatment, and subsides only with cannabis abstinence, reappearing in periods of consumption of this substance.

The etiology of this syndrome is unknown.

Up until June 2014, 83 cases of CHS were published worldwide, four of them in Spain.

The first patient of CHS at Mataró Hospital was diagnosed in 2012. Since then, five new cases have been identified. The average duration between the onset of acute CHS episodes and diagnosis is 6.1 years, similar to that observed in previously published cases, an average of 3.1 years. This "delay" of CHS diagnosis demonstrates a lack of awareness with respect to this medical condition in the healthcare profession.

With the objective of providing information concerning CHS and facilitating its timely diagnosis, a series of six new cases of CHS diagnosed in Mataró Hospital is presented along with a summary of cases published between 2004 and June 2014.

Keywords: cannabinoid hyperemesis, cannabis, cyclical vomiting, compulsive hot bathing.

Resumen

El sindrome de hiperemesis cannabinoide (SHC) es una entidad clínica descrita por primera vez en 2004, la cual afecta a consumidores crónicos de cannabis y se caracteriza por episodios cíclicos de vómitos incoercibles acompañados por baños en agua caliente compulsivos. Estos episodios tienen una duración de 2 a 4 días. Los vómitos se caracterizan por no responder al tratamiento antiemético habitual, cediendo unicamente con la abstinencia de cannabis, reapareciendo en períodos de consumo de esta sustancia.

Hasta Junio de 2014 fueron publicados 83 casos de SHC en el mundo, 4 de ellos en España, siendo la etiología de este sindrome aún desconocida.

En el hospital de Mataró se diagnosticó un primer paciente de SHC en 2012. Desde entonces se han identificado cinco nuevos casos. Destaca en ellos un tiempo promedio de 6,1 años entre el inicio de los episodios agudos de SHC y el diagnóstico (3,1 años en los casos previos publicados). Este tiempo de "retraso" del diagnóstico de SHC evidencia un desconocimiento respecto a esta entidad clínica en los servicios de salud.

Con el objetivo de aportar información respecto al SHC y facilitar con ello su diagnóstico oportuno, se presenta esta serie de seis nuevos casos de SHC diagnosticados en el Hospital de Mataró y un resumen de los casos publicados entre 2004 y Junio de 2014.

Palabras clave: hiperemesis cannabinoide, cannabis, vómitos cíclicos, baños en agua caliente compulsivos.

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Send correspondence to:
Carla Contreras Narváez. Carretera de Cirera s/n – 08304 Mataró. Barcelona. España.
E-mail: hcarla@gmail.com

Cannabis is one of the most commonly used addictive substances worldwide (United Nations Office on Drugs and Crime, n.d.).

In Spain, it is the illegal psychoactive substance used most widely at some point in life in the general population (27.4%), and the substance tried at the earliest age for the first time (18.7 years) (Spanish Observatory on Drugs, 2012; Delegación del Gobierno para el Plan Nacional sobre Drogas, 2010).

The effects of cannabinoids on the organism are mediated by the binding of exogenous cannabinoids found in the marihuana plant to the endocannabinoid receptors (CB1 and CB2) widely distributed throughout the organism (Table 1). Of the 66 exogenous cannabinoids, Delta-9- tetrahydrocannabinol (D9-THC) is the psychoactive component via its binding to the CB1 receptor.

The study of the effects of D9-THC on the organism has enabled the use of cannabis for therapeutic purposes (Duran & Capellà, 2004; Lorenzo & Leza, 2000), and one example of this is its application as an antiemetic for controlling nausea and vomiting in chemotherapy patients (Adler & Colbert, 2013; Rodriguez de Fonseca & Navarro, 2000).

In contrast to these antiemetic properties, in 2004 nine cases of a new syndrome, named cannabinoid hyperemesis (CHS), were published. This syndrome affects chronic cannabis users and is characterized by cyclical episodes of uncontrollable vomiting and compulsive bathing in hot water. These episodes subsided when abstaining from the substance and reappeared on renewed consumption (Allen, de Moore, Heddle, & Twartz, 2004).

Since the publication of Allen et al. (2004) until June 2014, 74 new cases were reported in various European countries, four of them in Spain (Aguilar-Urbano, Perez-Asia, Navarro-Jarabo, & Sánchez-Cantos, 2011; Alfonso, Ojeda, & Moreno-Osset, 2006; Ochoa-Mangado, Jiménez, Salvador, & Madoz-Gúrpide, 2013; Roca-Pallín, López-Pelayo, Sugranyes, & Balcells-Oliveró, 2013).

Some diagnostic criteria have been put forward for CHS (Table 2) (Simonetto, Oxentenko, Herman, & Szostek, 2012; Sontineni, 2009), as well as an algorithm for the diagnosis and treatment of the syndrome (Wallace,

Table 1. *Distribution of endocannabinoid receptors in the organism.*

Receptor	Location	Receptor	Location
CB1		CB2	
	Central nervous system		Central nervous system
	Cerebral cortex		Immune system
	Basal ganglia		
	Cerebellum		
	Hypothalamus		
	Hippocampus		
	Adipose tissue		
	Gastrointestinal tract		
	Respiratory system		
	Cardiac system		
	Reproductive system		

Table 2. *Proposed diagnostic criteria for Cannabinoid Hyperemesis Syndrome.*

Essential criterion	
	Chronic consumer of cannabis: longer than one year.
Main criteria	
	Severe nausea and vomiting
	Improvement with cannabis abstinence
	Relief of symptoms with bathing in hot water
	Epigastric or periumbilical abdominal pain
Supporting criterion	
	Younger than 50 years of age
	Loss of weight greater than 5 kilos
	Symptoms predominantly in the mornings
	Normal bowel habits
	Normal laboratory test, radiography and endoscopy results

Table 3. *Pathophysiology of Cannabinoid Hyperemesis Syndrome.*

Author	Theory
Darmani, 2002; Woods et al. 2014	In theory the antiemetic effect of cannabis is mediated by the binding of D9-THC to CB1as a partial agonist, producing antiemesis at low doses and hyperemesis at high doses.
Woods et al., 2014	In genetically susceptible individuals, high doses of cannabis could be mediated by a disorder of hepatic cytochrome p450 which metabolizes D9-THC, producing an increase in its concentration.
Allen et al., 2004	In genetically susceptible individuals, the high liposolubility of D9-THC would mediate an over-accumulation in fatty tissue.
Allen et al., 2004	Bathing in hot water may relieve a false sensation of cold mediated by the effect of D9-THC at the level of CB1 located in the hypothalamus.
Allen et al., 2004	Bathing in hot water may relieve a real sensation of cold caused by vasoconstriction of the superficial capillaries and vasodilatation of the deep capillaries produced by the union of D9-THC to CB1

Table 4. *Summary of treatments used in Cannabinoid Hyperemesis Syndrome.*

Drug	Indication and dose	Therapeutic response	Author
Serum NaCl 0.9% E.V.	Hydration 1-2 L bolus followed by 150-200 mL/h in 24-48 h	Clinical improvement	Allen et al. 2004; Price et al. 2011.
Morphine	Pain 4 mg IV on patient's demand	Clinical improvement	Price et al. 2011
Paracetamol	Cephalea 650 mg oral if pain	Clinical improvement	Price et al. 2011
Lorazepam	Nausea/vomiting 1mg IV x 1 OR 1 mg IV c/4 h on demand	Clinical improvement	Cox et al. 2012; Price et al. 2011.
Clorpromazine	Hiccough 25 mg IV on demand	Clinical improvement	Price et al. 2011
Haloperidol	5 mg IV frequency not described	Clinical improvement	Hickey et al. 2013.
Ondansetron	4 mg IV frequency not described	Clinical improvement	Hickey et al. 2013.

Andrews, Garmany, & Jelley, 2011). However, the etiology of CHS is still unknown, and Table 3 summarizes the pathophysiological theories so far proposed for CHS. Given this context, treatment for acute episodes is symptomatic (Table 4). The pathophysiology of CHS, and in more detail the clinical practice and therapeutic guidelines for the treatment of acute episodes can be found in the publications of the cases.

The first diagnosis of CHS was made in Mataró hospital in 2012. The patient was a 35-year old man, a chronic consumer of cannabis presenting with episodes of hyperemesis since 2002 and diagnosed with psychogenic vomiting. On the diagnosis of CHS, medical units of the hospital were alerted to the new medical condition, after which five new cases of CHS were identified up until June 2014 (Table 5).

Similarly to the cases previously published (Table 6), in this series of six new cases an average of period of over a year passed between initial symptoms and correct diagnosis of CHS. During this time, patients were subjected to medical tests with negative results, and more the 50% of patients were hospitalized at least once for etiological analysis.

With the aim of providing information about this new clinical condition and facilitating prompt diagnosis of CHS, this study offers a summary of previously published cases and a description of new cases diagnosed in Mataró hospital.

Method

Reports of new cases

Six adult patients (minimum age 22) labeled with the letters A, B, C, D, E, F were treated in various units of Mataró hospital between November 2012 and June 2014 for uncontrollable vomiting and hot baths, and diagnosed with CHS (Table 4). Three patients were referred by the emergency department to the emergency psychiatric unit to assess their "self-induced vomiting" and potomania (patients A, B and D). One patient was referred by a primary healthcare physician to a drug addiction center for cannabis cessation treatment (patient E); and two patients were hospitalized in the surgical unit for a study of vomiting, during which time consultation with a psychiatrist was sought on the grounds of anxiety (patients C and F).

Summary of published cases

A bibliographic review was carried out using the online PubMed database.

The search terms "cannabinoid hyperemesis syndrome" and "cannabinoid hyperemesis" were used. No time limits were set. All articles in English, Spanish, German, and French with explicit reference to this medical condition in the title and published prior to June 2014 were selected.

Of the 60 articles selected, 44 corresponded to reports (Table 6). One of these was excluded because it was a retrospective survey (Simonetto, Oxentenko, Herman, & Szostek, 2012). Four articles corresponded to bibliographic reviews (Galli, Andari, & Friedenberg, 2011; Nicolson, Denysenko, Mulcare, Vito, & Chabon, 2012; Sun & Zimmermann, 2013; Wallace et al., 2011), one of which also reports four cases (Nicolson et al., 2012); ten articles were letters to the editor (Aguilar-Urbano et al., 2011; Alfonso et al., 2006; Budhraja, 2009; Roca-Pallín et al., 2013; Roche & Foster, 2005; Roelofs, Vorel, Vorel-Havelkova, & Brombacher-Heerlen, 2005; Sannarangappa & Tan, 2009; Singh & Coyle, 2008; Torka & Sharma, 2012; Wolfhagen, 2014) of which seven also reported cases (Aguilar-Urbano et al., 2011; Alfonso et al., 2006; Roca-Pallín et al., 2013; Roche et al., 2005; Sannarangappa et al., 2009; Torka et al., 2012; Wolfhagen, 2014). Finally, two articles consisted of clinical notes, without presenting a case (Francis, 2011; Sullivan, 2010).

A table summarizing the published clinical cases of CHS up to June 2014 was drawn up (Table 5).

Table 5. *Clinical features of six new cases of CHS.*

	A	B	C	D	E	F
Age (years)	37	22	26	31	29	25
Sex	M	M	F	M	M	M
Cannabis onset age (years)	24	14	18	16	15	13
Units smoked/day	1	<1	1	3 to 6	10 to 12	1 to 2
Use of other toxic substances	Tobacco and alcohol	Tobacco and alcohol	No	Tobacco, alcohol, cocaine and heroin	Tobacco, cocaine, amphetamines and others	Tobacco and alcohol
Age onset of vomiting (years)	27	16	23	21	22	24
Bathing in hot water	Yes	No	Yes	Yes	Yes	Yes
Other symptoms during acute episode	Polydipsia	No	Polydipsia	No	Polydipsia	Epigastralgia
Duration of acute episode (days)	3 to 4	3 to 4	4 to 5	2 to 3	4 to 5	3 to 4
Annual frequency of acute episode	2 to 4	2	4	1 to 2	2 to 3	6
Years between onset of consumption and onset of vomiting	3	2	5	5	7	11
Years between onset of vomiting and diagnosis	10	6	3	10	7	1
N. of visits to emergency dept. before diagnosis	>30	4	6	12	4	6
N. of hospitalizations before diagnosis	>3	No	3	No	No	1
Abstinence after psychoeducation about CHS	No	Yes	Yes	No	Yes	No

Results

Series of six new cases identified in Mataró hospital

Table 5 presents a summary of the clinical features of the six patients diagnosed with CHS in Mataró hospital between November 2012 and June 2014. There were five men (83%) and one woman (17%), with an average age of 28.3 and average onset age of cannabis use of 16. All patients said they started smoking cannabis recreationally and continued using it for its anxiolytic effect.

The average quantity and frequency of cannabis use was 7.5 cigarettes per day (with a minimum of less than 1 and a maximum of 12 cigarettes per day). One patient (B) described smoking less than one cigarette per day. All other patients said they smoked more than one cannabis cigarette a day. All patients affirmed that they had been smoking cannabis for at least a year before the first acute episode of CHS; the average was 5.5 years (minimum 2, maximum 11).

The average length of time between the onset of symptoms and diagnosis of CHS was 6.1 years (minimum 1, maximum 10). During this period, the patients went to the emergency department an average of ten times with incoercible vomiting and were subjected to etiological analysis which included at least one abdominal X-ray, an upper endoscopy and a blood test per patient. Three of the six patients (C, E and F) had to be admitted to the surgery department for these and other diagnostic tests. However, none of these analyses detected any somatic pathology which could cause vomiting and compulsive hot bathing.

During acute episodes, patients needed treatment in the emergency department, where it was observed that the six patients had a generally uncooperative attitude and suffered from anxiety and compulsive hot bathing, taking up to ten baths a day (patient A) and at least four (patient D). Three patients had polydipsia (A, C and E). All six patients achieved clinical remission after an average of 3.6 days of cannabis abstinence (minimum 2, maximum 5), coinciding with the length of their stay in the emergency ward for the treatment of acute CHS symptoms. It was an enforced abstinence given that they were in hospital.

For the symptomatic treatment of the acute CHS episode, the six patients received metoclopramide, 20-30 mg/day intramuscularly, and ondansetron in 4 mg/day doses of intravenously. As an anxiolytic, diazepam was administered in doses of up to 40 mg/day orally. In acute episodes of vomiting, patient A was uncooperative, demanding treatment, distressed and suffering from psychomotor agitation; up to 40 mg/day of olanzapine was therefore administered orally or intramuscularly, and up to 20 mg/day of haloperidol administered intramuscularly or intravenously. The use of these drugs brought about a temporary therapeutic response, with relief of both nausea and anxiety for a minimum of one and a maximum of four hours, af-

ter which symptoms manifested themselves again with the same degree of intensity observed before the respective drug was administered.

After the CHS diagnosis, all patients were advised to abstain from cannabis use and were offered cessation treatment, which they accepted and to which responded differently.

Up until the presentation of this study, five patients (A, B, C, E and F) were monitored by drug dependency units. Of these, B, C and E achieved continued cannabis abstinence and a consequent absence of new CHS episodes. Of those who continued using cannabis, patient A relapsed into regular consumption and had on average one episode of acute CHS per month, while patient F reported reducing cannabis consumption from three to one cigarettes per day, without renewed CHS episodes being observed during outpatient monitoring.

The patient who abandoned treatment (D), did not register again for CHS treatment in emergency or primary care.

Summary of previously published cases

A total of 83 published cases of CHS were found (Table 5). The average age was 29.57 years (standard deviation 8.43), with a majority of male patients (72.2% of cases).

The average onset age of cannabis use was 17.38 (SD 6.69), and the average age when vomiting began was 25.89 (SD 8.239). The period of time between the onset of symptoms and diagnosis of CHS was observed to be between less than one year and 29 years (average 3.01 years, SD 4.1 years). Bathing in hot water was present in 91% of cases.

The described treatments administered were of a symptomatic nature. All studies concur in observing that standard antiemetics had "little or no" effect. The drugs used in treatment are summarized in Table 4.

Regarding the advice that continued abstinence is the most effective treatment for CHS, differences depending on the type of publication were observed. Giving this advice to patients was mentioned in 70 of the 83 cases. Of these 70 patients, 59 (84.2%) reported abstinence, while 11 patients reported maintaining use. Of the 59 remaining abstinent, 8 suffered new CHS episodes. In 13 cases the corresponding article failed to mention whether the advice to remain abstinent once CHS was diagnosed was given to the patients concerned.

Discussion

The six patients diagnosed with CHS in Mataró hostpital met the diagnostic criteria proposed by Simonetto et al. (2012) presented in Table 2. As observed in earlier publications, the patients were young, mostly male and had been suffering cyclic vomiting for more than a year. They had also been diagnosed wrongly and been subjected to etiological analyses with negative results.

After the first case of CHS was identified in Mataró hospital, the different medical units were informed about this new condition and patients presenting with cyclic vomiting and having a history of chronic cannabis consumption were subsequently referred to the mental health department for possible CHS. In such cases, hot bathing proved to be a decisive element for the correct diagnosis. This clinical sign, which was proposed as pathognomic of CHS (Wallace et al., 2011) was described by the six patients diagnosed in Mataró hospital, matching the observations made in the previously published cases (hot bathing is reported in 91%). This "compulsive" bathing is described as a learned behavior. During the hyperemetic phase, patients note their symptoms relieved during their usual bathing and therefore repeat the behavior. The relief observed is proportional to the water temperature (Allen et al., 2004). In terms of frequency, the description in the published cases is varied. In one report, for example, a patient had 15 baths a day (Mohammed, Panchoo, Bartholemew, & Maharaj, 2013), and in another, a patient claimed to spend four hours a day in the bath (Cox, Chhabra, Adler, Simmons, & Randlett, 2012). In our series, patient A "needed" more than ten baths per day, and the rest between three and five per day. As a complication of the bathing, erytheme ab igne was identified in one of the patients described who took five or six hot baths daily (Kraemer, La Hoz, & Willig, 2013).

During acute episodes of CHS, the six patients diagnosed in our hospital needed intravenous rehydration and were kept under observation in the emergency department for a minimum of 48 hours. In addition, patient A was admitted to intensive care on two occasions with symptoms of acute renal failure, a complication described in one previously published case (Habboushe & Sedor, 2014).

Other complications of CHS described in previous publications are: weight loss (Allen et al., 2004; Singh et al., 2007) and esophagitis (Allen et al., 2004; Chang & Windish, 2009; Sontineni, 2009).

It must be noted that abstinence was not observed in the all the cases where patients were offered medical advice about the link between cannabis consumption and CHS. In our series of cases, the patient with the greatest number of acute episodes of CHS and with the most serious complications (patient A), is the only one who has continued using cannabis habitually (and subsequently suffered monthly episodes of CHS) to date. This situation is consistent with the deleterious effect cannabis can have on the control of decision-making (Alameda-Bailén, Salguero-Alcañiz, Merchán-Clavellino, & Paíno-Quesada, 2014), which increases the likelihood among susceptible individuals of continuing consumption, and with it the episodes of CHS.

Table 6. *Cases of Cannabinoid Hyperemesis Syndrome published up to June 2014.*

Author	No. of case	Age (years)	Sex	Bathing in hot water	Age of cannabis onset (years)	Years of consumption before onset of vomiting	Years of consumption before diagnosis	Improvement with abstinence
Allen et al.	1	23	male	yes	19	3	1.3	yes
	2	29	female	yes	17	3	9	yes
	3	44	male	yes	16	6	12	yes
	4	37	male	yes	17	17	3	yes
	5	21	male	yes	12	5	4	no
	6	38	male	yes	17	17	4	yes
	7	36	female	yes	12	2	3	yes
	8	21	female	yes	14	3	0.5	yes
	9	49	female	no	18	14	6	no
Boeckxstaens	10	30	male	yes	14	not mentioned	not mentioned	not mentioned
Roche and Foster	11	38	male	yes	not mentioned	not mentioned	2	yes
Alfonso Moreno et al	12	49	female	yes	18	2	29	yes
Wallace et al	13	30	male	not mentioned	18	7	5	yes
Chapyala & Olden	14	38	male	yes	18	17	3	yes
Singh & Coyle	15	46	male	yes	not mentioned	not mentioned	not mentioned	yes
Chang & Windish	16	25	female	yes	19	5	1	yes
Ochoa-Mangado et al	17	25	female	yes	19	11	7	yes
Sannarangappa & Tan	18	34	male	yes	19	55	10	yes
Sontinent et al	19	22	male	yes	16	5	0.2	yes
Watts	20	32	male	yes	16	13	3	yes
Donnino et al	21	22	male	yes	not mentioned	not mentioned	2.1	yes
	22	23	male	yes	20	1	1.7	yes
	23	51	male	yes	not mentioned	not mentioned	2	yes
Soriano-Co et al	24	34	male	yes	20	19	1	yes
	25	34	female	yes	13	19	2	no
	26	26	male	yes	14	9	5	yes
	27	34	male	yes	10	21	3	yes
	28	38	female	yes	15	15	8	yes
	29	27	male	yes	9	19	o	no
	30	35	male	yes	15	20	0	no
	31	31	female	yes	13	16	2	no improvement
Price et al	32	30	male	yes	not mentioned	not mentioned	not mentioned	not mentioned
Shmid et al	33	36	male	yes	13	not mentioned	not mentioned	yes
Miller et al	34	17	male	yes	14	1	1	yes
	35	18	female	yes	16	2	1.5	yes
Patterson et al	36	20	male	yes	16	3	3	no abstinence
	37	27	male	yes	17	10	9	no abstinence
	38	31	male	yes	15	16	5	no abstinence
	39	43	male	yes	15	28	4	no abstinence
Aguilar-Urbano et al	40	19	male	yes	not mentioned	not mentioned	1	not mentioned
	41	40	male	yes	34	6		not mentioned
Wild & Wilson	42	21	female	no	14	7	0	not mentioned
Bagdure et al	43	27	male	yes	21	5	6	yes

Author	No. of case	Age (years)	Sex	Bathing in hot water	Age of cannabis onset (years)	Years of consumption before onset of vomiting	Years of consumption before diagnosis	Improvement with abstinence
Nicolson et al	44	27	male	yes	17	7	9	no abstinence
	45	22	female	yes	17	5	5	no abstinence
	46	24	male	yes	14	8	10	not mentioned
	47	20	female	yes	16	2.5	3.5	yes
Torka & Sharma	48	20	male	yes	18	2	2	not mentioned
	49	42	male	yes	39	3m	3m	yes
Cox et al	50	28	male	yes	18	10	10	yes
Achanta & Kelkhoff	51	20	male	not mentioned	16	20	not mentioned	yes
Morris & Fisher	52	20	female	yes	16	20	‹1	yes
Fabries et al	53	28	female	not mentioned	21	7	not mentioned	yes
	54	40	male	not mentioned		›10	not mentioned	yes
	55	24	male	not mentioned	not mentioned	not mentioned	not mentioned	yes
	56	19	female	not mentioned	15	4	not mentioned	yes
	57	22	male	not mentioned	10	12	not mentioned	yes
	58	35	female	not mentioned	not mentioned	not mentioned	not mentioned	yes
	59	27	female	not mentioned	not mentioned	not mentioned	not mentioned	yes
Hickey, Ribaud &Puidupin	60	34	male	yes	1	14	10	not mentioned
Kraemer; La Hoz & Willig	61	42	male	yes	not mentioned	not mentioned	not mentioned	not mentioned
Sofka & Lerfald	62	28	male	yes	17	7	11	no abstinence
	63	32	male	yes	19	11	2	no abstinence
	64	23	female	yes	15	7	1	no abstinence
	65	22	male	yes	13	9	6m	yes
Hopkins &Gilchrist	66	30	male	yes	13	not mentioned	not mentioned	yes
Enuh. Chin & Nfonoyim	67	47	male	yes	17	not mentioned	not mentioned	not mentioned
Mohammed et al	68	26	male	yes	24	1.5	1.5	yes
Roca-Pallín et al	69	36	female	yes	31	5	5	yes
Williamson et al	70	39	male	yes	19	33	6	yes
	71	19	male	yes	17	not mentioned	not mentioned	yes
Gupta, Ojo &Muruthettuwegama	72		female	yes	not mentioned	not mentioned	not mentioned	yes
Woods et al	73	37	male	yes	not mentioned	14	14	no
Habboushe & Sedor	74	25	male	yes	17	not mentioned	not mentioned	no
Fleig & Brunkhorst	75	28	male	yes	17	10›	‹1	no abstinence
Barmstedt & Dissmann	76	36	male	yes	12	not mentioned	not mentioned	not mentioned
Bonet, Chang & Schebaum	77	27	male	yes	16	not mentioned	not mentioned	yes
Lieb et al	78	29	female	yes	18	not mentioned	not mentioned	yes
Stuijvenberg, Ramaekers & Bijpost	79	22	male	not mentioned	12	3	7	yes
	80	22	female	yes	not mentioned	not mentioned	1	yes
	81	25	female	yes	not mentioned	not mentioned	not mentioned	not mentioned
Sannarangappa & Tan	82	34	male	yes	19	5	10	no abstinence
Wolfhagen	83	46	male	si	10	19	8	not mentioned

Conclusions

The effects of exogenous cannabinoids on the organism are still not known in their entirety. In the context of the high prevalence of cannabis consumption in Spain, however, we consider it necessary to raise the awareness of healthcare providers about the existence of this syndrome, since a timely diagnosis can avoid unnecessary examinations, which are unpleasant for the patient and costly for the healthcare system.

Further studies are necessary in order to understand the pathophysiological mechanism by which cannabis induces hyperemesis.

Given that the treatment of acute CHW episodes is symptomatic, and that hot bathing constitute a learned behavior which relieves the symptoms of nausea and vomiting, we propose that this behavior is accepted as part of the treatment. For example, agreement could be reached with the patient, setting the number of baths per day and the most suitable temperature to prevent health risks to the patient during the acute phase of CHS.

Limitations of the study

In the summary of cases published to date, articles were included which were written in a variety of formats, with some of them omitting information included in Table 6. When studying the data in this table, only those patients describing a feature in the respective publication were taken into account in its analysis.

Conflict of Interests

The writers of this article declare no conflict of interests.

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Long term follow-up of a tobacco prevention and cessation program in cystic fibrosis patients

Seguimiento a largo plazo de un programa de prevención y cesación tabáquica en pacientes con fibrosis quística

Juan Antonio Ortega-García*, Joseph E. Perales*, Alberto Cárceles-Álvarez*, Miguel Felipe Sánchez-Sauco*, Seiichi Villalona*, Pedro Mondejar-López**, María Dolores Pastor-Vivero**, Pilar Mira Escolano***, Diana Carolina Jaimes-Vega*, Manuel Sánchez-Solís**

*Unidad de Salud Medioambiental Pediátrica; **Neumología Pediátrica y Fibrosis Quística; ***Área de Medicina Preventiva; Hospital Clínico Universitario Virgen de la Arrixaca. Murcia, España.

Abstract

This study evaluates the impact over time of a telephone-based intervention in tobacco cessation and prevention targeting patients with cystic fibrosis (CF) in the Mediterranean region of Murcia, Spain. We conducted an experimental prospective study with a cohort of CF patients using an integrative smoking cessation programme, between 2008 and 2013. The target population included family members and patients from the Regional CF unit. The study included an initial tobacco exposure questionnaire, measurement of lung function, urinary cotinine levels, anthropomorphic measures and the administered intervention at specific time intervals. Of the 88 patients tracked through follow-up, active smoking rates were reduced from 10.23% to 4.55% (p = 0.06). Environmental tobacco exposure was reduced in non-smoker patients from 62.03% to 36.90% (p < 0.01) during the five year follow-up. Significant reductions in the gradient of household tobacco smoke exposure were also observed with a decrease of 12.60%, from 31.65% (n = 25/79) to 19.05% (n = 16/84) in 2013 (p = <0.01). Cotinine was significantly correlated with both active and passive exposure (p<0.01) with a significant reduction of cotinine levels from 63.13 (28.58-97.69) to 20.56 (0.86-40.27) ng/ml (p<0.01). The intervention to significantly increase the likelihood of family quitting (smoke-free home) was 1.26 (1.05-1.54). Telephone based interventions for tobacco cessation and prevention is a useful tool when applied over time. Trained intervention professionals in this area are needed in the environmental health approach for the treatment of CF.

Key words: Environmental tobacco smoke, cystic fibrosis, smoking prevention and cessation.

Resumen

Este estudio evalúa el impacto en el tiempo de una intervención telefónica de prevención y cesación tabáquica dirigida a pacientes con fibrosis quística (FQ) en la Región de Murcia, España. Estudio prospectivo experimental en una cohorte de pacientes con FQ utilizando un programa integrativo de cesación tabáquica, entre 2008 y 2013. La población diana incluye a pacientes y familiares de la unidad regional de FQ. El estudio incluyó un cuestionario inicial de exposición al tabaco, medición de la función pulmonar, niveles de cotinina en orina, medidas antropomórficas y la intervención realizada en intervalos de tiempo. De los 88 pacientes seguidos, la tasa de fumadores activos se redujo de 10,23% a 4,55% (p = 0,06). La exposición al humo ambiental de tabaco se redujo en los pacientes no fumadores de 62,03% a 36,90% (p < 0,01) durante los cinco años de seguimiento. Se observaron reducciones significativas en la exposición al humo ambiental de tabaco en los hogares, de 31,65% (n = 25/79) a 19,05% (n = 16/84) en 2013 (p = <0,01). La cotinina se correlacionó significativamente con la exposición al tabaco activa y pasiva (p < 0,01) con una reducción significativa de los niveles de cotinina de 63,13 (28,58-97,69) a 20,56 (0,86-40,27) ng/ml (p < 0,01). La intervención para aumentar significativamente la probabilidad de abandono familiar (hogar libre de humo) fue de 1,26 (1,05-1,54). La intervención telefónica mantenida en el tiempo es una herramienta útil para la prevención y cesación tabáquica. Profesionales entrenados en este modelo de intervención con enfoque en salud medioambiental son necesarios para mejorar el tratamiento de FQ.

Palabras clave: Humo ambiental de tabaco, fibrosis quística, prevención y cesación tabáquica.

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Send correspondence to:
Dr. Juan Antonio Ortega-García, Unidad de Salud Medioambiental Pediátrica, Instituto Murciano de Investigación Biosanitaria (IMIB), Hospital Clínico Universitario Virgen de la Arrixaca, 30120, Murcia, España. E-mail: ortega@pehsu.org.

Cystic fibrosis (CF) is an autosomal recessive disease detected in 0.73 per 10,000 people in the Europe Union (Farrell, 2008), whose major manifestations are: pancreatic insufficiency, malabsorption, progressive deterioration of lung function and growth retardation (Beers & Berkow, 1999; Tyc & Throckmorton-Belzer, 2006). Patients with CF possess an increased risk for harm from exposure to tobacco smoke (Kopp et al., 2015; Ortega-García et al., 2012a; Raju et al., 2013). Several studies report that prenatal and/or postnatal exposure to tobacco smoke adversely affects children's lung function. The published CF studies report a prevalence of exposure to tobacco smoke from 6% to 21% lower than in general population (Mc Ewan, Hodson & Simmonds, 2012; Ortega-García et al., 2012a; Stern, Byard, Tomashefski & Doershuk, 1987; Verma, Clough, McKenna, Dodd & Webb, 2001). Smoking is known to irritate mucosal linings and increase coughing and phlegm production in the respiratory tract, resulting in increased likelihood of bacterial infections, worsening of symptoms, and increased hospitalizations in patients with CF. Several studies have even found a dose-dependent relationship between the number of cigarettes smoked and the severity of respiratory disease in these patients.(Cook, Strachan & Carey, 1998; Ortega-García et al., 2012a; Smyth, O'Hea, Williams, Smyth & Heaf, 1994; Verma et al., 2001). Despite evidence of the deleterious effects of CF more studies are needed that evaluate interventions among CF patients and smoking cessation (Cook et al., 1998).

Telephone-based assistance programs are a useful methodology in tobacco cessation but more exploration is needed to measure its efficacy in CF patient populations (Lancaster & Stead, 2005). Additionally, the benefits of telephone assisted interventions plus counseling have yielded success (Lancaster et al., 2005; Ramon et al., 2013; Stead, Hartmann-Boyce, Perera & Lancaster, 2013). This intervention modality for smoking prevention and cessation in CF patients and their families has shown adequate adherence during one year follow-up (Ortega-García et al., 2012a). The objective of the present study is to evaluate the longitudinal impact of an integrated telephone based tobacco prevention and cessation intervention program amongst a cohort of CF patients during five-year follow-up in Murcia, Spain.

Patients and Methods

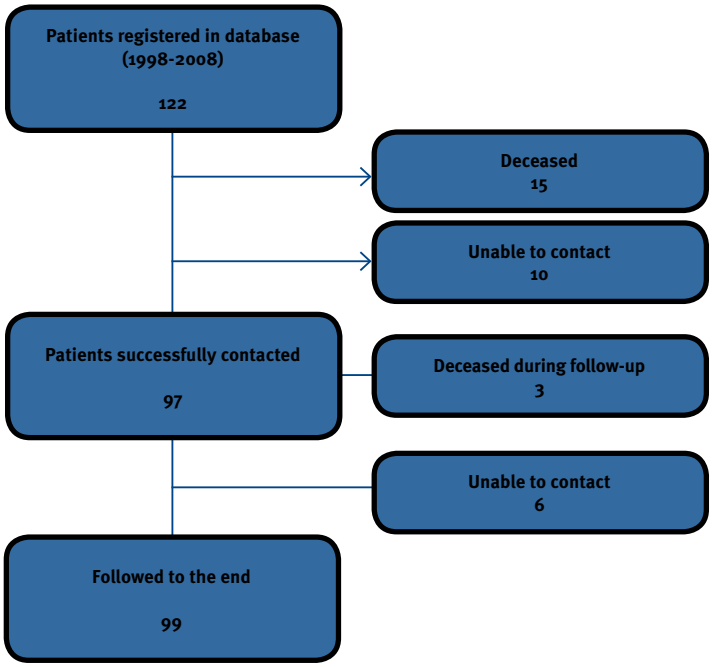
We conducted an experimental prospective study with one cohort of patients in the Region of Murcia, Spain. The study follows CF patients before and after an integrative smoking cessation program with proactive telephonic brief counselling, between 2008 and 2013. The study included all CF patients registered at the Regional CF Unit of the University Hospital, Virgen of the Arrixaca from 1998 to 2008. More than 95% of the study sample was obtained from the regional hospital unit's patient registry. The study was approved by the hospital network ethics committees and the institutional review boards.

Patients were verified for positive CF diagnosis through medical record review and assignment into the regional hospital unit; from 2007, patients were also diagnosed through neonatal screening. The study followed 88 of the 122 patient participants enrolled from the Pneumology and Environmental Health units. Figure 1 shows the algorithm for enrollment and follow-up in the intervention.

Initial contact with families was made via the mailing of an introduction letter from the Regional CF unit announcing the study's inception. The letter introduced the program and provided health education on the importance of maintaining a tobacco-free home for patients with CF and instructed participants that a trained tobacco cessation counsellor would be in contact in the incoming weeks.

Those families that consented to participate in the intervention were contacted by a nurse or physician from the Paediatric Environmental Health Specialty Unit (PEHSU) trained in tobacco cessation. Intervention staff completed a tobacco cessation training that consisted of 40 hours of theoretical and 100 hours of practical training. The intervention was made up of telephone based brief counseling and follow-up, carried out 2 or 3 times per year for five years.

Once contacted, the participants were screened with an introductory questionnaire that assessed active and passive environmental tobacco exposures during critical periods of the patient's development. Socio-demographic variables of interest included: tobacco exposure and consumption, family composition, income, structural aspects of patient



Note. 34 participants were lost to follow-up and were not included in the analysis as they did not complete the five year follow-up. The requisite five attempts were made to each participant in order to contact them, as per protocol. Eighteen participants exited the study as a result of death; of the known causes of death, two were from cardiac arrest related to complications from CF.

Figure 1. Enrollment and follow-up algorithm

household, education level of the patients and their parents. Results regarding these data collected at baseline were previously published by the authors (Ortega-García et al., 2012a).

We have used the following classification of smoking (Ferris, 1978). 1. Non-smoker: a) no tobacco smoke exposure, and b) passive smoker, exposure to smoke from individuals in their social and family environment. 2. Occasional smoker: does not smoke daily. 3. Smoker: smokes at least 1 or more cigarettes/day. 4. Ex-smoker: does not smoke at the time of the study, and has not smoked for at least 6 months.

With all this data, we created an "exposure at home" variable, which collects any type of tobacco exposure of special interest, especially in non-smoking patients: 1. Non-smoker without exposure at home. 2. Non-smoker living with smokers at home. To assess the effect of genetic mutations associated with CF, participants were divided into three groups: F508del homozygotes, F508del heterozygotes, and those without the F508del mutation. *Pseudomonas aeruginosa* (Pa) colonization (yes/no) was also considered.

Participant height and weight were obtained via self-reported by patients or their families in order to calculate body mass index (BMI). The BMI was constructed utilizing standard deviations by age and gender as defined by the World Health Organization. BMI was then categorized into three areas within two standard deviations: underweight, <2SD (<10th percentile), normal (between 10th – 85th percentile), and overweight >2SD (>85th percentile).

Cotinine urine levels were solicited from the CF cohort participants. Cotinine levels reveal concentrations with a cut-off of <10 ng/ml in patients not exposed to tobacco smoke, with corresponding concentrations increasing with a higher grade of exposure. Cotinine has been analyzed as a dichotomous, valuable variable in intervals (intervals < 10 ng/ml; 10 – 50 ng/ml; 51 – 200 ng/ml; 201 – 400 ng/ml; > 400 ng/ml), and as a continuous variable; we imputed a value of "9" for those patients with <10ng/ml.

Clinical variables such as spirometric values of forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC relation (all expressed as a percentage of the predicted value) were obtained through medical records. Data obtained before 5 years of age or after lung transplantation were excluded.

Intervention phases

The intervention logarithm below is adapted from the Tyc & Throckmorton-Belzer (2006) model for clinician delivered tobacco-use counselling strategies for adolescents with chronic illness as well as the *5 steps*, called the 5 A's: ask for advice/or advise, assess, assist, and arrange follow-up mentioned in our previous work (Ortega-García et al., 2012a). The intervention with proactive telephone counselling included:

1. Educate through brief counseling in short and long-term physical/medical effects of smoking in patients with CF and health benefits of quitting.
2. Assess participant's exposure to environmental passive tobacco in and outside of the home.
3. If any tobacco exposure was assessed, participants were given psycho-health education about the importance of reducing their exposure.
4. Assess participant desire to quit smoking; desire to quit is based on phase determination according to Prochaska and DiClemente (pre-contemplation, contemplation, preparation, action and relapse).
5. Classification of level of dependence and motivation according to Fagerström and Richmond's tests.
6. Provide brief counseling on how to select a quit date and strategies on how to choose that date.
7. Reinforce the benefits of quitting.
8. Selection of the next appointment, telephonic or face to face.

Calls were placed to participants to recruit them into the intervention and schedule interviews. During the follow-up, sequenced calls from a trained cessation counsellor were made every 6 months (in homes with no smoker present) and every 4 months (in homes where a smoker was present). Interviews were conducted between 2008 and 2013 with each interview lasting between 5 to 20 minutes depending on the details of their smoking exposure. All patients received tobacco prevention and cessation counseling at each appointment as per usual in the pediatric pulmonology unit. As a compliment to the intervention, trained tobacco cessation counsellors collected and assessed CF patient's passive environmental tobacco exposure. These variables are defined as passive tobacco exposure at home (yes or no), and gradient of global environmental tobacco exposure measured as, active, passive or no exposure.

SPSS version 15.0 was utilised for data analysis, established quality control measures and protocols for fidelity to the study model were preserved throughout the investigation. Distribution, frequency measures and contingency tables were constructed for univariate analysis and parametric tests were conducted for paired measurements. Spearman correlation was utilized for continuous and interval variables. To assess measurements of association and impact of the intervention, we calculated risk relative, absolute risk reduction and NNT (number needed to treat).

Results

88 patients completed the 5 year follow-up; 49 (56.32%) were male and 38 (43.68%) were female. The mean age of participants was 23.61 (95% CI 20.93 – 26.29). Table 1 shows the socio-demographic characteristics of sample.

Tobacco smoke exposure

The number of active smokers was reduced by half at the end of follow-up, from 10.23% (n=9) to 4.55% (n=4), p=0.06. In 2008, these patients smoked a mean of 45.25

(95% CI 13.07 - 77.43) cigarettes per week and started smoking at a mean age of 15.3 (95% CI 13.6 - 17.2).

Any passive exposure to environmental tobacco in non-smokers (n=49 vs 29) was reduced by 25.1 % during the five year intervention (62.0 % vs 36.9%, p<0.01). Figure 2 demonstrates significant reductions annually in the active and passive tobacco exposures at the end of follow-up. Figure 3 shows the time trend of the variable "exposure at home" during the five year follow-up.

Urinary Cotinine Levels

Urinary cotinine levels were consistent with tobacco exposure reduction. Levels compared between baseline samples in 2008-2009 and samples in 2012-2013 showed a reduction of 27.38% (p=0.006) from 63.13 (28.58- 97.69) to 20.56 (0.86 - 40.27) ng/ml (p<0.01). Differences in the categorical and continuous variable are presented in table 2. Cotinine was significantly correlated with active (31%) and exposure at home (32%), p=0.02.

We found a negative correlation with family's monthly net income and education level in 2008 (0.38, p<.001) and no correlation with any in 2013.

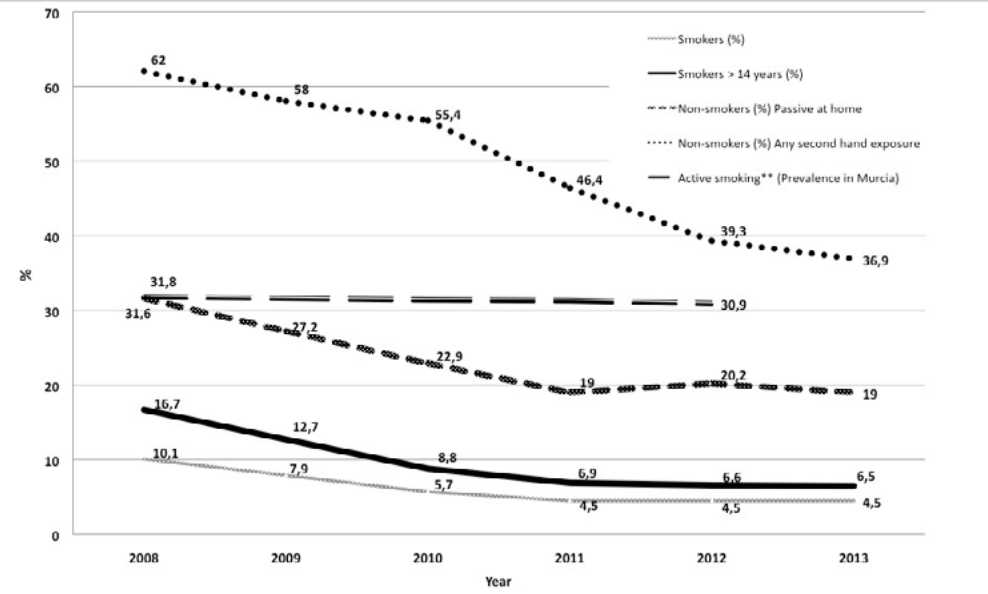
Smoking cessation and intervention effect

A total of 47 smokers were found (9 patients, 2 wives, 2 siblings, 16 fathers, 17 mothers and 1 grandfather). At the five year follow-up, serious efforts were made to achieve smoking cessation and ultimately leaving 18 (38.29%) of them as non-smokers (5 patients, 6 fathers, 5 mothers, 2 siblings and 1 wife) during the last 6 months (cooximetry of 0 in patients). Two patients, 1 mother and 1 father stopped smoking after going through a personalized consultation. Of these, only two were treated with nicotine replacement therapy.

Upon comparing the active tobacco smoke exposure at baseline (n=9) and after follow-up (n=4) our findings suggest that the risk of smoking is 56% lower with a relative risk

Table 1. *Socio-demographic characteristics at baseline*

Baseline Characteristics	
	n %
Sex	
Male	49 (56.32)
Female	38 (43.68)
Age (mean)	23.61 (20.93-26.29. CI 95%)*
Education	
None	29 (36.25)
Primary	18 (22.5)
Secondary	22 (27.5)
University	11 (13.75)
Income (€/month)	
< €800	11 (17.19)
€800-1500	22 (34.38)
€1500-2000	14 (21.88)
€2000-2500	9 (14.06)
> €2500	8 (12.50)



Note. **Smoking prevalence is adapted from the Spanish National Health Survey 2006, 2008 and 2011-2012. Prevalence measures are reflective of 2006, 2009 and 2011-2012 data and respectively reflect consumers of tobacco in Spain in populations over 16 (2006, 2009) and 15 years of age (2011-2012).

Figure 2. Time trend comparison of active smoking and passive exposure to environmental tobacco in the homes without any smoker present with prevalence of active smokers in Region of Murcia**

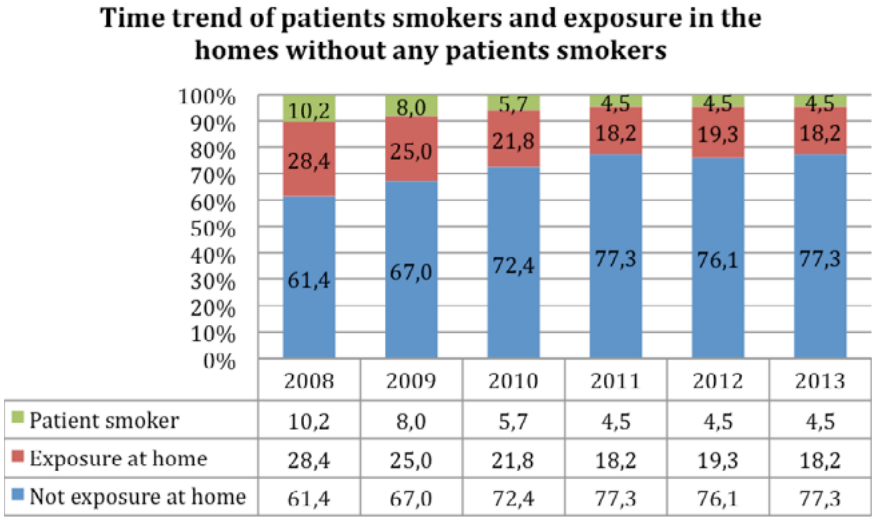


Figure 3. Time trend of exposure at home in cystic fibrosis cohort

Table 2. *Summary of analysis*

Variable	**2008**	**2013**	***p* value for paired samples**
Tobacco Exposure			
Active Smokers	10.23 (9/88)	4.55 (4/88)	0.062
Environmental exposure in the home	31.65 (25/79)	19.05 (16/84)	<0.01
Cotinine Levels			
>10	52.38 (33/63)	25.00 (12/48)	0.230
Cotinine Intervals *	**2008/2009**	**2011/2012**	
<10 ng/mL	34.1 (30/88)	39.8 (35/88)	
10-50 ng/mL	28.4 (25/88)	12.5 (11/88)	
51-200 ng/mL	2.3 (2/88)	-------	
201-400 ng/mL	1.1 (1/88)	-------	
>400 ng/mL	5.7 (5/88)	1.1 (1/88)	
Dat Imputed	28.4 (25/88)	46.6 (41/88)	
Continuos Cotinine (ng/mL)	63.13 (28.58- 97.69)	20.56 (0.86 - 40.27)	0.0001
Spirometric Parameters**			
FVC (%)	86.534 (TE 3.1643)	93.06 (TE 3.040)	0.017
FEV_1 (%)	78.884 (TE 3.4891)	80.147 (TE 3.6364)	0.637
FEV_1/FVC (%)	83.11 (TE 2.176)	74.864 (TE 2.4152)	<0.001
FEF_{25-75} (%)	52.637 (TE 4.5619)	52.431 (TE 5.2767)	0.952
Other Covariates			
Pseudomonas colonization	45.45 (35/77)	41.27 (26/63)	0.238
Genetics			
F508 del Homozygous		12.05 (10/83)	
F508del Heterozygous		45.78 (38/83)	
Other Mutations		42.17 (35/83)	
BMI			
Normal (p10-85)		61.19 (41/67)	
Underweight (<p10)		19.4 (13/67)	
Overweight (>p85)		19.4 (13/67)	

Note. *Cotinine Levels are reported for 2008/2009 baseline and 2011/201 follow-up and include values imputed.
**Values are indicative of Spirometric value comparisons 2009 and combined 2012-2013, reported with median values and values for typical error (TE).

Table 3. *Multivariate analysis of spirometric parameters as outcomes adjusted by age and gender*

Outcomes	Predictor Variable	Regression Coefficient	95% CI	p Value
FEV_1	Pseudomonas	-13.844	-28.300 – 0.644	0.002
	BMI *underweight*	20.862	1.813 – 39.911	0.033
FEF_{25-75}	Pseudomonas	-24.537	-44.599 – -4.475	0.088
	BMI *underweight*	27.599	1.255 – 53.942	0.041
FVC	Pseudomonas	-12.034	84.294 – 122.599	<0.001
FEV_1/FVC	Pseudomonas	-0.411	-0.715 – -0.106	0.009

(RR) not significant of 0.44 (CI 95% 0.14-1.39). A significant reduction was observed in environmental tobacco exposure 'smoke-free homes' with a RR 0.59 (CI 95% 0.37-0.94) and RAR 0.16 (CI 95% 0.02-0.29) with a NNT=7 (CI 95% 4-41). The intervention to significantly increase the likelihood of family quitting (smoke-free home) was 1.26 (1.05-1.54). In 2008 54 from 88 homes had at least one smoker and in 2013 only 20 households still had tobacco smoke exposure.

Lung function

We observed an increase in the global spirometric parameters at the end of follow-up in regards to baseline measures with significant differences in FVC and FEV1/FVC.

No significant differences were seen in the student T-test for spirometric parameters among patients exposed to active or passive tobacco exposures between baseline and end of follow-up outcomes. In the multivariate analysis, see table 3, we found that Pa colonization was a predictive factor for all spirometric parameters. Underweight BMI was also associated with FEV_1 and FEF_{25-75}, after adjusting for age and gender. Other clinical variables assessed yielded no significance in the multivariate analysis.

Discussion

In this study we observed that longitudinally active and passive environmental smoking exposures reduced consistently among the CF patients that participated in the integrated telephone prevention and cessation program. Our results suggest that interventions which actively involve patients and relatives could promote an adequate perception of tobacco risk so as it promote behaviour change. The available scientific evidence evaluating tobacco consumption among CF populations is limited. Nonetheless, studies in the United States have reported that tobacco consumption amongst CF patients is 11%, and smoking amongst youth with a CF diagnosis is 20% (Stern et al., 1987). Another study in the United Kingdom that investigated "risky behaviours" in adults with CF revealed that 6% were smokers (Mc Ewan et al., 2012).

Previous studies have demonstrated an inverse relationship between the number of cigarettes smoked and the result of spirometric variability in CF patients (Ortega-García et al., 2012a). Nevertheless, in this study, the relationship was statistically insignificant most likely attributed to the small sample size of the representative group of smokers.

Kopp et al. (2015) recently demonstrated that exposure to tobacco smoke is associated with higher rates of colonization by methicillin-resistant *Staphylococcus aureus* and other anaerobic bacteria. Tobacco smoke is also associated with increased bronchodilator responsiveness, air trapping, and decreased growth during the first year of life (Kopp et al., 2015). The screening of tobacco smoke exposure and treatment for smoking cessation in all family members should be an important part in the care of CF patients.

Interventions developed with the goal of preventing and eliminating tobacco consumption have evolved through different applications. The implementation strategies included face-to-face and telephone interviewing. Telephone-based tobacco cessation programs have reported 12% reductions in cessation with high satisfaction in the intervention population (Redmond, Adsit, Kobinsky, Theobald & Fiore, 2010). Telephone interventions have demonstrated effective when used with pharmacological tobacco cessation therapies resulting in improvements of 10 to 25% (Stead & Lancaster, 2012). This suggests that outcomes improve with increased follow-up and contact. Tobacco cessation interventions have shown better results in programs that incorporate elements sensitive to stage of change, motivational enhancement and cognitive behavioural therapy, rather than pharmacological interventions (Stanton & Grimshaw, 2013).

Our brief interventions have proven to be effective although most are not on-site or in person. Other programs such as computerized interventions have resulted in tobacco abstinence of 32% (Chen et al., 2012). Here, the telephone interview has demonstrated the effectiveness in utilizing family members of patients in implementing smoking cessation programs (Carreras Castellet et al., 2012; Winickoff, Hillis, Palfrey, Perrin & Rigotti, 2003). Our results reinforce the utility and sustainability of tobacco cessation in the context of the phone intervention. The value of telephone-based interventions must be recognized and it's vital to make them an available option to individuals interested in quitting smoking. Currently, telephone counselling and

nursing interventions are useful modalities in approaching tobacco cessation; RR 1.37, CI: 1.26 – 1.50 and RR 1.29, CI: 1.20 – 1.39, respectively (Rice, Hartmann-Boyce & Stead, 2013; Stead et al., 2013).

Limitations include potential biases related to participant memory re-call. Standardized interventions were employed by personnel with specialized training in the conceptual and procedural aspects of tobacco cessation to manage these types of patients and biases. Moreover, the impetus to maintain a rigorous follow-up methodology mediates this impact on our results.

Another limitation of this study is the lack control group for the basis of scientific comparison. This aspect was considered in the experimental design but was quickly outweighed by the ethical medical responsibility to provide treatment to vulnerable CF populations in need of care. Results that reflect passive environmental tobacco exposure may be skewed partially due to the recent anti-tobacco legislation that regulates the use of tobacco in closed establishments in the country (Anti-Tobacco Law of 2010). But, our results reflect an observed reduction that occurred prior to the legislation passing and persisted after its implementation, see figure 2. Another potential factor associated with the decrease in tobacco consumption is the legislation's impact on social tobacco use and access due to increases in cost. Ng et al. (2014) recently discussed the significant reduction in prevalence of exposure to tobacco smoke in 187 countries between 1980 to 2012. The Region of Murcia is of particular interest in developing integrated smoking interventions when considering the 30.9% statewide tobacco consumption was higher in 2012 relative to Spain´s 27.0% national tobacco consumption (Ministry of Health, 2007). Unlike the natural tendency in many countries and regions, Murcia has increased slightly the prevalence of tobacco compared to previous years (MurciaSalud, 2006). Additionally, recent studies investigating the level of tobacco exposure indicate up to 62% of healthy children in Murcia are exposed to environmental tobacco smoke (Ortega-García et al., 2012b). Our findings are geographically significant, given that the smoking prevalence has increased in the Region of Murcia over the last 5 years (Ministry of Health, 2007; MurciaSalud, 2006). Economic system variability, instability in employment and inconsistencies in participant incomes were not evaluated and could potentially influence outcomes. In analyzing the socioeconomic variables previously noted we observed the protective effect of increased income in relation to passive environmental tobacco exposure, and an associated reduction of passive exposure as age increases, OR = 0.12 (1.09 – 1.17), p=0.02.

Our study has strived to remain below the threshold of acceptable missing data (15%), however, as some patients exited the study due to death or were lost to follow-up it was necessary to utilize multiple imputation methods for certain values, including imputed cotinine levels <9.

These data are reinforced by the objective measure of urinary cotinine levels, which directly reflect tobacco exposure. The subjective bias present in the patient self-report is mitigated by the solid evidence provided by cotinine levels. Further strengths of our study include our systematic method of data collection, delivery of our screening tool by trained tobacco cessation counsellors.

The preceding indicates that this intervention can assist in the cessation of tobacco use amongst CF patients. The findings are significant from multiple perspectives. For instance, the associated annual pharmacological treatment costs associated with CF in adults (>17) is an estimated € 21,603 per patient/year (Eidt-Koch, Wagner, Mittenford & Graf von der Schulenburg, 2010). Our findings bolster the need to expand tobacco cessation programs available to CF patients. Further implementation of these interventions could alleviate the cost burden associated with treating the long-term impacts of tobacco related diseases.

A future aspect to consider is the role that smokers in the house of minors play in CF disease burden; as a significant percentage of the patients in the cohort were minors. Broadening the availability of tobacco cessation programs is relevant as children are most vulnerable to passive tobacco exposure. Children and minors rely on their caretakers to ensure the environmental safety of their homes and lack the ability to advocate for environmental justice in their communities. This responsibility lies with us, the adults, medical staff and public health workforce sanitarians entrusted to ensure their environmental safety. Nonetheless, more than a third (36.5%) of minors under the age of 19 live with a smoker, and in the Region of Murcia half of all children live in homes with at least one smoker (Ortega García, Ferrís Tortajada & Sánchez Solís, 2008). The literature reports reductions of up to 80% in tobacco consumption in youth's family members with chronic pathologies (Butz & Rosenstein, 1999).

Telephone based interventions in CF populations are an integrative and sustainable modality that is relevant to the family environment where tobacco is consumed around patients with CF. A paramount implication of our research is that the reduction of passive tobacco exposure is more noteworthy after two years of follow-up due to the intervention. This data contributes to the lacking research in intervention methods with vulnerable CF populations. Previous evidence and natural history of the disease allow for us to consider the use and amplification of telephone based interventions and its training with a global perspective in Europe and the world alike.

What is known on this subject

Patients with CF possess an increased risk for harm from exposure to tobacco smoke. Telephone assisted interventions is a useful tool in tobacco cessation and prevention. More research is needed in evaluating tobacco intervention programs over time

What this study adds

Telephone based interventions for tobacco cessation and prevention targeting patients with cystic fibrosis (CF) is a feasible and effective tool when applied over long periods of time.

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Association between personality traits and substance use in Spanish adolescents

Asociación entre rasgos de personalidad y consumo de sustancias en adolescentes españoles

María T. González*, José P. Espada*, Alejandro Guillén-Riquelme*, Roberto Secades**, Mireia Orgilés*

*Universidad Miguel Hernández; **Universidad de Oviedo.

Abstract

Substance use is considered one of the most frequent risk behaviors during adolescence. Personality factors are linked to consumption during adolescence. Although there are studies on personality and consumption among Spanish adolescents, some outcomes are contradictory, and more studies including larger samples and using validated measures are needed. The aim of this study is to analyze the relationship between different personality factors and substance use among Spanish adolescents. Participants were 1,455 students aged between 13-18 years. The adaptation of the 16PF-IPIP Personality Inventory was applied to assess Warmth, Stability, Gregariousness, Friendliness, Sensitivity, Trust, Openness to experience, Sociability, Perfectionism, and Calmness. Participants were asked about their different consumption substances during their lifetime. Results provide evidence for a relationship between personality factors and psychoactive substance use. There are different distributions of alcohol use regarding personality traits. Furthermore, personality factors have some influence on consumption of alcohol, cannabis, and cocaine. Trust and Calmness influence average alcohol, cannabis, and cocaine consumption, whereas Sociability had no statistically significant influence on any of the three substances. The results from this study are highly useful in the design of preventive programs, as they provide more evidence of the role of personality traits as a risk factor.

Keywords: substance use, alcohol, cannabis, cocaine, personality.

Resumen

El consumo de sustancias está considerado como una de las conductas de riesgo más frecuentes durante la adolescencia. Los factores de personalidad están relacionados con el consumo en la adolescencia. Aunque existen estudios sobre personalidad y consumo en adolescentes españoles, algunos resultados son contradictorios y son necesarios más estudios con muestras de mayor tamaño y que utilicen medidas validadas. El objetivo de este estudio es analizar la relación entre los diferentes factores de personalidad y el consumo de sustancias en adolescentes españoles. Participaron 1,455 estudiantes de secundaria entre 13 y 18 años. Se aplicó la adaptación del Inventario de Personalidad 16PF-IPIP para evaluar Calidez, Estabilidad, Gregarismo, Amigabilidad, Sensibilidad, Confianza, Apertura, Sociabilidad, Perfeccionismo y Calma. Se preguntó a los participantes acerca de las diferentes sustancias que habían consumido a lo largo de su vida. Los resultados evidencian la relación entre las variables de personalidad y el consumo de sustancias psicoactivas. El consumo de alcohol presenta diferentes distribuciones con respecto a los rasgos de personalidad. Por otra parte, los factores de personalidad tienen cierta influencia en el consumo de alcohol, cannabis y cocaína. Confianza y Calma tienen influencia en el consumo de alcohol, cannabis y cocaína, mientras que Sociabilidad no presenta ninguna influencia estadísticamente significativa en ninguna de las tres sustancias. Los resultados de este estudio son de gran utilidad a la hora de diseñar programas preventivos, ya que proporcionan mayor evidencia sobre el papel de los rasgos de personalidad como factores de riesgo.

Palabras clave: consumo, alcohol, cannabis, cocaína, personalidad.

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Send correspondence to:
María T. González, Departamento de Psicología de la Salud, Universidad Miguel Hernández. Av. de la Universidad, s/n. 03202. Elche, Alicante. Tel.: 96-665 83 44. Fax: 96-665 89 04. E-mail: mgonzalvez@umh.es

Adolescence is a critical period when the onset and experimentation with psychoactive substances typically occur. Occasional use of alcohol and other drugs during adolescence is normative within the Spanish cultural context (Spanish Drug Observatory, 2009). Furthermore, in recent years have been highlighted the heavy alcohol, or binge drinking, which constitutes the most common problem drug use during adolescence (López-Caneda et al., 2014). Substance use has increased in adolescents in recent years and become a threat to this population due to short- and long-term consequences to their health (Vinet & Faúndez, 2012). International studies have observed high percentages of experimentation with legal drugs (Torregrosa, Inglés, Delgado, Martínez-Monteagudo, & Garcia-Fernández (2007), such as alcohol and tobacco, in addition to others like cannabis and amphetamine derivatives (Becoña & Míguez, 2006; Gómez-Fraguela, Fernández, Romero, & Luengo, 2008; Sirvent, Moral, & Rodríguez, 2007).

Addictive behaviors respond to a wide range of variables, and indicators of personality may influence the predisposition to consume substances in youth (Llorens, Palmer, & Perelló, 2005). The DSM-IV-TR (2002) considers personality traits to be persistent patterns of ways of perceiving, relating to others, and thinking. Certain individual characteristics and factors of vulnerability exist that may facilitate or predispose consumption (Fantin, 2006). The explanation for the association between substance use and personality traits presents some difficulties, since it is unknown whether drug use modulates a number of previous traits, whether personality determines drug use, or if they are independent. Llorens et al. (2005) studied the probability of future consumption in subjects according to their personality traits, showing that indicators of personality influence different substances and the type of consumption differently.

One of the factors most commonly associated with alcohol consumption is personality (Kyrkcaldy, Siefen, Surall, & Bischoff, 2004), and broad evidence exists that personality factors are linked to alcohol consumption in adolescence. The highest prevalence of substance use in adolescents is related to high psychoticism (Knyazev, Slobodskaya, Kharchenko, & Wilson, 2004) and elevated sensation seeking (Kuo, Yang, Soong, & Chen, 2002). Impulsivity, sensation seeking, self-concept, and antisocial behavior are found among the risk factors in addictive substance use in adolescents (Llorens et al., 2005). Impulsivity and disinhibition are those most consistently related with alcohol consumption behaviors (Aragues, Jurado, Quinto, & Rubio, 2011). Furthermore, impulsivity is related to the quantity of alcohol ingested (Cortés, Giménez, Motos, & Cadaveira, 2014), and during adolescence predicts a pattern of alcohol abuse in adulthood (Chassin, Flora, & King, 2004). The extraversion/sociability trait is related with alcohol use in adolescents (Kuntsche, Rehm, & Gmel, 2004). Moreover, extraversion scores constitute the greatest predictor for alcohol consumption, followed by neuroticism (Anderson, Scheweinsburg, Paulus, Brown, & Tarpet, 2005). In addition, psychoticism seems to show a greater relationship and predictive capacity with respect to alcohol consumption, and youngsters who use cannabis are more impulsive and greater sensation seekers (Bravo de Medina, Echeburúa, & Aizpiri, 2010).

According to Fantin (2006), adolescent users present specific personality characteristics, with a trend to relate to others aggressively, to be irresponsible and impulsive, in addition to being indifferent to the needs of others, showing rebellious and oppositional behavior in family relationships. Some authors coincide in that antisocial personality traits are directly linked to drug use. While social fears and social phobia are characterized by their high prevalence in adolescents with a pattern of drug abuse, several studies have found that certain maladaptive behaviors, such as impulsive, disruptive, antisocial, and aggressive behaviors are potent predictors of tobacco (Bergen, Martin, Roeger, & Allison, 2005; Kollins, McClernon, & Fuemmeler, 2005) and alcohol use (Bergen et al., 2005; Blum & Ireland, 2004; Paschall, Flewelling, & Russell, 2004). However, other studies demonstrate that prosocial, assertive, and socially skilled adolescents, as compared to antisocial students, are less likely to manifest risk behaviors to their health, such as using drugs (Sussman, Unger, & Dent, 2004). Grant et al. (2004) affirm that disorders from the consumption of alcohol and other drugs are related more with the antisocial, histrionic, and dependent personality. Likewise, in a study carried out with Spanish adolescents, Inglés et al. (2007) concluded that alcohol use is related with extraversion and psychoticism scores, with only extraversion identified as a risk factor. Becoña et al. (2011) found important differences in personality features between stimulant users (cocaine and ecstasies) and non-users.

Although there are studies on personality and consumption among Spanish adolescents, some outcomes are contradictory and more studies are needed including larger samples and using validated measures. With this background in mind, the goal of the present study is to examine substance use patterns and their relation with personality factors in a sample of Spanish adolescents, through the 16PF-IPIP Personality Inventory to an Orientation Context (Pérez, Cupani, & Beltramino, 2004), a genuine personality questionnaire. An additional aim is to analyze the differences between personality traits and the use of specific substances. According to previous studies we hypothesize that: (1) relationship between substance use and personality factors will be found, (2) personality traits as sociability, friendliness, stability, calmness, warmth, gregariousness, perfectionism, and trust will be related to lower consumption, (3) sensitivity and openness to experience will be linked to higher rates of consumption.

Method

Participants

The sample was comprised of 1,547 adolescents from 17 public schools in five Spanish provinces (Alicante, Oviedo, Castellón, Granada, and Murcia). 92 adolescents were excluded for not compliment correctly the questionnaire. The total final sample was comprised of 1,455 adolescents. Every adolescent had the family consent. The recruitment was incidental. Of the total sample, 720 (49.5%) were female with a mean age of 14.96 years (*SD* = 1.15). Regarding academic course, 53.3% were ninth graders, 35% tenth graders, 6.5% were first-year initial vocational training students, and 5.2% were second-year initial vocational training students. Most of the adolescents either had parents who were married or living together at the time of the evaluation (77.1%), while 21.2% of them were separated or divorced; the remaining 1.6% had been widowed. About the socio-economical level, 3.4% have a low level, 55% a medium level, and 41.6% a high level (206 adolescents of the total sample did not answer the socio-economic questions).

Instruments

A survey was administered to collect socio-demographic data such as gender, age, family characteristics (living or not with both parents or other family, and parents marital status), academic year, school center, and province. In addition, the participants were asked about their consumption of different substances during their lifetime [ever use and/or during the last month (1 = yes; 0 = no)].

Along with these questions, various scales from the Adaptation of the 16PF-IPIP Personality Inventory to an Orientation Context (Pérez, Cupani, & Beltramino, 2004) were administered, created from the International Personality Item Pool. This instrument was used as the presenting smaller time application. Being an adolescent sample, this instrument allowed the subjects completed all items. The applied scales were *Warmth*, *Stability*, *Gregariousness*, *Friendliness*, *Sensitivity*, *Trust*, *Openness to experience*, *Sociability*, *Perfectionism*, and *Calmness*. In all, there were 100 items, each having 5 response alternatives (from 1 = *strongly disagree*, to 5 = *strongly agree*). Internal consistency for this sample was α = .66, and for each subscale was: *Warmth* = .72; *Stability* = .70; *Gregariousness* = .70; *Friendliness* = .70; *Sensitivity* = .64; *Trust* = .64; *Openness to experience* = .61; *Sociability* = .66; *Perfectionism* = .69; and *Calmness* = .72.

Procedure

After approval by the ethics committee, schools were contacted to establish collaboration. Participants and their parents provided written informed assent and consent, respectively, to participate in this study. Two researchers went to the schools during school hours to administer the questionnaires electronically. These were administered collectively in classrooms. Printed questionnaires were used at schools that did not possess adequate electronic infrastructure. There is evidence that the assessment on paper and online (of the same instrument) produce similar and comparable results (Ritter, Lorig, Laurent, & Matthews, 2004; Riva, Teruzzi, & Anolli, 2003). Following this, the data were unified into a single database.

Data analysis

To analyze the average of consumers of alcohol in the last month in relation to groups of level in each trait was calculated using *probit* analysis. This technique is recommended for to analyze the relation between a dichotomous variable and a cluster variable (Ashford, & Sowden, 1970). For the analysis in a first step the cases with missing data were deleted. After, we selected only the adolescent consumers of drugs in the last years. For these adolescents, ten levels were established like one group for each 10% of the distribution of scores in the personality trait. We conducted the *probit* analysis with total sample. This analysis was made for alcohol, cannabis and cocaine month consume or not. At the end we replicate the analysis for each gender separately. The recodifications clusters were recalculated for men and women. Finally we conducted a new analysis for gender and substance.

Results

Personality relation with drug use without gender control

We analyzed, first, how personality is related to the consumption of psychoactive substances. No separation was made here for gender.

After we decided to conduct the analysis without gender separation, the average of consumers of alcohol in relation to groups of level in each trait was calculated (the cases with missing data were deleted). Ten levels were established like one group for each 5% of the distribution of scores. The results for consume or not during last 30 days are presented in Table 1, which shows different distributions: a) the lower and higher groups had more consumers of alcohol, like *Warmth*; b) the central groups had more consumers of alcohol, like *Trust*; c) the higher groups had more consumers, like *Openness to experience*; d) the higher groups had less consumers, like *Gregariousness*.

To analyze the differences in average distribution we used *probit* analysis. In Table 2 adjust of models was presented for each trait included. We can see that for alcohol consumers, the statistically significant models were *Stability*, *Gregariousness*, *Friendliness*, *Sensitivity*, *Trust*, *Openness to experience*, *Perfectionism*, and *Calmness*. For cannabis consumers *Gregariousness*, *Friendliness*, *Sensitivity*, *Trust*, *Openness to experience*, *Perfectionism*, and *Calmness* were statistically significant. In the cocaine average of consumers, only *Warmth*, *Trust*, and *Calmness* were statistically significant.

Trust and *Calmness* were the variables that have influence on the three models. In the first of these, the adolescents in lower groups and the three higher groups had lower averages of having consumed any of these drugs, while the intermediate groups had at least a 5% greater chance to have consumed alcohol. In the cannabis consumers frequency the average of consumers per group had a distribution similar to that of alcohol. In the cocaine average of consumers, the frequency is low but the tendency is different. In this case, an adolescent in a higher group had less chance to have consumed cocaine in the last year.

In *Calmness*, the average of alcohol consumers was higher in the lower groups: adolescents with more calm have a lower chance to have consumed alcohol in the last year, and the differences between groups reached 22%. For the cannabis and cocaine frequency of consumers in the last year, the tendency is similar in all groups. The participants were also asked about other substances they had used, and of these, the most common were MDMA (n = 7), ketamine (n = 6), and hallucinogenic mushrooms (n = 2). The frequencies for these substances were too low to be included in the analyses.

Table 1. *Percentage of alcohol consumers in the last 30 days for groups of level in personality traits.*

Level Groups	Warmth	Stability	Gregariousness	Friendliness	Sensitivity	Trust	Openness to experience	Sociability	Perfectionism	Calmness
0	81.65	72.52	89.47	86.36	70.09	75.70	64.57	69.16	57.66	87.94
1	83.33	79.49	86.83	86.76	73.28	85.21	68.37	82.35	66.92	87.50
2	82.35	72.48	87.59	81.01	80.15	84.80	84.44	73.77	76.92	85.37
3	78.02	76.19	86.52	81.32	83.52	84.55	76.99	74.42	79.50	80.68
4	76.79	84.26	84.34	80.10	80.91	78.45	81.76	83.95	87.10	88.70
5	70.81	84.47	79.52	79.38	76.76	80.39	73.68	78.81	82.96	80.77
6	84.38	75.44	76.56	77.30	78.26	83.41	86.21	81.44	86.92	77.30
7	81.58	80.22	80.28	76.61	81.25	77.32	80.70	78.01	83.64	74.67
8	80.00	81.93	71.90	79.29	80.79	72.92	84.65	80.77	81.60	66.10
9	79.50	84.67	59.21	69.80	83.87	71.43	88.28	81.88	84.21	68.62

Note. Groups were made as follows: Warmth: 0 = 0-15; 1 = 16-18; 2 = 19-20; 3 = 21; 4 = 22; 5 = 23-24; 6 = 25; 7 = 26-27; 8 = 28-29; 9 = > 30; Stability: 0 = 0-18; 1 = 19-20; 2 = 21-22; 3 = 23; 4 = 24-25; 5 = 26; 6 = 27-28; 7 = 29; 8 = 30-32; 9 = > 33; Gregariousness: 0 = 0-15; 1 = 16-18; 2 = 19-20; 3 = 21; 4 = 22-23; 5 = 24; 6 = 25-26; 7 = 27; 8 = 28-30; 9 = > 31; Friendliness: 0 = 0-16; 1 = 17-19; 2 = 20-21; 3 = 22; 4 = 23-24; 5 = 25; 6 = 26-27; 7 = 28-29; 8 = 30-31; 9 = > 32; Sensitivity: 0 = 0-19; 1 = 20-22; 2 = 23-24; 3 = 25-26; 4 = 27; 5 = 28-29; 6 = 30; 7 = 31-32; 8 = 33-35; 9 = > 36; Trust: 0 = 0-27; 1 = 28-30; 2 = 31-32; 3 = 33; 4 = 34; 5 = 35; 6 = 36-37; 7 = 38; 8 = 39-40; 9 = > 41; Openness to experience: 0 = 0-24; 1 = 25-26; 2 = 27; 3 = 28-29; 4 = 30; 5 = 31; 6 = 32; 7 = 33; 8 = 34-36; 9 = > 37; Sociability: 0 = 0-23; 1 = 24-26; 2 = 27-28; 3 = 29; 4 = 30-31; 5 = 32; 6 = 33; 7 = 34-35; 8 = 36-38; 9 = > 39; Perfectionism: 0 = 0-19; 1 = 20-22; 2 = 23-24; 3 = 225-26; 4 = 27; 5 = 228-29; 6 = 30; 7 = 31-32; 8 = 33-34; 9 = > 35; Calmness: 0 = 0-26; 1 = 27-28; 2 = 29; 3 = 30-31; 4 = 32-33; 5 = 34; 6 = 35-36; 7 = 37-38; 8 = 39-40; 9 = > 41.

Table 2. *Estimate parameters for drug use in logit models (n = 1,455).*

Trait	Alcohol Estimation (n = 1,153)	*SE*	*Z*	Cannabis Estimation (n = 401)	*SE*	*Z*	Cocaine Estimation (n = 23)	*SE*	*Z*
Warmth	0.01	0.01	0.65	0.01	0.01	1.63	0.07	0.02	3.71***
Stability	0.02	0.01	2.64**	0.01	0.01	1.69	0.04	0.02	2.04*
Gregariousness	0.06	0.01	-7.68***	-0.03	0.01	-5.06***	0.01	0.02	0.47
Friendliness	-0.07	0.02	-4.87***	-0.02	0.01	-2.05*	0.01	0.02	0.60
Sensitivity	0.02	0.01	2.54*	0.02	0.01	3.34***	0.03	0.02	1.79
Trust	-0.03	0.01	-3.16**	-0.03	0.01	-3.67***	-0.04	0.02	-2.05*
Openness to experience	0.05	0.01	5.32***	0.03	0.01	2.86**	-0.02	0.02	1
Sociability	0.01	0.01	1.70	-0.01	0.01	-0.79	-0.01	0.02	-0.74
Perfectionism	0.04	0.01	5.77***	0.02	0.01	2.83**	0.00	0.02	0.05
Calmness	-0.05	0.01	-6.33***	-0.04	0.01	-5.68***	-0.05	0.02	-2.54**

Note. * p < .05; ** p < .01; *** p < .001; *SE* = standard error.

Table 3. *Estimate parameters for drug use in logit models for women (n = 723).*

Trait	Alcohol Estimation	*SE*	*Z*	Cannabis Estimation	*SE*	*Z*	Cocaine Estimation	*SE*	*Z*
Warmth	0.07	0.1	0.57	-0.01	0.01	-0.09	0.08	0.05	1.67
Stability	0.03	0.01	2.42*	0.2	0.01	2*	0.09	0.5	1.83
Gregariousness	-0.08	0.01	-7.18***	-0.4	0.1	-4.3***	0.03	0.03	1.02
Friendliness	-0.04	0.1	-3.84***	-0.02	0.01	-1.63	0.03	0.04	0.91
Sensitivity	0.03	0.01	2.99**	0.02	0.01	1.59	0.08	0.04	1.92
Trust	-0.02	0.01	-1.35	-0.03	0.01	-2.87**	0.01	0.04	0.3
Openness to experience	0.06	0.01	4.33***	0.03	0.01	2.49*	-0.07	0.05	-1.37
Sociability	0.02	0.01	2.27*	0.01	0.01	0.52	0.03	0.04	0.77
Perfectionism	0.05	0.01	5.27***	0.03	0.01	2.71**	0	0.03	0.08
Calmness	-0.05	0.01	-4.88***	-0.03	0.01	-3.32**	-0.28	0.04	-0.76

Note. * $p < .05$; ** $p < .01$; *** $p < .001$; *SE* = standard error.

Tabla 4. *Estimación de los parámetros de consumo de drogas en modelos logit para los varones (n = 732).*

Trait	Alcohol Estimation	*SE*	*Z*	Cannabis Estimation	*SE*	*Z*	Cocaine Estimation	*SE*	*Z*
Warmth	-0.01	0.01	-0.47	0.01	0.01	0.7	0.05	0.03	1.73
Stability	0.02	0.01	1.38	0.01	0.01	1.03	0.04	0.02	1.67
Gregariousness	-0.04	0.01	-3.57***	-0.03	0.01	-3.62***	-0.01	0.02	-0.32
Friendliness	-0.03	0.01	-2.12*	-0.02	0.1	-1.91	0	0.2	-0.15
Sensitivity	0.01	0.01	1.03	0.01	0.01	1.27	0	0.01	-0.18
Trust	-0.04	0.01	-3.15**	-0.03	0.01	-2.94**	-0.07	0.03	-2.61**
Openness to experience	0.05	0.02	3.13**	0.03	0.01	1.92	-0.01	0.03	-0.22
Sociability	0	0.01	-0.04	-0.01	0.01	-1.18	-0.02	0.02	-1.01
Perfectionism	0.03	0.01	2.68**	0.01	0.01	1.13	0	0.02	-0.06
Calmness	-0.04	0.01	-3.98***	-0.04	0.01	-4.38***	-0.04	0.02	-1.83

Note. * $p < .05$; ** $p < .01$; *** $p < .001$; *SE* = standard error.

Personality relation with drug use without gender control

We analyzed how personality is related to the consumption of psychoactive substances by sex. We used *Probit* analysis for men and women independently. In Table 3 adjust of models was presented for each trait included for women, and for men in Table 4. We can see that in women alcohol consumers, the statistically significant models were *Gregariousness*, *Friendliness*, *Sensitivity*, *Openness to experience*, *Sociability Perfectionism*, and *Calmness*. For cannabis, *Gregariousness*, *Trust*, *Openness to experience*, *Perfectionism*, and *Calmness*. For cocaine no variables were significant. For men *Gregariousness*, *Friendliness*, *Trust*, *Openness to experience*, *Perfectionism*, and *Calmness* were significant for alcohol. In the cannabis the significant variables were *Gregariousness*, *Trust*, and *Calmness*. For cocaine consume only *Trust* was significant.

Discussion

The purpose of this study was to analyze the relationship between various personality factors and the consumption of alcohol, cannabis, and cocaine in a sample of Spanish adolescents. The outcomes reveal that personality variables have some influence on using different substances, as hypothesized. Regarding the average of alcohol consumers for level groups, the distributions are based on the personality, not counting the same trend for all personality traits.

Regarding the influence of personality traits on consumption, only *Trust* and *Calmness* have a statistically significant influence on the three models, while *Sociability*, related to extraversion, doesn't influence any of the three. Initially hypothesized that sociability adolescents will have a low consumption. Extroverts are characterized by a strong need

for stimulation (Eysenck & Zuckerman, 1978). This sensation-seeking trait could explain the positive relationship between extraversion and the use of legal and illicit drugs. Persons most in need of stimuli will be more inclined to perform behaviors involving stimulation and risk (Pérez & García-Sevilla, 1986), and will therefore have a greater probability of using drugs. Teichman, Barnea, & Rabay (1989) consider that sensation seeking is a better predictor for drug use than either anxiety or depression. In this sense, Luengo, Otero-López, Romero, & Gómez (1996) assert that sensation seeking is a relevant variable for differentiating consumers from non-consumers in adolescents. Sáiz et al. (1999) conclude that substance use is associated in both sexes with higher levels of emotional instability, greater extraversion and psychoticism, as well as a marked sensation seeking profile. However, the results of this study agree with Sussman, Unger, & Dent (2004), who demonstrate that prosocial, assertive, and socially skilled adolescents are less likely to using drugs.

Personality traits are similarly correlated with alcohol and cannabis consumption. All of them correlated statistically significant with alcohol and cannabis consumption, except *Warmth* and *Sociability*. In the case of cannabis consumption, either *Stability* correlates. In cocaine consumption, personality traits that correlate are *Warmth*, *Stability*, *Trust*, and *Calmness*. Contrary to what was initially hypothesized, *Stability* and *Perfectionism* are not correlated with lower consumption. However, the results are in favor of our hypothesis in the case of *Sensitivity* and *Openness to experience*, with higher consumption, and *Calmness* and *Trust*, with lower consumption. In the case of *Gregariousness* and *Friendliness* our hypothesis is true for alcohol and cannabis consumption. López, Santín, Torrico, & Rodríguez (2003), starting from the model of the Big Five factors, found slight differences in the personality structure of young persons in terms of substance use. In their study, they conclude that consuming subjects are more open, sociable, dynamic, active, energetic, and loquacious than non-users. At the same time, they find differences in favor of regular consumers of alcohol on the open-mindedness scale, while such differences between consumers and non-consumers are not found on the scale of emotional stability or trait impulsivity. As for young cannabis users, the authors affirm that these have a greater propensity for novel experiences and are fairly open towards values and lifestyles that are distinct from their own. The highest score in extraversion may be related to a greater tendency for early contact with substances and an increased neural sensitivity toward them (Pedrero, 2007). The same study concluded that young users obtain lower scores in emotional stability and open-mindedness.

In this study, different distributions of alcohol consumption regarding personality traits were found and it can be concluded that personality factors are significantly related with the use of psychoactive substances among adolescents.

The relationship between personality variables and the use of psychoactive substances appears clear. Furthermore, personality traits have influence not only on alcohol consumption but also on cannabis and cocaine consumption. This is important for establishing prevention programs based on such variables. Still, there are several notable limitations. First, the use of the 16PF-IPIP makes it difficult to compare the results with similar studies. Also, the instrument used has a low consistency in the scales, so future studies should consider the suitability of the use of this instrument. This study, however, is limited by being a cross-sectional study, so cause-effect cannot be established. Further research must determine whether these variables have a causal relationship and the potential benefits for preventive programs by considering the personality characteristics of the target population. However, the results of this study are not generalizable to the Spanish adolescent population. The findings provide new (albeit modest) data on the association of variables.

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Conflicts of interest

There are no conflicts of interest.

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Alcohol in Primary Care. Differential characteristics between alcohol-dependent patients who are receiving or not receiving treatment

El Alcohol en Atención Primaria. Características diferenciales entre los pacientes dependientes del alcohol que han solicitado o no tratamiento

Pablo Barrio*,***, Laia Miquel*,**,***, Jose Moreno-España*, Alicia Martínez*, Lluisa Ortega*,***, Lidia Teixidor*,***, Jakob Manthey****, Jürgen Rehm****-******** , Antoni Gual*,**,***

*Grup de recerca en Addiccions Clínic (Clinical Addictions Research Group), Unitat de conductes addictives (Addictive Behaviors Unit). Hospital Clínic Universitari de Barcelona (University Hospital Clinic of Barcelona), Institut Clínic de Neurociencies, España (Clinic Institute of Neurosciences), Spain. **IDIBAPS (August Pi i Sunyer Biomedical Research Institute). ***Red de Trastornos Adictivos (RTA) (Addictive Disorders Network). ****Institute of Clinical Psychology and Psychotherapy & Center of Clinical Epidemiology and Longitudinal Studies (CELOS), Technische Universität Dresden, Germany. *****Centre for Addiction and Mental Health, Toronto, Canada. ******Addiction Policy, Dalla Lana School of Public Health, University of Toronto, Canada. *******Institute of Medical Science, University of Toronto, Faculty of Medicine, Canada. ********Department of Psychiatry, University of Toronto, Canada.

Abstract

Despite its high associated morbidity and mortality, few alcohol-dependent (AD) patients receive treatment. However, many use primary health care services for other reasons. The aim of the present study is to describe the differential characteristics of AD patients in primary care, distinguishing between those who receive treatment and those who do not, and their reasons for not seeking it.

In a cross-sectional study patients were evaluated by their general practitioner (GP) and interviewed by a member of the research team. Sociodemographic, diagnostic and clinical data were collected.

From 1,372 patients interviewed in Catalonia, 118 (8.6%) were diagnosed as AD. These patients showed a lower socioeconomic status (48.3% vs 33.3%, odds ratio 2.02), higher unemployment rates (32.2% vs 19.2 %, odds ratio 2.11), and greater psychological distress and disability. Patients with AD receiving treatment (16.9%), were older (44 vs 36 years of age), reported higher unemployment rates (66% vs 25.5%, odds ratio 6.32) and higher daily alcohol consumption (61.5 vs 23.7 grams), suggesting a more advanced disease. Patients with AD in general showed a higher degree of comorbidity compared to other patients, with patients in treatment showing the most elevated level. The main reasons given for not seeking treatment were shame, fear of giving up drinking and barriers to treatment. Taken together, the data suggest the need to implement earlier strategies for the detection and treatment of AD.

Keywords: alcohol, alcohol dependence, primary care, treatment.

Resumen

A pesar de la elevada morbi-mortalidad de la dependencia del alcohol (DA), pocos pacientes afectos reciben tratamiento. Sin embargo, muchos de ellos son visitados en atención primaria por otras razones. El objetivo del presente estudio es describir las características diferenciales de los pacientes dependientes del alcohol atendidos en Atención Primaria, distinguiendo también entre aquellos que realizan tratamiento o no, y los motivos por los que no lo solicitan.Se trata de un estudio transversal en el que los pacientes fueron entrevistados tanto por sus médicos de atención primaria (MAP) como por un investigador del estudio. Se recabaron datos sociodemográficos, diagnósticos y clínicos.De 1372 entrevistados, 118 (8,6%) fueron diagnosticados de DA. Éstos presentaron un nivel socioeconómico más bajo (48.3% vs 33.3%, odds ratio 2.02), más desempleo (32.2% vs 19.2 %, odds ratio 2.11), y mayores niveles de malestar psicológico y de incapacidad. Los que recibían tratamiento (16,9%), tenían más edad (44 vs 36 años), mayores tasas de desempleo (66% vs 25.5%, odds ratio 6.18) y mayor consumo diario de alcohol (61.5 vs 23.7 gramos), sugiriendo una mayor evolución de la enfermedad. La mayoría de variables clínicas analizadas mostraron una mayor comorbilidad en los pacientes afectos de dependencia del alcohol, y dentro de éstos, una mayor gravedad en los que recibían tratamiento respecto a los que no lo hacían. Las principales razones esgrimidas para no acudir a tratamiento fueron la vergüenza, el miedo a dejar de beber y las barreras para acceder al tratamiento. Estos datos sugieren pues la necesidad de implementar estrategias de detección y tratamiento precoces de la DA.

Palabras clave: alcohol, dependencia del alcohol, atención primaria, tratamiento.

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Send correspondence to: Pablo Barrio, c/Villarroel 170 08036, Barcelona. E-mail: pbarrio@clinic.ub.es

The consumption of alcohol is a major public health problem, both nationally and internationally. On a world level, it is calculated that some 3.8% of premature deaths and 4.6% of disability-adjusted life years can be attributed to alcohol (Lim et al., 2012; Rehm et al., 2009). Europe, specifically, is one of the areas of the world where there is a greater prevalence of this problem, with 15 million persons affected by alcohol dependence (Rehm et al., 2015b; Witchen et al., 2011). This means there are clear and well-documented repercussions on health, with multiple organic, psychological and even cognitive problems (Soler González, Balcells Oliveró, & Gual Solé, 2014), not only for the individuals concerned but also for their families and society at large. In the same way, it implies an increase in costs for the health system, the judicial system and the welfare system (Ezzati, López, Rodgers, Van de Hoorn, & Murray, 2002). In Spain, alcohol is the second cause of disease burden, with 11% of disability-adjusted life years (DALYs) lost among persons between the ages of 15 and 29 (Catalá-López, Gènova-Maleras, Alvarez-Martín, Fernández de Larrea-Baz, & Morant-Ginestar, 2013) being attributable to alcohol and also 8.4% and 12.3% of premature deaths in women and men respectively, between the ages of 15 and 64 (Rehm, Rehm, Shield, Gmel, & Gual, 2013a).

Despite the high prevalence of alcohol dependence, the majority of patients do not seek treatment. In fact, alcohol-related problems show the lowest treatment rate within mental illnesses (Kohn, Saxena, Levav, & Saraceno, 2004), it being estimated that in Europe up to 92% of affected patients do not receive treatment (Alonso et al., 2004). Multiple previous studies of this point to shame and stigma as being among the most important causes of this (Room, 2005), as well as other reasons such as the fear of giving up drinking, ignorance of the options available or the perception that treatment is ineffective (Andréasson, Danielsson, & Wallhed-Finn, 2013).

Previous researches indicate that patients who attend treatment show traits that differentiate them from those

Table 1. *Comparison of clinical and sociodemographic variables in patients without and with a diagnosis of alcohol dependence*

	No AD diagnosis (N=1254)	**AD diagnosis by CIDI or GP (N=118)**	**Odds ratio (95 % confidence interval)**	**Regression coefficient (95% confidence interval)**
Average age (SD)	43.7 (12.8)	37.4 (13)		-6.541 (-8.99 - -4.09) p<.001 b
Low socioeconomic level % (CI)	33.3 (30.69 - 35.91)	48.3 (39.28 - 57.32)	2.02 (1.37 - 3) p<.001 b	
Unemployed % (CI)	19.2 (17.02-21.38)	32.2 (23.77-40.63)	2.11 (1.38 - 3.24) p=.001 b	
Smokers % (CI)	28.7 (26.2-31.2)	54.2 (45.24 -63.1)	2.32 (1.56 - 3.45) p<.001 b	
Hypertension % (CI)	15.7 (13.69 - 17.71)	11.9 (6.06 - 17.74)	1.11 (0.59 - 2.1)p=0.749	
Hepatic problems % (CI)	1.7 (0.98 - 2.42)	4.2 (0.58 - 7.58)	2.68 (0.945 - 7.59) p=0.064	
Depression % (CI)	10.7 (9.0 - 12.41)	14.4 (8.07 - 20.73)	2.25 (1.26 - 4.02) p=0.006	
Anxiety % (CI)	16.3 (14.26 - 18.34)	17.8 (10.9 - 24.7)	1.47 (0.88 - 2.46) p=0.14	
K10 % (CI)	7.6 (6.13 - 9.07)	15.3 (8.8 - 21.8)	2.67 (1.51 - 4.73) p=.001 b	
Total mean score (SD)	8.63 (7.2)	11.9 (8.4)		3.95 (2.55 - 5.35) p<.001 b
WHODAS 2.0 average (SD) Number of days unable to carry out normal activities or work owing to health reasons.	2.49 (6.4)	3.83 (7.8)		1.22 (-0.036 - 2.48) p=0.053
Total score (SD)	10.97 (13.5)	15.06 (16.02)		5.16 (2.5 - 7.82) p<.001 b
Average daily amount of alcohol (in grams) (SD)	4.7 (10.8)	30.1 (45.7)		23.94 (20.69 - 27.18) p<.001 b
Chronic excessive consumption of alcohol % (CI) At least 100g of alcohol daily	0.1% (0.00 - -0.27)	7.6% (2.82 - 12.38)	102.47 (12.01 - 868.88) p<.001 b	
Binge-drinking % (CI) At least 200g of ethanol weekly	0.2% (0 - 0.45)	5.9% (1.65 - 10.15)	23.01 (4.31 - 122.88) p<.001 b	

Note. AD= Alcohol dependence in the last 12 months. CIDI= Composite International Diagnostic Interview. GP= General Practitioner. SD= standard deviation. CI= 95% confidence interval. BMI= Body Mass Index. K10= Kessler scale of psychological distress. Cut-off point for severe psychological distress of 21 points, on a scale of 0 to 40. WHODAS 2.0= World Health Organization Disability Assessment Schedule 2.0, range of scores from 0 to 100.

a Regression coefficients adjusted for gender and age.

b p significant with Bonferroni correction (p<0.05/16=0.003125)

who do not. In a similar way, all of them show that patients who are in treatment are older, have more problems related to consumption and more comorbid health problems, as well as a more precarious psychosocial situation (Berglund, Fahlke, Berggren, Eriksson, & Balldin, 2006).

The objective of the present study is to describe the main differences between patients who are attended to in primary care according to whether they have been diagnosed or not with alcohol dependence over the last twelve months, as well as describing the differences between patients who suffer alcohol dependence according to whether they are in receipt of specialized treatment or not, and the reasons for which they do not seek it.

Material and methods

Subjects and measures

This study was part of a multi-centric European study whose aim was to find out the prevalence of alcohol use disorders, which include the abuse of and the dependence on alcohol, in the primary care population, to describe the main characteristics of diagnosed patients, evaluate the degree of detection of the disease on the part of primary care doctors, determine the percentage of patients who receive specialized treatment and study the barriers that impede access to the same. The methodology has been amply described in a previous article (Manthey et al., 2014).

The study, carried out in Catalonia, is cross-sectional and included 30 randomly-selected GPs from 20 primary care centers. Only three declined to participate while two others were excluded as there was already a sufficient sample. Each GP was asked to respond to a questionnaire referring to patients visited on one day chosen at random. The patients who were visited by the doctor and who consented after signing the informed consent statement, were later interviewed on the same day of the visit by a member of the research team. Some 1,994 patients were interviewed. Of these, the questionnaire completed by the doctor was only obtained from 1,372. The clinical diagnoses made by the doctor were collected, as well as the various health and sociodemographic measures obtained by means of the Composite International Diagnostic Interview (CIDI) (Kessler & Ustün, 2004), which diagnoses the presence of alcohol consumption disorders based on the criteria of the DSM-IV (American Psychiatry Association, 2000), the Kessler screening questionnaire (Furukawa, Kessler, Slade, & Andrews, 2003; Kessler et al., 2003), that measures psychological distress, and the World Health Organization Disability Assessment Schedule (WHODAS 2.0.) (Ustün et al., 2010), that measures the degree of disability, the latter three being administered by the research team. Our principal variable in access to treatment or getting professional help is derived from a combination of the questions that doctors and patients were asked respectively. Professional help comprises advice or assessment, individual or group psychological interventions, or pharmacotherapy. As well as the closed questions, there were open questions regarding treatment received and the providers of this treatment, which were later classified as professional or non-professional by the authors. A wide definition was used, but professionals such as herbalists and priests were excluded.

Statistical analysis

A description and comparison of patients is made, grouping them together according to whether or not they have been diagnosed as being alcohol-dependent in the last twelve months. A comparison is also made within the sub-group of alcohol dependents, according to whether they are receiving specialized treatment or not. These comparisons are made by means of logistical or linear regression models according to the nature of the variable, adjusting the results for age and gender. The Bonferroni correction procedure for multiple comparisons was applied to the habitual statistical significance of 0.05.

Results

Of the 1,372 patients who were interviewed, and from whom the questionnaire completed by their GP was collected once they had been visited, 118 (8.6%) were diagnosed with alcohol dependence, either by their doctor or by means of the CIDI.

Table 1 shows the differences in the variables studied between the patients who attend primary care, whether they suffer alcohol dependence or not. Among these variables, a greater proportion of patients who are classified as being below the average socioeconomic level stand out, with worse results for the dependent cohort (48.3% vs 33.3%), who also present higher rates of unemployment (32.2% vs 19.2%), smoking (54.2% vs 28.7%), serious psychological distress (15.3% vs 7.6%) and higher scores on the WHODAS disability scale (15.06 vs 10.97). The patients with alcohol dependence were also younger (37.4 years of age (SD13.0) vs 43.7 years of age (SD12.8)). All of these differences turned out to be statistically significant, even after adjusting for age and gender. There were also higher rates of depression, anxiety and hepatic problems in the cohort with alcohol dependence, without these differences reaching levels of statistical significance. Patients with alcohol dependence consumed more grams of alcohol per day (30.1 vs 4.7; p<001), and also showed higher rates of consumption in the form of binge-drinking (5.9% vs 0.2%; p<001).

Only 20 (16.9%) of the patients with dependence on alcohol were in receipt of treatment at the time of the study. Of these 20 patients, the GP diagnosed 14 as dependents, while the CIDI diagnosed 19 of them. One patient was diagnosed by the GP and not by the CIDI. Table 2 shows the principal reasons given for attending to receive treatment

Table 2. *Reasons for not seeking treatment*

	n (total=94)
Fear of giving up drinking	11
Shame	18
Desired treatment not offered	7
Stigma	8
Denial	1
Barrier	11
Treatment considered ineffective	1
Did not know how to access it/Did not know it existed	1
Lack of willpower	1
Lack of information	1
Inexistence of professional help	1
Considers alcohol to be different from other drugs	1
It is an incurable disease	1

or not. Shame and stigma, with 27.6% of the total answers given, were the main reasons for not attending, followed by fear of giving up drinking and barriers to access, each with 11.7% of the answers.

In Table 3 the differences in the variables studied between the patients who attend for treatment and those who do not can be seen. It was found that those who attend for treatment are older (44 vs 36 years of age), although after applying the statistical correction for multiple comparisons the difference turned out not to be significant. Unemployment rates were also higher for the sub-group in receipt of treatment (65% vs 25.5%). Also in a significant way, the grams of alcohol consumed on a daily basis were higher for the sub-group in receipt of treatment (61.5 vs 23.7). Although not reaching statistically significant levels, the group in receipt of treatment also presented a higher proportion of smokers, depression, anxiety, psychological distress, levels of disability and consumption of alcohol in the form of binge-drinking.

Table 3. *Differences between patients with alcohol dependence according to whether they receive treatment or not*

	No treatment (N=98)	Treatment (N=20)	Odds ratioa (95 %confidence interval)	Regression coefficient (95% confidence interval)
Average age (SD)	35.98 (13.12)	44.05 (10.5)		8.1 (1.93 - 14.28) p=0.011
Low socioeconomic level % (CI)	49 (39.1 – 58.9)	45 (23.2 - 66.8)	0.74 (0.27 - 2) p=0.551	
Unemployed % (CI)	25.5 (16.9 - 34.1)	65(44.1 - 85.9)	6.3 (2.14 - 18.67) p=0.001 b	
Smokers % (CI)	49.4 (39.5 -59.3)	68.4 (48 - 88.8)	2.24 (0.76 – 6.6) p=0.143	
Hypertension % (CI)	13.3 (6.6 - 20)	5 (0.00 - 14.55)	0.152 (0.016 – 1.41) p=0.098	
Hepatic problems % (CI)	4.1 (0.17 - 8)	5 (0.00 – 14.55)	0.81 (0.081 – 8.2) p=0.862	
Depression % (CI)	13.3 (6.6 - 20)	20 (2.5. – 37.5)	1.23 (0.33 – 4.56) p=0.753	
Anxiety % (CI)	14.3 (7.4 - 21.2)	35 (14.1 - 55.9)	3 (0.98 – 9.2) p=0.054	
K10 severe % (CI)	14.3 (7.4 - 21.2)	20 (2.5. – 37.5)	1.25 (0.348 – 4.45) p=0.731	
Total mean score (SD)	11.2 (8.1)	15.3 (9.)		3.5 (-0.54 – 7.6) p=0.088
WHODAS 2.0 average (SD) Number of days unable to carry out normal activities or work owing to health reasons.	3.1 (6.8)	7.5 (10.9)		4 (0.2 – 7.9) p=0.039
Total mean score (SD)	113.7 (14.2)	21.8 (22.3)		7 (-0.91 - 14.94) p=0.028
Average daily amount of alcohol (in grams) (SD)	23.7 (33.3)	61.5 (77.4)		39.4 (17.5 - 61.4) p<.001 b
Chronic excessive consumption of alcohol % (CI) At least 100g of alcohol daily	4.1 (0.17 - 8)	25 (6 - 44)	8.7 (1.88– 40.3) p=0.006	
Binge-drinking % (CI) At least 200g of ethanol weekly	5.1 (0.74 - 9.5)	10 (0.0 - 23.15)	4.3 (0.6 – 30.66) p=0.146	

Note. AD= Alcohol dependence in the last 12 months. CIDI= Composite International Diagnostic Interview. GP= General Practitioner. SD= standard deviation. CI= 95% confidence interval. BMI= Body Mass Index. K10= Kessler scale of psychological distress. Cut-off point for severe psychological distress of 21 points, on a scale of 0 to 40. WHODAS 2.0= World Health Organization Disability Assessment Schedule 2.0, range of scores from 0 to 100.

a Regression coefficients adjusted for gender and age.

b p significant with Bonferroni correction (p<0.05/16=0.003125)

Discussion

This study underlines a clear differentiation between patients who are dependent on alcohol vis-à-vis the overall number of patients who are attended to at primary care centers, highlighting greater disability, greater levels of psychological distress, a worse socioeconomic situation and higher rates of unemployment. All of these data point to a fact that is already known, such as the repercussions, both somatic and psychosocial, that dependence on alcohol imposes on those patients who suffer it. It also highlights the scanty proportion of patients who receive treatment and the shame and stigma which are the main causes of this.

If we analyze in detail the clinical differences between patients who attend for treatment and those who do not, it can be observed that those who do attend are more serious cases, are older, drink larger amounts and suffer more repercussions derived from their dependence on alcohol: higher levels of unemployment, anxiety, depression and disability. Although previous studies have shown that there are cases of alcoholism that are not progressive, or are intermittent (Vaillant, 2003), alcohol dependence generally becomes worse over time. The average age of the patients in the group in receipt of treatment was higher, although after adjusting for multiple comparisons the difference was not statistically significant. Even still, the higher age and the greater severity observed in the sub-group of patients who seek treatment lead one to think that it is only when the problem reaches a certain level of seriousness that patients either seek or are persuaded to attend treatment. In other words, doctors and patients seem to act in accordance with the old myth that only contemplates the recovery of the alcoholic when he or she has 'hit rock bottom'. From a health perspective, however, quite the opposite may be deduced: the need for earlier interventions with the aim, precisely, of preventing the disease from reaching levels of greater severity. On this point it would be useful to highlight the data from a recent study (Miquel et al., 2014), wherein it can be seen that GPs recognize alcohol dependence more in patients who are older whereas semi-structured interviews such as the CIDI questionnaire identify this group of patients at an earlier age. All of this, together with the enormous costs that the disease means for society (Rehm et al., 2009), emphasize the idea of implementing universal screening for alcohol dependence by means of tools designed specifically for that purpose in primary care, as many guides already recommend (Anderson, Gual, & Colom, 2005; Moyer, 2013; Pascual, Guardia, Pereiro, & Bobes, 2013). This would allow for early detection of the disease and would offer the possibility of preventing its progress. In addition to this, the fact that in our sample some 30% of the patients who attend for treatment were not diagnosed by their GP as being alcohol-dependent underlines the importance of the aforementioned universal screening test as a further option for improving treatment rates.

Even still, as previous studies have shown (Alonso et al., 2004; Kohn et al., 2004), there is still a serious problem regarding the low proportion of patients who receive or seek treatment. Our study found that only 16.98% of patients suffering from alcohol dependence receive treatment, a figure that sits between the 8.3% and the 21.9% indicated in the aforementioned studies; but it is one that is lower than the data obtained in European countries as a whole (20.4%) (Rehm et al., 2015a). In any case, all studies coincide in indicating that the problems related to alcohol are, within mental illnesses, those that show the lowest treatment rates.

The main reason for the absence of treatment is shame, followed by fear of giving up alcohol and barriers that impede access to treatment, data that concur with previous studies (Andréasson et al., 2013; Room, 2005). One way of reducing the associated shame and stigma could be the introduction of quantitative parameters such as "heavy use over time", that allows problems derived from alcohol to be described in a continuum, thus avoiding stigmatizing labels (alcoholic vs non-alcoholic) (Rehm et al., 2013b). On the other hand, barriers to access account for 11.7% of the replies, a fact that implies, on the part of the providers, the need to improve access to treatment for patients.

Various methodological limitations have to be borne in mind when it comes to interpreting the results of this study. Firstly, and most importantly, it is a cross-sectional study, which impedes the establishment of causal relationships in a reliable way. Much of the information that was gathered came via interviews and self-reporting tools, a fact that implies the possibility of skewed data, although previous studies do suggest that the risk is low for the tools used (Furukawa et al., 2003; B. Ustün et al., 1997). We should also be cautious when interpreting data derived from the comparison of patients with alcohol dependence and who receive treatment and those who do not, owing to the fact that the sample size of one of the groups is small. On the other hand, one of the strengths of the study is the high index of participation on the part of the GPs, as well as ample external validity coming from the range of primary care centers in the territory. In this sense, our results concur with the majority of previous studies existing in the literature.

Conclusions

Patients who have alcohol dependence constitute a collective that is clearly differentiated from the remainder of patients within the ambit of primary care. They are patients with a more serious condition and with more comorbidities that are both somatic and psychiatric. Despite this, many of them go unnoticed by the professionals who attend to them, and as previous studies have pointed out, the proportion who are in treatment is frankly low. The data suggest, as well, that the ones who do receive treatment are those whose level of dependency has reached a more serious level, with

them having developed more negative consequences, which presupposes a worse prognosis. Overall, the study suggests the need to implement earlier screening and treatment strategies, it being necessary to take into account the main reasons that the patients give for not attending for treatment and the means available to overcome them.

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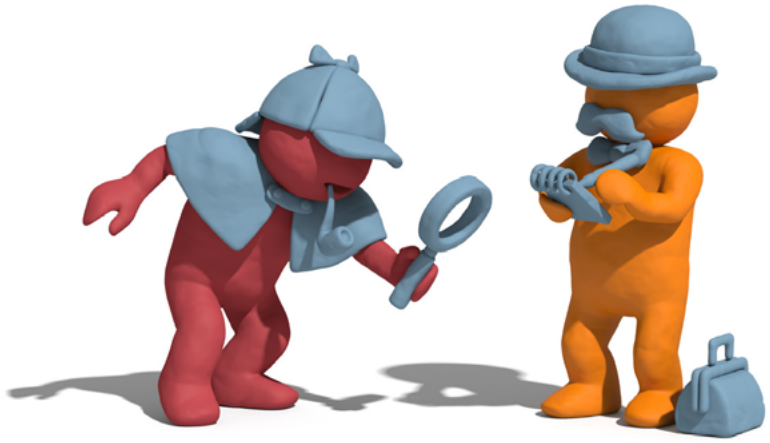

EFICACIA PARA SENTIRSE BIEN

FARMACOCINÉTICA[1, 2]

EFICACIA[1]

SIN SUPLEMENTACIÓN ORAL[3]

MONOTERAPIA[1, 4, 5]

TOLERABILIDAD CONTRASTADA[3, 7 *]

METABOLISMO HEPÁTICO LIMITADO[3]

CLARIDAD DE PENSAMIENTO[8]

FLEXIBILIDAD DE PAUTA POSOLÓGICA[3]

*Para más información sobre efectos adversos consultar apartado 4.8 de la Ficha Técnica

Janssen-Cilag, S.A.

Paseo de las Doce Estrellas, 5-7
28042 Madrid
www.janssen.es

janssen
PHARMACEUTICAL COMPANIES OF Johnson&Johnson

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1. NOMBRE DEL MEDICAMENTO. Xeplion 50 mg suspensión inyectable de liberación prolongada. Xeplion 75 mg suspensión inyectable de liberación prolongada. Xeplion 100 mg suspensión inyectable de liberación prolongada. Xeplion 150 mg suspensión inyectable de liberación prolongada. **2. COMPOSICION CUALITATIVA Y CUANTITATIVA.** Xeplion 50 mg/ml suspensión inyectable. Cada jeringa precargada contiene 78 mg de palmitato de paliperidona equivalentes a 50 mg de paliperidona. Xeplion 75 mg/ml suspensión inyectable. Cada jeringa precargada contiene 117 mg de palmitato de paliperidona equivalentes a 75 mg de paliperidona. Xeplion 100 mg/ml suspensión inyectable. Cada jeringa precargada contiene 156 mg de palmitato de paliperidona equivalentes a 100 mg de paliperidona. Xeplion 150 mg/ml suspensión inyectable. Cada jeringa precargada contiene 234 mg de palmitato de paliperidona equivalentes a 150 mg de paliperidona. Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACEUTICA.** Suspensión inyectable de liberación prolongada. La suspensión es de color blanco a blanquecino. La suspensión tiene un pH neutro (aproximadamente 7,0). **4. DATOS CLINICOS. 4.1. Indicaciones terapéuticas.** Xeplion está indicado para el tratamiento de mantenimiento de la esquizofrenia en pacientes adultos estabilizados con paliperidona o risperidona. En determinados pacientes adultos con esquizofrenia y respuesta previa a paliperidona o risperidona oral, Xeplion puede ser utilizado sin necesidad de estabilización previa con tratamiento oral si los síntomas psicóticos son leves o moderados y es necesario un tratamiento con un inyectable de acción prolongada. **4.2. Posología y forma de administración.** Posología. Se recomienda iniciar Xeplion con una dosis de 150 mg en el día 1 de tratamiento y 100 mg una semana después (día 8), ambos administrados en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). La tercera dosis se debe administrar un mes después de la segunda dosis de inicio. La dosis de mantenimiento mensual recomendada es de 75 mg; algunos pacientes pueden beneficiarse de dosis inferiores o superiores dentro del rango recomendado de 25 a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. Los pacientes con sobrepeso u obesos pueden requerir dosis situadas en la parte superior del intervalo (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. El ajuste de la dosis de mantenimiento se puede hacer mensualmente. Al realizar ajustes de la dosis, se deben tener en cuenta las características de liberación prolongada de Xeplion (ver sección 5.2), dado que el pleno efecto de las dosis de mantenimiento puede no resultar evidente durante varios meses. *Cambio desde paliperidona oral o risperidona oral.* El tratamiento recibido previamente con paliperidona oral o risperidona oral puede ser interrumpido en el momento de iniciar el tratamiento con Xeplion. Algunos pacientes se pueden beneficiar de una retirada gradual. Xeplion debe iniciarse según se describe al principio de la sección 4.2 anterior. *Cambio desde Risperidona inyectable de acción prolongada.* Al realizar el cambio de tratamiento de los pacientes desde risperidona inyectable de acción prolongada, inicie el tratamiento con Xeplion en lugar de la siguiente inyección programada. A partir de entonces, Xeplion se debe continuar en intervalos mensuales. No es necesario seguir el régimen de dosificación inicial de una semana incluyendo las inyecciones intramusculares (día 1 y 8, respectivamente) según se describe en la sección 4.2 anterior. Los pacientes previamente estabilizados con diferentes dosis de risperidona inyectable de acción prolongada pueden alcanzar una exposición similar a paliperidona en estado estacionario durante el tratamiento de mantenimiento con dosis mensuales de Xeplion según se describe a continuación:

Dosis de risperidona inyectable de acción prolongada y Xeplion necesaria para alcanzar una exposición a paliperidona similar en estado estacionario

Dosis previa de risperidona inyectable de acción prolongada	Inyección de Xeplion
25 mg cada 2 semanas	50 mg mensualmente
37,5 mg cada 2 semanas	75 mg mensualmente
50 mg cada 2 semanas	100 mg mensualmente

La interrupción de los medicamentos antipsicóticos debe realizarse de acuerdo a una apropiada información de prescripción. En caso de interrupción de Xeplion, se deben considerar sus características de liberación prolongada. Se ha de reevaluar periódicamente la necesidad de continuar con la administración de los medicamentos actuales para el tratamiento de los síntomas extrapiramidales (SEP). Dosis omitidas. *Medidas para evitar la omisión de dosis.* Se recomienda que la segunda dosis de iniciación de Xeplion se administre una semana después de la primera dosis. Para evitar la omisión de esta dosis, los pacientes pueden recibir la segunda dosis 4 días antes o después del momento de administración semanal (día 8). Del mismo modo, se recomienda administrar mensualmente la tercera inyección y las siguientes después del régimen de iniciación. Para evitar la omisión de la dosis mensual, los pacientes pueden recibir la inyección hasta 7 días antes o después del momento de administración mensual. Si se omite la fecha límite para la segunda inyección de Xeplion (día 8 ± 4 días), el momento de reinicio recomendado depende del tiempo que haya transcurrido desde la primera inyección del paciente. *Omisión de la segunda dosis de iniciación (<4 semanas desde la primera inyección).* Si han transcurrido menos de 4 semanas desde la primera inyección, se le debe administrar al paciente la segunda inyección de 100 mg en el músculo deltoides tan pronto como sea posible. Se debe administrar una tercera inyección de Xeplion de 75 mg en el músculo deltoides o en el glúteo 5 semanas después de la primera inyección (independientemente del momento en el que se haya administrado la segunda inyección). A partir de entonces, se debe seguir el ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (entre 4 y 7 semanas desde la primera inyección).* Si han transcurrido entre 4 y 7 semanas desde la primera inyección de Xeplion, reanude la administración con dos inyecciones de 100 mg de la siguiente manera: 1. una inyección en el deltoides tan pronto como sea posible, 2. otra inyección en el deltoides una semana más tarde, 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la segunda dosis de iniciación (>7 semanas desde la primera inyección).* Si han transcurrido más de 7 semanas desde la primera inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. *Omisión de la dosis de mantenimiento mensual (1 mes a 6 semanas).* Tras la iniciación, el ciclo de inyección recomendado de Xeplion es mensual. Si han transcurrido menos de 6 semanas desde la última inyección, entonces se debe administrar la dosis previamente estabilizada tan pronto como sea posible, seguida de inyecciones a intervalos mensuales. *Omisión de la dosis de mantenimiento mensual (>6 semanas a 6 meses).* Si han transcurrido más de 6 semanas desde la última inyección de Xeplion, la recomendación es la siguiente: *Para los pacientes estabilizados con dosis de 25 a 100 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de la misma dosis en la que el paciente se estabilizó previamente. 2. otra inyección en el deltoides (misma dosis) una semana más tarde (día 8). 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Para los pacientes estabilizados con 150 mg.* 1. una inyección en el deltoides tan pronto como sea posible, de una dosis de 100 mg. 2. otra inyección en el deltoides una semana más tarde (día 8) de una dosis de 100 mg. 3. reanudación del ciclo normal de inyecciones mensuales, ya sea en el músculo deltoides o en el glúteo, de 25 mg a 150 mg en función de la tolerabilidad y/o eficacia individual del paciente. *Omisión de la dosis de mantenimiento mensual (>6 meses).* Si han transcurrido más de 6 meses desde la última inyección de Xeplion, inicie la administración según las pautas recomendadas para la iniciación de Xeplion recogidas anteriormente. Poblaciones especiales. *Población de edad avanzada.* No se ha establecido la eficacia y la seguridad en la población de edad avanzada >65 años. En general, la dosis recomendada de Xeplion en los pacientes de edad avanzada con función renal normal es la misma que para los pacientes adultos más jóvenes con función renal normal. Sin embargo, ya que los pacientes de edad avanzada pueden tener disminuida la función renal, puede ser necesario ajustar la dosis (ver *Insuficiencia renal* más adelante para conocer las recomendaciones de dosificación en pacientes con insuficiencia renal). *Insuficiencia renal.* No se ha estudiado Xeplion sistemáticamente en los pacientes con insuficiencia renal (ver sección 5.2). En los pacientes con insuficiencia renal leve (aclaramiento de creatinina ≥50 a <80 ml/min), se recomienda iniciar Xeplion con una dosis de 100 mg el día 1 del tratamiento y 75 mg una semana después, ambos administrados en el músculo deltoides. La dosis de mantenimiento mensual recomendada es de 50 mg con un rango de 25 a 100 mg, en función de la tolerabilidad y/o eficacia individual del paciente. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver sección 4.4). *Insuficiencia hepática.* Basándose en la experiencia con paliperidona oral, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. Dado que paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave, se recomienda precaución en estos pacientes. *Población pediátrica.* No se ha establecido la seguridad y la eficacia de Xeplion en niños y adolescentes <18 años de edad. No hay datos disponibles. Forma de administración. Xeplion se utiliza únicamente para uso intramuscular. Se debe inyectar lentamente, profundamente en el músculo. Cada inyección debe ser administrada por un profesional sanitario. La administración debe realizarse en una sola inyección. La dosis no se debe administrar en inyecciones divididas. La dosis no se debe administrar por vía intravascular o subcutánea. Las dosis de iniciación del día 1 y del día 8 se deben administrar ambas en el músculo deltoides para alcanzar concentraciones terapéuticas rápidamente (ver sección 5.2). Después de la segunda dosis de inicio, las dosis de mantenimiento mensuales se pueden administrar tanto en el músculo deltoides como en el glúteo. Se debe cambiar del glúteo al deltoides (y viceversa) en caso de dolor en el lugar de inyección si no se tolera bien el malestar en el lugar de inyección (ver sección 4.8). También se recomienda alternar entre los lados izquierdo y derecho (ver más adelante). Para consultar las instrucciones de uso y manipulación de Xeplion, ver prospecto (información destinada únicamente a médicos o profesionales del sector sanitario). *Administración en el músculo deltoides.* El tamaño de la aguja recomendado para la administración inicial y de mantenimiento de Xeplion en el músculo deltoides viene determinado por el peso del paciente. En los pacientes ≥90 kg, se recomienda la aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). En los pacientes <90 kg, se recomienda la aguja de calibre 23 de 1 pulgada (25,4 mm x 0,64 mm). Las inyecciones en el deltoides se deben alternar entre los dos músculos deltoides. *Administración en el músculo glúteo.* El tamaño de la aguja recomendado para la administración de mantenimiento de Xeplion en el músculo glúteo es el de una aguja de calibre 22 de 1½ pulgadas (38,1 mm x 0,72 mm). La administración se debe realizar en el cuadrante superior externo de la zona glútea. Las inyecciones en el glúteo se deben alternar entre los dos músculos glúteos. **4.3. Contraindicaciones.** Hipersensibilidad al principio activo, a risperidona o a alguno de los excipientes incluidos en la sección 6.1. **4.4. Advertencias y precauciones especiales de empleo.** Uso en pacientes que se encuentran en un estado sumamente agitado o psicótico grave. Xeplion no se debe utilizar para el tratamiento de estados agitados agudos o psicóticos graves cuando esté justificado el control inmediato de los síntomas. Intervalo QT. Se debe tener precaución al recetar paliperidona a pacientes con enfermedad cardiovascular conocida o antecedentes familiares de prolongación del intervalo QT, y en caso de uso concomitante con otros medicamentos que prolonguen el intervalo QT. Síndrome neuroléptico maligno. Se han notificado casos del Síndrome Neuroléptico Maligno (SNM), que se caracteriza por hipertermia, rigidez muscular, inestabilidad autonómica, alteración de la consciencia y elevación de los niveles séricos de creatina fosfocinasa relacionados con paliperidona. Otros signos clínicos pueden ser mioglobinuria (rabdomiólisis) e insuficiencia renal aguda. Si un paciente desarrolla signos o síntomas indicativos del SNM, se debe interrumpir la administración de todos los antipsicóticos, incluido paliperidona. Discinesia tardía. Los medicamentos con propiedades antagonistas del receptor de la dopamina se han asociado con la inducción de discinesia tardía, caracterizada por movimientos rítmicos involuntarios, predominantemente de la lengua y/o la cara. Si aparecen signos y síntomas de discinesia tardía, se debe considerar la interrupción de la administración de todos los antipsicóticos, incluido paliperidona. Leucopenia, neutropenia y agranulocitosis. Se han notificado casos de leucopenia, neutropenia y agranulocitosis con Xeplion. La agranulocitosis ha sido notificada en muy raras ocasiones (<1/10.000 pacientes) durante la experiencia post-comercialización. Pacientes con un historial de un bajo recuento de glóbulos blancos clínicamente significativo (GB) o una leucopenia/neutropenia inducida por el medicamento deben ser monitorizados durante los primeros meses de tratamiento y se considerará discontinuar el tratamiento con Xeplion si aparecen los primeros signos de disminución clínicamente significativa de GB, en ausencia de otros factores causales. Pacientes con neutropenia clínicamente significativa deben ser cuidadosamente monitorizados por la fiebre u otros síntomas o signos de infección y se deben tratar inmediatamente en caso de aparecer estos síntomas o signos. En pacientes con neutropenia grave (recuento total de neutrófilos $<1x10^9$/L) se debe discontinuar el tratamiento con Xeplion y controlar los niveles de GB hasta la recuperación. Reacciones de hipersensibilidad. Durante la experiencia pos-comercialización se han notificado raramente reacciones anafilácticas en pacientes que previamente han tolerado risperidona oral y paliperidona oral (ver las secciones 4.1 y 4.8). Si ocurren reacciones de hipersensibilidad, interrumpir el tratamiento con Xeplion, iniciar medidas generales de soporte clínicamente apropiadas y vigilar al paciente hasta que los signos y síntomas se resuelvan (ver las secciones 4.3 y 4.8). Hiperglucemia y diabetes mellitus. Se ha notificado hiperglucemia, diabetes mellitus y exacerbación de diabetes pre-existente durante el tratamiento con paliperidona. En algunos casos, se ha notificado un aumento de peso previo que puede ser un factor de predisposición. Se ha notificado en muy raras ocasiones la asociación con cetoacidosis y en raras ocasiones con coma diabético. Se recomienda una monitorización clínica adecuada de acuerdo con las guías antipsicóticas utilizadas. A los pacientes tratados con antipsicóticos atípicos, incluido Xeplion, se les deben monitorizar los síntomas de la hiperglucemia (tales como polidipsia, poliuria, polifagia y debilidad) y a los pacientes con diabetes mellitus se les debe monitorizar regularmente el empeoramiento del control de glucosa. Aumento de peso. Se ha notificado un aumento de peso significativo con el uso de Xeplion. El peso debe controlarse regularmente. Hiperprolactinemia. Los estudios de cultivo de tejidos sugieren que la prolactina puede estimular el crecimiento de células en los tumores de mama humanos. Aunque hasta ahora los estudios clínicos y epidemiológicos no han demostrado la existencia de una asociación clara con la administración de antipsicóticos, se recomienda precaución en pacientes con antecedentes patológicos de interés. Paliperidona debe utilizarse con precaución en pacientes con posibles tumores dependientes de prolactina. Hipotensión ortostática. Paliperidona puede inducir hipotensión ortostática en algunos pacientes sobre la base de su actividad alfa-bloqueante. Según los datos agrupados de los tres ensayos controlados con placebo, de dosis fijas y 6 semanas de duración con comprimidos orales de paliperidona de liberación prolongada (3, 6, 9 y 12 mg), el 2,5% de los pacientes tratados con paliperidona oral comunicaron hipotensión ortostática, en comparación con el 0,8% de los sujetos tratados con placebo. Xeplion debe utilizarse con precaución en pacientes con enfermedad cardiovascular conocida (p. ej., insuficiencia cardíaca, infarto de miocardio o isquemia, trastornos de la conducción), enfermedad cerebrovascular o afecciones que predispongan al paciente a la hipotensión (p. ej. deshidratación e hipovolemia). Convulsiones. Xeplion debe utilizarse con precaución en pacientes con antecedentes de convulsiones u otros trastornos que potencialmente puedan reducir el umbral convulsivo. Insuficiencia renal. Las concentraciones plasmáticas de paliperidona aumentan en pacientes con insuficiencia renal y por tanto, se recomienda un ajuste de la dosis en pacientes con insuficiencia renal leve. Xeplion no está recomendado en pacientes con insuficiencia renal moderada o grave (aclaramiento de creatinina <50 ml/min) (ver secciones 4.2 y 5.2). Insuficiencia hepática. No se dispone de datos en pacientes con insuficiencia hepática grave (clase C de Child-Pugh). Se recomienda precaución si se utiliza paliperidona en dichos pacientes. Pacientes de edad avanzada con demencia. No se ha estudiado Xeplion en pacientes de edad avanzada con demencia. Xeplion se debe utilizar con precaución en pacientes de edad avanzada con demencia y con factores de riesgo de padecer ictus. La experiencia con risperidona citada más adelante se considera válida también para paliperidona. *Mortalidad global.* En un metanálisis de 17 ensayos clínicos controlados, los pacientes de edad avanzada con demencia tratados con otros antipsicóticos atípicos, tales como risperidona, aripiprazol, olanzapina y quetiapina, tenían un mayor riesgo de mortalidad en comparación con placebo. Entre los pacientes tratados con risperidona, la mortalidad fue del 4% frente al 3,1% con placebo. *Reacciones adversas cerebrovasculares.* Se ha observado un aumento de aproximadamente 3 veces del riesgo de reacciones adversas cerebrovasculares en los ensayos clínicos aleatorizados controlados con placebo en la población con demencia al utilizar algunos antipsicóticos atípicos, tales como risperidona, aripiprazol y olanzapina. Se desconoce el mecanismo de este aumento del riesgo. Enfermedad de Parkinson y demencia con cuerpos de Lewy. Los médicos deben sopesar los riesgos y los beneficios de prescribir Xeplion a los pacientes con enfermedad de Parkinson o Demencia con Cuerpos de Lewy (DCL), ya que ambos grupos pueden tener mayor riesgo de padecer Síndrome Neuroléptico Maligno, así como tener una mayor sensibilidad a los antipsicóticos. Las manifestaciones de este aumento de la sensibilidad pueden incluir confusión, obnubilación, inestabilidad postural con caídas frecuentes, además de síntomas extrapiramidales. Priapismo. Se ha notificado que los medicamentos antipsicóticos (incluida risperidona) con efectos de bloqueo alfa adrenérgico inducen priapismo. Durante la vigilancia post-comercialización, también se han notificado casos de priapismo con paliperidona oral, que es el metabolito activo de risperidona. Se ha de informar a los pacientes de la necesidad de acudir al médico urgentemente en caso de que el priapismo no haya sido resuelto en el transcurso de 3 a 4 horas. Regulación de la temperatura del organismo. Se ha atribuido a los medicamentos antipsicóticos la interrupción de la capacidad del organismo para reducir la temperatura corporal central. Se aconseja proceder con especial cautela cuando se prescriba Xeplion a pacientes que vayan a experimentar circunstancias que puedan contribuir a una elevación de la temperatura corporal central, p. ej. ejercicio físico intenso, exposición a calor extremo, que reciban medicamentos concomitantes con actividad anticolinérgica o que estén sujetos a deshidratación. Tromboembolismo venoso. Se han notificado casos de tromboembolismo venoso (TEV) con medicamentos antipsicóticos. Dado que los pacientes tratados con antipsicóticos suelen presentar factores de riesgo adquiridos de TEV, se han de identificar todos los posibles factores de riesgo de TEV antes y durante el tratamiento con Xeplion y adoptar medidas preventivas. Efecto antiemético. Se observó un efecto antiemético en los estudios preclínicos con paliperidona. Este efecto, si se produce en humanos, puede enmascarar los signos y síntomas de la sobredosis de determinados medicamentos o de enfermedades como la obstrucción intestinal, el síndrome de Reye y los tumores cerebrales. Administración. Se debe tener cuidado para evitar la inyección involuntaria de Xeplion en un vaso sanguíneo. Síndrome del Iris Flácido Intraoperatorio. Se ha observado síndrome del iris flácido intraoperatorio (IFIS) durante la cirugía de cataratas en pacientes tratados con medicamentos con efecto antagonista alfa1a-adrenérgico, como Xeplion (ver sección 4.8). El IFIS puede aumentar el riesgo de complicaciones oculares durante y después de la intervención. El oftalmólogo debe ser informado del uso actual o pasado de medicamentos con efecto antagonista alfa1a-adrenérgico antes de la cirugía. El beneficio potencial de la interrupción del tratamiento con bloqueantes alfa1 antes de la cirugía de cataratas no ha sido establecido y debe ser sopesado frente al riesgo de interrumpir el tratamiento antipsicótico. **4.5. Interacción con otros medicamentos y otras formas de interacción.** Se recomienda precaución al prescribir Xeplion con medicamentos que prolonguen el intervalo QT, p. ej. antiarrítmicos de clase IA (p. ej., quinidina, disopiramida) y antiarrítmicos de clase III (p. ej. amiodarona, sotalol), algunos antihistamínicos, algunos otros antipsicóticos y algunos antipalúdicos (p. ej. mefloquina). Esta lista es indicativa y no exhaustiva. Posibilidad de que Xeplion afecte a otros medicamentos. No se espera que paliperidona produzca interacciones farmacocinéticas clínicamente relevantes con medicamentos que sean metabolizados por las isoenzimas del citocromo P-450. Dada que los efectos principales de paliperidona se ejercen sobre el sistema nervioso central (SNC) (ver sección 4.8), Xeplion debe utilizarse con precaución en combinación con otros medicamentos de acción central, p. ej., ansiolíticos, la mayoría de los antipsicóticos, hipnóticos, opiáceos, etc. o con el alcohol. Paliperidona puede antagonizar el efecto de levodopa y otros agonistas de dopamina. Si se considera necesario administrar esta combinación, sobre todo para la enfermedad de Parkinson terminal, se debe recetar la dosis mínima eficaz de cada tratamiento. Debido a la posibilidad de que induzca hipotensión ortostática (ver sección 4.4), se puede observar un efecto aditivo si se administra Xeplion con otros tratamientos que también tengan esta posibilidad, p.ej., otros antipsicóticos, tricíclicos. Se recomienda precaución cuando se coadministre paliperidona junto con otros medicamentos que disminuyan el umbral convulsivo (es decir, fenotiazinas o butirofenonas, tricíclicos o ISRS, tramadol, mefloquina, etc.). La administración concomitante de comprimidos orales de paliperidona de liberación prolongada en estado estacionario (12 mg una vez al día) con comprimidos de divalproex sódica de liberación prolongada (de 500 mg a 2000 mg una vez al día) no afectó a la farmacocinética en estado estacionario de valproato. No se ha realizado ningún estudio de interacción entre Xeplion y el litio, sin embargo, no es probable que se produzca una interacción farmacocinética. Posibilidad de que otros medicamentos afecten a Xeplion. Los estudios *in vitro* indican que las enzimas CYP2D6 y CYP3A4 pueden tener una intervención mínima en el metabolismo de la paliperidona, pero no hay indicios *in vitro* ni *in vivo* de que esas isoenzimos desempeñen un papel significativo en el metabolismo de paliperidona. La administración conjunta de paliperidona oral con paroxetina, un potente inhibidor de la CYP2D6, no tuvo un efecto clínicamente significativo sobre la farmacocinética de paliperidona. La administración concomitante de paliperidona oral de liberación prolongada una vez al día y carbamazepina 200 mg dos veces al día originó una disminución de aproximadamente un 37% de la media de la C_{ma} y del AUC en el estado estacionario de paliperidona. Esta disminución se debe en gran parte a un aumento de un 35% del aclaramiento renal de paliperidona, probablemente como resultado de la inducción de la P-gp renal por carbamazepina. Una disminución menor de la cantidad del principio activo inalterado excretado en la orina sugiere que durante la administración concomitante con carbamazepina, hubo un efecto mínimo en el metabolismo del CYP o en la biodisponibilidad de paliperidona. Con dosis más altas de carbamazepina, podrían aparecer disminuciones mayores de las concentraciones plasmáticas de paliperidona. Al inicio del tratamiento con carbamazepina, se debe reevaluar y aumentar la dosis de Xeplion, si es necesario. Por el contrario, en caso de interrupción del tratamiento con carbamazepina, se debe reevaluar y disminuir la dosis de Xeplion, si es necesario. La administración concomitante de una sola dosis de un comprimido de paliperidona oral de liberación prolongada de 12 mg con comprimidos de divalproex sódico de liberación prolongada (dos comprimidos de 500 mg una vez al día) tuvo como resultado un aumento de aproximadamente el 50% en la C_{ma} y el AUC de paliperidona, probablemente como resultado de un aumento de la absorción oral. Dado que no se observó ningún efecto sobre el aclaramiento sistémico, no se espera que se produzca una interacción clínicamente significativa entre los comprimidos de divalproex sódico de liberación prolongada y la inyección intramuscular de Xeplion. Esta interacción no se ha estudiado con Xeplion. Uso concomitante de Xeplion y risperidona o paliperidona oral. Debido a que paliperidona es el principal metabolito activo de risperidona, se debe tener precaución cuando Xeplion sea administrado de forma conjunta con risperidona o con paliperidona oral durante períodos prolongados de tiempo. Los datos de seguridad relacionados con el uso concomitante de Xeplion con otros antipsicóticos son limitados. **4.6. Fertilidad, embarazo y lactancia.** Embarazo. No existen datos suficientes sobre la utilización de paliperidona durante el embarazo. El palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral no fueron teratógenos en estudios en animales, pero se observaron otros tipos de toxicidad reproductiva (ver sección 5.3). Los recién nacidos expuestos a paliperidona durante el tercer trimestre de embarazo están en peligro de sufrir reacciones adversas como síntomas extrapiramidales y/o síndromes de abstinencia que pueden variar en gravedad y duración tras la exposición. Se han notificado casos de síntomas de agitación, hipertonía, hipotonía, temblor, somnolencia, dificultad respiratoria o alteraciones alimenticias. Por consiguiente, se debe vigilar estrechamente a los recién nacidos. Xeplion no se debe utilizar durante el embarazo salvo que sea claramente necesario. Lactancia. Paliperidona se excreta por la leche materna en tal medida que es probable que se produzcan efectos en el lactante si se administra en dosis terapéuticas a mujeres lactantes. Xeplion no debe utilizarse durante la lactancia. Fertilidad. No se observaron efectos relevantes en estudios no clínicos. **4.7. Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia de paliperidona sobre la capacidad para conducir y utilizar máquinas es pequeña o moderada debido a sus posibles efectos sobre el sistema nervioso y la vista, tales como sedación, somnolencia, síncope, visión borrosa (ver sección 4.8). Por tanto, se debe aconsejar a los pacientes que no conduzcan ni utilicen máquinas hasta conocer su sensibilidad individual a Xeplion. **4.8. Reacciones adversas.** Resumen del perfil de seguridad. Las reacciones adversas a medicamentos (RAMs) notificadas con más frecuencia en los ensayos clínicos fueron insomnio, cefalea, ansiedad, infección de las vías respiratorias altas, reacción en el lugar de la inyección, parkinsonismo, aumento de peso, acatisia, agitación, sedación/somnolencia, náuseas, estreñimiento, mareos, dolor musculoesquelético, taquicardia, temblar, dolor abdominal, vómitos, diarrea, fatiga y distonia. De estas, la acatisia y la sedación/somnolencia parecían estar relacionadas con la dosis. Tabla de reacciones adversas. A continuación se recogen todas las RAMs notificadas con paliperidona en función de la frecuencia estimada de ensayos clínicos llevados a cabo con Xeplion. Se aplican los siguientes términos y frecuencias: *muy frecuentes* (≥1/10), *frecuentes* (≥1/100 a <1/10), *poco frecuentes* (≥1/1000 a <1/100), *raras* (≥1/10.000 a <1/1000), *muy raras* (<1/10.000), y *frecuencia no conocida* (no puede estimarse a partir de los datos disponibles).

Sistema de clasificación de órganos	Reacción adversa al medicamento — Frecuencia				
	Muy frecuentes	Frecuentes	Poco frecuentes	Raras	No conocidas
Infecciones e infestaciones		infección de las vías respiratorias superiores, infección del tracto urinario, gripe	neumonía, bronquitis, infección del tracto respiratorio, sinusitis, cistitis, infección de oídos, infección de ojos, amigdalitis, celulitis, acarodermatitis, absceso subcutáneo	onicomicosis	
Trastornos de la sangre y del sistema linfático			disminución del recuento de glóbulos blancos, anemia, disminución del hematocrito, aumento del recuento de eosinófilos	agranulocitosis[a] neutropenia, trombocitopenia	
Trastornos del sistema inmunológico			hipersensibilidad	reacción anafiláctica[a]	
Trastornos endocrinos		hiperprolactinemia[a]		secreción inapropiada de la hormona antidiurética	presencia de glucosa en orina
Trastornos del metabolismo y de la nutrición		hiperglucemia, aumento de peso, disminución de peso, aumento de los triglicéridos en sangre	diabetes mellitus[c], hiperinsulinemia, aumento del apetito, anorexia, disminución del apetito, aumento del colesterol en sangre	intoxicación por agua[a], cetoacidosis diabética[a], hipoglucemia, polidipsia	
Trastornos psiquiátricos	insomnio[a]	agitación, depresión, ansiedad	trastorno del sueño, manía, estado de confusión, disminución de la líbido, nerviosismo, pesadillas	embotamiento afectivo[a], anorgasmia	
Trastornos del sistema nervioso	cefalea	parkinsonismo[a], acatisia[a], sedación/somnolencia, distonía[a], mareos, discinesia[a], temblor	discinesia tardía, convulsión[a], síncope, hiperactividad psicomotora, mareo postural, alteración de la atención, disartria, disgeusia, hipoestesia, parestesia	síndrome neuroléptico maligno, isquemia cerebral, sin respuesta a estímulos, pérdida de la consciencia, disminución del nivel de consciencia, coma diabético[a], trastorno del equilibrio, coordinación anormal[a], titubeo de la cabeza[a]	
Trastornos oculares			visión borrosa, conjuntivitis, sequedad de ojos	glaucoma[a], trastornos del movimiento del ojo, giros de los ojos, fotofobia, aumento del lagrimeo, hiperemia ocular	
Trastornos del oído y del laberinto			vértigo, acúfenos, dolor de oído		
Trastornos cardiacos		bradicardia, taquicardia	fibrilación auricular, bloqueo auriculoventricular, QT prolongado en el electrocardiograma, síndrome de taquicardia postural ortostática, anomalías del electrocardiograma, palpitaciones	arritmia sinusal	
Trastornos vasculares		hipertensión	hipotensión, hipotensión ortostática	embolismo pulmonar[a], trombosis venosa, isquemia[a], rubor	
Trastornos respiratorios, torácicos y mediastínicos		tos, congestión nasal	disnea, congestión pulmonar, sibilancias, dolor faringeolaríngeo, epistaxis	síndrome de apnea del sueño[a], hiperventilación[a], neumonía por aspiración[a], congestión del tracto respiratorio distonía[a]	
Trastornos gastrointestinales		dolor abdominal, vómitos, náuseas, estreñimiento, diarrea, dispepsia, dolor de muelas	malestar abdominal, gastroenteritis, sequedad de boca, flatulencia	pancreatitis, obstrucción del intestino[a], íleo, hinchazón de la lengua, incontinencia fecal, fecaloma, disfagia, queilitis[a]	
Trastornos hepatobiliares		aumento de las transaminasas	aumento de la gamma-glutamiltransferasa, aumento de las enzimas hepáticas	ictericia[a]	

Trastornos de la piel y del tejido subcutáneo		erupción cutánea	urticaria, prurito, alopecia, eccema, sequedad de la piel, eritema, acné	angioedema[#], erupción debida al medicamento, hiperqueratosis, decoloración de la piel[#], dermatitis seborreica[#], caspa	
Trastornos musculoesqueléticos y del tejido conjuntivo		dolor musculoesquelético, dolor de espalda	espasmos musculares, rigidez en las articulaciones, dolor de cuello, artralgia	rabdomiolisis[#], aumento de la creatina fosfoquinasa en sangre, anomalía postural[#], inflamación de las articulaciones, debilidad muscular	
Trastornos renales y urinarios	incontinencia urinaria, poliquiuria, disuria			retención urinaria	
Embarazo, puerperio y enfermedades perinatales				síndrome de abstinencia neonatal (ver sección 4.6)[#]	
Trastornos del aparato reproductor y de la mama			disfunción eréctil, trastorno de la eyaculación, amenorrea, retraso en la menstruación, trastornos menstruales[#], ginecomastia, galactorrea, disfunción sexual, secreción vaginal	priapismo[#], dolor de las mamas, malestar de las mamas, congestión de las mamas, aumento de las mamas, secreción mamaria	
Trastornos generales y alteraciones en el lugar de administración		pirexia, astenia, fatiga, reacción en el lugar de la inyección	edema facial, edema[#], alteración de la marcha, dolor de pecho, malestar de pecho, malestar, endurecimiento	hipotermia, disminución de la temperatura corporal[#], escalofríos, aumento de la temperatura corporal, sed, síndrome de abstinencia a medicamentos[#], absceso en el lugar de la inyección, celulitis en el lugar de la inyección, quiste en el lugar de la inyección[#], hematoma en el lugar de la inyección	
Lesiones traumáticas, intoxicaciones y complicaciones de procedimientos terapéuticos			caídas		

[#]Referido a "Hiperprolactinemia" a continuación. [§]Referido a "Síntomas extrapiramidales" a continuación. [£]En ensayos controlados con placebo, se notificó diabetes mellitus en un 0,32% de los pacientes tratados con Xeplion comparado con un 0,39% del grupo placebo. En general, la incidencia en todos los ensayos clínicos fue de un 0,47% en todos los pacientes tratados con Xeplion. **[a]Insomnio incluye:** insomnio inicial, insomnio medio; **Convulsión incluye:** convulsión del gran mal; **Edema incluye:** edema generalizado, edema periférico, edema con fóvea. **Trastornos menstruales incluyen:** menstruación irregular, oligomenorrea. [b]Observado en la experiencia tras la comercialización con paliperidona.

Reacciones adversas notificadas con las formulaciones de risperidona. Paliperidona es el metabolito activo de risperidona, por lo tanto, los perfiles de las reacciones adversas de estos compuestos (incluyendo ambas formulaciones la oral y la inyectable) son relevantes entre sí. Además de las reacciones adversas anteriormente mencionadas, se han notificado las siguientes reacciones adversas con el uso de risperidona, las cuales se espera que aparezcan con Xeplion. **Trastornos del sistema nervioso:** trastorno cerebrovascular. **Trastornos oculares:** síndrome del iris flácido (intraoperatorio). **Trastornos respiratorios, torácicos y mediastínicos:** estertores. **Trastornos generales y alteraciones en el lugar de administración:** (observadas con la formulación inyectable de risperidona): necrosis en el lugar de la inyección, úlcera en el lugar de la inyección. Descripción de algunas reacciones adversas. ***Reacción anafiláctica.*** Durante la experiencia post comercialización, en raras ocasiones se han notificado casos de una reacción anafiláctica después de la inyección de Xeplion en pacientes que previamente han tolerado risperidona oral o paliperidona oral (ver sección 4.4). ***Reacciones en el lugar de la inyección.*** La reacción adversa relacionada con el lugar de la inyección notificada con mayor frecuencia fue el dolor. La mayoría de estas reacciones se notificaron con gravedad de leve a moderada. Las evaluaciones del dolor en el sitio de la inyección en los sujetos, basada en una escala analógica visual, indican que el dolor tiende a disminuir en frecuencia e intensidad con el tiempo en todos los estudios de fase 2 y 3. Las inyecciones en el músculo deltoides se perciben como un poco más dolorosas que las correspondientes inyecciones en el glúteo. Otras reacciones en el lugar de la inyección fueron en su mayoría de intensidad leve e incluyeron induración (frecuente), prurito (poco frecuente) y nódulos (raro). ***Síntomas extrapiramidales (SEP).*** SEP incluye un análisis agrupado de los siguientes términos: parkinsonismo (incluye hipersecreción salival, rigidez musculoesquelética, parkinsonismo, babeo, rigidez en rueda dentada, bradicinesia, hipoacinesia, facies en máscara, tensión muscular, acinesia, rigidez de la nuca, rigidez muscular, modo de andar parkinsoniano y reflejo de la glabella anormal, temblor en reposo parkinsoniano), acatisia (incluye acatisia, inquietud, hipercinesia y síndrome de las piernas inquietas), discinesia (discinesia, calambres musculares, coreatetosis, atetosis y mioclonía), distonía (incluye distonía, hipertonía, torticolis, contracciones musculares involuntarias, contracturas musculares, blefarospasmo, giro ocular, parálisis lingual, espasmo facial, laringoespasmo, miotonía, opistótonos, espasmo orofaríngeo, pleurotótonos, espasmo lingual y trismo) y temblor. Hay que destacar que se incluye un espectro más amplio de síntomas que no tienen forzosamente su origen en el trastorno extrapiramidal. ***Aumento de peso.*** En el estudio de 13 semanas de duración que incluyó un régimen de dosificación inicial de 150 mg, la proporción de sujetos con un aumento anormal de peso ≥7% mostró una tendencia relacionada con la dosis, con una tasa de incidencia del 5% en el grupo placebo, en comparación con tasas del 6%, 8%, y 13% en los grupos tratados con 25 mg, 100 mg y 150 mg de Xeplion, respectivamente. Durante el período abierto de transición/mantenimiento de 33 semanas de duración del ensayo de prevención de recidivas a largo plazo, el 12% de los pacientes tratados con Xeplion cumplieron este criterio (aumento de peso de ≥7% desde la fase doble ciego hasta el final del estudio); la media (DE) del cambio de peso desde el nivel basal del periodo abierto fue de +0,7 (4,79) kg. ***Hiperprolactinemia.*** En ensayos clínicos, se observaron medianas de aumento de la prolactina sérica en sujetos de ambos sexos que recibieron Xeplion. Las reacciones adversas que pueden sugerir un aumento de los niveles de prolactina (p. ej., amenorrea, galactorrea, alteraciones de la menstruación, ginecomastia) se notificaron en <1% de los sujetos. Efectos de clase. Con antipsicóticos puede aparecer prolongación del QT, arritmias ventriculares (fibrilación ventricular, taquicardia ventricular), muerte súbita inexplicable, parada cardíaca y Torsades de pointes. Se han notificado casos de tromboembolismo venoso, incluidos casos de embolismo pulmonar y de trombosis venosa profunda, con el uso de medicamentos antipsicóticos (frecuencia no conocida). Notificación de sospechas de reacciones adversas. Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano: https://www.notificaram.es. **4.9. Sobredosis.** Síntomas. En general, los signos y síntomas previstos son los resultantes de la exageración de los efectos farmacológicos conocidos de paliperidona, es decir, somnolencia y sedación, taquicardia e hipotensión, prolongación del intervalo QT y síntomas extrapiramidales. Se han notificado Torsades de pointes y fibrilación ventricular en un paciente en relación con la sobredosis de paliperidona oral. En caso de sobredosis aguda, se debe tener en cuenta la posibilidad de que estén implicados varios medicamentos. Administración: Al evaluar el tratamiento necesario y la recuperación hay que tener en cuenta la naturaleza de liberación prolongada del medicamento y la prolongada vida media de eliminación de paliperidona. No hay ningún antídoto específico para paliperidona. Se utilizarán medidas de apoyo generales. Hay que establecer y mantener una vía respiratoria despejada y garantizar que la oxigenación y la ventilación sean adecuadas. El control cardiovascular debe empezar inmediatamente e incluir un control electrocardiográfico continuo para controlar posibles arritmias. La hipotensión y el fracaso circulatorio deben tratarse con las medidas terapéuticas adecuadas, como administración de líquidos por vía intravenosa y/o de simpaticomiméticos. En caso de síntomas extrapiramidales intensos, se administrará medicación anticolinérgica. Se debe mantener una supervisión y un control estrictos hasta que el paciente se recupere. **5. PROPIEDADES FARMACOLÓGICAS. 5.1. Propiedades farmacodinámicas.** Grupo farmacoterapéutico: Psicolépticos, otros antipsicóticos. Código ATC: N05AX13. Xeplion contiene una mezcla racémica de paliperidona (+) y (-). Mecanismo de acción. Paliperidona es un agente bloqueante selectivo de los efectos de las monoaminas, cuyas propiedades farmacológicas son diferentes de las de los neurolépticos tradicionales. Paliperidona se une firmemente a los receptores serotoninérgicos 5-HT2 y dopaminérgicos D2. Paliperidona también bloquea los receptores adrenérgicos alfa1 y bloquea, en menor medida, los receptores histaminérgicos H1 y los adrenérgicos alfa2. La actividad farmacológica de los enantiómeros (+) y (-) de paliperidona es similar desde el punto de vista cualitativo y cuantitativo. Paliperidona no se une a los receptores colinérgicos. Aunque paliperidona es un antagonista D2 potente, motivo por el que se cree que alivia los síntomas positivos de la esquizofrenia, produce menos catalepsia y reduce las funciones motrices en menor medida que los neurolépticos tradicionales. La preponderancia del antagonismo central de la serotonina puede reducir la tendencia de paliperidona a producir efectos secundarios extrapiramidales. Eficacia clínica. ***Tratamiento agudo de la esquizofrenia.*** La eficacia de Xeplion en el tratamiento agudo de la esquizofrenia fue establecida en cuatro ensayos doble ciego, aleatorizados, controlados con placebo, de dosis fija, a corto plazo (uno de 9 semanas y tres de 13 semanas de duración) en pacientes adultos ingresados con recidiva aguda que cumplían los criterios para la esquizofrenia del DSM-IV. Las dosis fijas de Xeplion en estos estudios se administraron en los días 1, 8, y 36 en el estudio de 9 semanas de duración, y, además, el día 64 en los estudios de 13 semanas de duración. No fue necesario administrar suplementos antipsicóticos orales adicionales durante el tratamiento agudo de la esquizofrenia con Xeplion. El criterio principal de eficacia del estudio se definió como una reducción de las puntuaciones totales de la Escala de los Síndromes Positivo y Negativo (PANSS), como se muestra en la siguiente tabla. La PANSS es un inventario multi-elemento validado compuesto por cinco factores destinados a evaluar los síntomas positivos, los síntomas negativos, el pensamiento desorganizado, la hostilidad/excitación incontrolada y la ansiedad/depresión. La función se evaluó mediante la escala de Funcionamiento Personal y Social (PSP). La PSP es una escala homologada que mide la capacidad del paciente para desempeñar sus actividades personales y sociales en cuatro áreas del comportamiento: las actividades socialmente útiles (incluidos el trabajo y el estudio), las relaciones personales y sociales, el cuidado personal y los comportamientos disruptivos y agresivos. En un estudio de 13 semanas de duración (n=636) que comparó tres dosis fijas de Xeplion (inyección inicial en el deltoides de 150 mg seguida por tres dosis en el glúteo o en el deltoides de cualquiera de 25 mg/4 semanas, 100 mg/4 semanas o 150 mg/4 semanas) con placebo, las tres dosis de Xeplion fueron superiores a placebo en términos de la mejoría de la puntuación total de la PANSS. En este estudio, tanto los grupos de tratamiento con 100 mg/4 semanas como con 150 mg/4 semanas, pero no el 25 mg/4 semanas, demostraron una superioridad estadística respecto a placebo en cuanto a la puntuación de PSP. Estos resultados respaldan la eficacia a lo largo de toda la duración del tratamiento y la mejoría de la PANSS, que se observaron ya en el día 4, con una separación significativa respecto a placebo en los grupos tratados con 25 mg y 150 mg de Xeplion en el día 8. Los resultados de los otros estudios arrojaron resultados estadísticamente significativos a favor de Xeplion, a excepción de la dosis de 50 mg en un estudio (ver tabla siguiente).

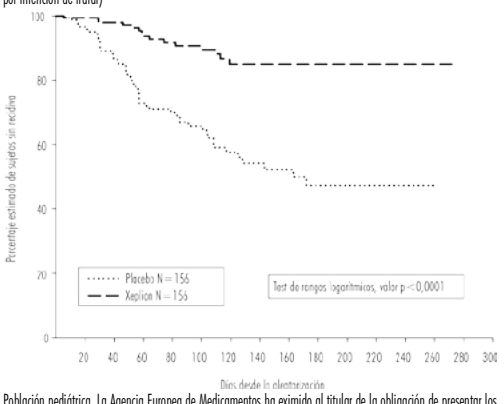
Puntuación total de la escala de los síndromes positivo y negativo de la esquizofrenia (PANSS). Variación entre el momento basal y el final del estudio-LOCF para los estudios R092670-SCH-201, R092670-PSY-3003, R092670-PSY-3004 y R092670-PSY-3007: Grupo de análisis del criterio principal de valoración de la eficacia

	Placebo	25 mg	50 mg	100 mg	150 mg
R092670-PSY-3007*	n=160	n=155		n=161	n=160
Media basal (DE)	86,8 (10,31)	86,9 (11,99)	--	86,2 (10,77)	88,4 (11,70)
Variación media (DE)	-2,9 (19,26)	-8,0 (19,90)		-11,6 (17,63)	-13,2 (18,48)
Valor p (frente a placebo)	--	0,034		<0,001	<0,001
R092670-PSY-3003	n=132		n=93	n=94	n=30
Media basal (DE)	92,4 (12,55)	--	89,9 (10,78)	90,1 (11,66)	92,2 (11,72)
Variación media (DE)	-4,1 (21,01)		-7,9 (18,71)	-11,0 (19,06)	-5,5 (19,78)
Valor p (frente a placebo)	--		0,193	0,019	--
R092670-PSY-3004	n=125	n=129	n=128	n=131	
Media basal (DE)	90,7 (12,22)	90,7 (12,25)	91,2 (12,02)	90,8 (11,70)	--
Variación media (DE)	-7,0 (20,07)	-13,6 (21,45)	-13,2 (20,14)	-16,1 (20,36)	
Valor p (frente a placebo)	--	0,015	0,017	<0,001	
R092670-SCH-201	n=66		n=63	n=68	
Media basal (DE)	87,8 (13,90)	--	88,0 (12,39)	85,2 (11,09)	--
Variación media (DE)	6,2 (18,25)		-5,2 (21,52)	-7,8 (19,40)	
Valor p (frente a placebo)	--		0,001	<0,0001	

*En el estudio R092670-PSY-3007, se administró una dosis de iniciación de 150 mg a todos los sujetos de los grupos de tratamiento con Xeplion el día 1 y, a partir de entonces, la dosis asignada. Nota: un cambio negativo de la puntuación denota mejoría.

Mantenimiento del control de los síntomas y retraso de la recidiva de la esquizofrenia. La eficacia de Xeplion en el mantenimiento del control de los síntomas y el retraso de la recidiva de la esquizofrenia se determinó en un estudio doble ciego, controlado con placebo, de dosis flexible, con un plazo más largo, en el que participaron 849 sujetos adultos no ancianos que cumplían los criterios para la esquizofrenia del DSM-IV. Este estudio incluyó un tratamiento abierto agudo de 33 semanas de duración y una fase de estabilización, una fase aleatorizada, doble ciego, controlada con placebo para observar la recidiva, y un período de extensión abierto de 52 semanas. En este estudio, las dosis de Xeplion fueron 25, 50, 75 y 100 mg administrados mensualmente; la dosis de 75 mg solamente estaba permitida en la extensión abierta de 52 semanas. Inicialmente, los sujetos recibieron dosis flexibles (25-100 mg) de Xeplion durante un período de transición de 9 semanas de duración, seguido de un período de mantenimiento de 24 semanas, en el que los sujetos debían tener una puntuación PANSS ≤75. Los ajustes de la dosis sólo se permitieron en las primeras 12 semanas del período de mantenimiento. Se realizó la asignación aleatoria de un total de 410 pacientes estabilizados a Xeplion (mediana de la duración de 171 días [intervalo de 1 día a 407 días]) o a placebo (mediana de la duración de 105 días [intervalo de 8 días a 441 días]) hasta que experimentaran una recidiva de los síntomas de la esquizofrenia en la fase doble ciego de duración variable. El ensayo se suspendió antes de tiempo por motivos de eficacia, dado que se observó un tiempo significativamente más largo hasta la recidiva (p<0,0001, Figura 1) en los pacientes tratados con Xeplion en comparación con el placebo (cociente de riesgos=4,32; IC 95%: 2,4-7,7).

Figura 1: Gráfico de Kaplan-Meier del tiempo hasta la recidiva. Análisis intermedio (grupo de análisis intermedio por intención de tratar)



Población pediátrica. La Agencia Europea de Medicamentos ha eximido al titular de la obligación de presentar los resultados de los ensayos realizados con Xeplion en los diferentes grupos de la población pediátrica en esquizofrenia. Ver sección 4.2 para consultar la información sobre el uso en población pediátrica. **5.2. Propiedades farmacocinéticas.** Absorción y distribución. Palmitato de paliperidona es el profármaco en forma de éster de palmitato de la paliperidona. Debido a su hidrosolubilidad extremadamente baja, el palmitato de la paliperidona se disuelve lentamente después de la inyección intramuscular antes de ser hidrolizado a paliperidona y se absorbe en la circulación sistémica. Después de una dosis única por vía intramuscular, las concentraciones plasmáticas de paliperidona se elevan gradualmente hasta alcanzar las concentraciones plasmáticas máximas a una mediana de T_{max} de 13 días. La liberación de la sustancia activa se inicia desde el día 1 y tiene una duración de al menos 4 meses. Después de la inyección intramuscular de dosis únicas (de 25 mg a 150 mg) en el músculo deltoides, en promedio, se observó una C_{max} un 28% superior en comparación con la inyección en el músculo glúteo. Las dos inyecciones iniciales intramusculares en el deltoides de 150 mg el día 1 y 100 mg en el día 8 contribuyen a alcanzar concentraciones terapéuticas rápidamente. El perfil de liberación y el régimen de dosificación de Xeplion se traducen en concentraciones terapéuticas mantenidas. La exposición total de paliperidona tras la administración de Xeplion fue proporcional a la dosis en un rango de dosis de 25 mg a 150 mg, y menos que proporcional a la dosis en el caso de la C_{max} para dosis superiores a 50 mg. El promedio del pico en el estado estacionario: a través del ratio para una dosis de 100 mg de Xeplion fue de 1,8 después de la administración en el glúteo y de 2,2 después de la administración en el deltoides. La mediana de la vida media aparente de paliperidona tras la administración de Xeplion a lo largo del rango de dosis de 25 mg a 150 mg osciló entre 25 y 49 días. La biodisponibilidad absoluta del palmitato de paliperidona tras la administración de Xeplion es del 100%. Tras la administración de palmitato de paliperidona, los enantiómeros (+) y (-) de paliperidona se interconvierten, de modo que se alcanza un cociente de AUC (+) a (-) de aproximadamente 1,6-1,8. La unión a proteínas plasmáticas de paliperidona racémica es del 74%. Biotransformación y eliminación. Una semana después de la administración de una sola dosis oral de 1 mg de paliperidona de liberación inmediata marcada con C^{14}, el 59% de la dosis fue eliminado intacta por la orina, lo que indica que paliperidona no experimenta un intenso metabolismo por el hígado. Se recuperó aproximadamente el 80% de la radiactividad administrada en la orina y el 11% en las heces. Se han identificado cuatro vías metabólicas *in vivo*, ninguna de las cuales representó más del 6,5% de la dosis: desalquilación, hidroxilación, deshidrogenación y escisión de benzisoxazol. Aunque en estudios *in vitro* se señaló que las enzimas CYP2D6 y CYP3A4 pueden intervenir en el metabolismo de paliperidona, no hay datos *in vivo* que demuestren que estas isoenzimas desempeñen un papel significativo en el metabolismo de paliperidona. En los análisis de farmacocinética de la población no se observó ninguna diferencia apreciable del aclaramiento aparente de paliperidona tras la administración de paliperidona oral entre los metabolizadores rápidos y lentos de los sustratos de la CYP2D6. En estudios *in vitro* realizados con microsomas hepáticos humanos se demostró que la paliperidona no inhibe sustancialmente el metabolismo de los medicamentos metabolizados por las isoenzimas del citocromo P450, como CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 y CYP3A5. En estudios *in vitro* se ha demostrado que paliperidona es un sustrato de la P-gp y un inhibidor débil de la P-gp a altas concentraciones. No existen datos de estudios *in vivo* y se desconoce la importancia clínica. Inyección de palmitato de paliperidona de acción prolongada en comparación con paliperidona oral de liberación prolongada. Xeplion está diseñado para liberar paliperidona a lo largo de un período mensual, mientras que la paliperidona oral de liberación prolongada se administra a diario. El régimen de iniciación de Xeplion (150 mg/100 mg en el músculo deltoides en el día 1 /día 8) ha sido diseñado para alcanzar rápidamente las concentraciones de estado estacionario de paliperidona al iniciar el tratamiento sin necesidad de administrar suplementos orales. En términos generales, los niveles plasmáticos globales de iniciación con Xeplion se encontraron dentro del intervalo de exposición observado con entre 6 y 12 mg de paliperidona oral de liberación prolongada. El uso del régimen de iniciación de Xeplion permitió a los pacientes permanecer dentro de este margen de exposición de entre 6 y 12 mg de paliperidona oral de liberación prolongada incluso en los días de concentración mínima previos a la dosis (días 8 y 36). Debido a la diferencia en la mediana de los perfiles farmacocinéticos entre los dos medicamentos, se debe tener precaución al realizar una comparación directa de sus propiedades farmacocinéticas. Insuficiencia hepática. Paliperidona no se metaboliza ampliamente en el hígado. Aunque Xeplion no se ha estudiado en pacientes con insuficiencia hepática, no es preciso ajustar las dosis en los pacientes con insuficiencia hepática leve o moderada. En un estudio con paliperidona oral en pacientes con insuficiencia hepática moderada (Child-Pugh clase B), las concentraciones plasmáticas de paliperidona libre fueron similares a los de individuos sanos. Paliperidona no se ha estudiado en pacientes con insuficiencia hepática grave. Insuficiencia renal. La eliminación de una sola dosis de un comprimido de 3 mg de paliperidona de liberación prolongada se estudió en sujetos con diversos grados de función renal. La eliminación de la paliperidona disminuye si lo hace el aclaramiento de creatinina estimado. El aclaramiento total de la paliperidona disminuyó un promedio del 32% en sujetos con insuficiencia renal leve (CrCl=50 a <80 ml/min), un 64% en sujetos con insuficiencia renal moderada (CrCl=30 a <50 ml/min) y un 71% en sujetos con insuficiencia renal grave (CrCl =10 a <30 ml/min), lo que corresponde con un aumento promedio de la exposición (AUC_{ss}) de 1,5, 2,6 y 4,8 veces, respectivamente, en comparación con los sujetos sanos. Sobre la base del número limitado de observaciones con Xeplion en sujetos con insuficiencia renal leve y de los resultados de las simulaciones farmacocinéticas, se recomienda administrar una dosis reducida (ver sección 4.2). Población de edad avanzada. No se recomienda ajustar la dosis únicamente en función de la edad. Sin embargo, puede ser necesario realizar el ajuste de la dosis debido a las disminuciones en el aclaramiento de creatinina relacionadas con la edad (ver Insuficiencia renal más arriba y la sección 4.2). Peso. Los estudios farmacocinéticos con palmitato de paliperidona han demostrado unas concentraciones plasmáticas de paliperidona algo menores (entre el 10% y el 20%) en pacientes con sobrepeso u obesidad en comparación con los pacientes con un peso normal (ver sección 4.2). Raza. En el análisis farmacocinético de los datos de la población procedentes de los ensayos con paliperidona oral, no se observaron indicios de que existan diferencias relacionadas con la raza en la farmacocinética de la paliperidona tras la administración de Xeplion. Sexo. No se han observado diferencias clínicamente significativas entre hombres y mujeres. Tabaquismo. Según estudios *in vitro* realizados con enzimas hepáticas humanas, paliperidona no es sustrato de la CYP1A2; por lo tanto, el consumo de tabaco no debería afectar a la farmacocinética de paliperidona. Un análisis farmacocinético de la población basado en los datos obtenidos con comprimidos orales de paliperidona de liberación prolongada mostró una exposición ligeramente más baja a paliperidona en fumadores en comparación con los no fumadores. No obstante, se cree que es poco probable que la diferencia tenga relevancia clínica. No se evaluó el tabaquismo con Xeplion. **5.3. Datos preclínicos sobre seguridad.** Los estudios de toxicidad a dosis repetidas de palmitato de paliperidona inyectado por vía intramuscular y paliperidona administrada por vía oral en ratas y perros mostraron efectos principalmente farmacológicos, como sedación y efectos mediados por la prolactina, en las glándulas mamarias y en los genitales. En los animales tratados con palmitato de paliperidona, se observó una reacción inflamatoria en el lugar de la inyección intramuscular. Se produjo la formación ocasional de abscesos. En estudios sobre la reproducción de las ratas utilizando risperidona oral, que se convierte masivamente a paliperidona en ratas y en seres humanos, se observaron efectos adversos en el peso al nacer y de la supervivencia de las crías. No se observó embriotoxicidad ni malformaciones tras la administración intramuscular de palmitato de paliperidona a ratas preñadas a la dosis más alta (160 mg/kg/día), correspondiente a 4,1 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Otros antagonistas de la dopamina han tenido efectos negativos en el desarrollo motor y del aprendizaje en las crías cuando se administraron a animales preñados. Palmitato de paliperidona y paliperidona no fueron genotóxicos. En estudios sobre el poder carcinógeno de risperidona oral en ratas y ratones se observaron aumentos de los adenomas hipofisarios (ratón), de los adenomas del páncreas endocrino (rata) y de los adenomas de las glándulas mamarias (en ambas especies). Se evaluó el potencial carcinogénico de palmitato de paliperidona inyectado por vía intramuscular en ratas. Se constató un aumento estadísticamente significativo en los adenocarcinomas de las glándulas mamarias en las ratas hembras a dosis de 10, 30 y 60 mg/kg/mes. Las ratas macho mostraron un aumento estadísticamente significativo de los adenomas y carcinomas de las glándulas mamarias a las dosis de 30 y 60 mg/kg/mes, que equivalen a 1,2 y 2,2 veces el nivel de exposición en humanos a la dosis máxima recomendada de 150 mg. Estos tumores pueden estar relacionados con el antagonismo prolongado de la dopamina D2 y con la hiperprolactinemia. Se desconoce la trascendencia de estos hallazgos tumorales en roedores para el riesgo en seres humanos. **6. DATOS FARMACÉUTICOS. 6.1. Lista de excipientes.** Polisorbato 20. Polietilenglicol 4000. Ácido cítrico monohidrato. Fosfato ácido disódico anhidro. Fosfato diácido de sodio monohidratado. Hidróxido de sodio (para ajuste del pH). Agua para preparaciones inyectables. **6.2. Incompatibilidades.** Este medicamento no debe mezclarse con otros medicamentos. **6.3. Periodo de validez.** 2 años. **6.4. Precauciones especiales de conservación.** No conservar a temperatura superior a 30°C. **6.5. Naturaleza y contenido del envase.** Jeringa precargada (cíclico-olefina-copolímero) con un tapón de tipo émbolo, tope trasero y un protector para la punta (goma de bromobutilo) con una aguja de seguridad del calibre 22 de 1½ pulgadas (0,72 mm x 38,1 mm) y una aguja de seguridad del calibre 23 de 1 pulgada (0,64 mm x 25,4 mm). Tamaños de envase: El envase contiene 1 jeringa precargada y 2 agujas. **Presentaciones y precios.** Xeplion 50 mg suspensión inyectable de liberación prolongada: PVL: 180,64 €; PVP: 226,55 €; PVP (IVA): 235,61 €. Xeplion 75 mg suspensión inyectable de liberación prolongada: PVL: 234,82 €; PVP: 285,73 €; PVP (IVA): 297,16 €. Xeplion 100 mg suspensión inyectable de liberación prolongada: PVL: 289,04 €; PVP: 339,95 €; PVP (IVA): 353,55 €. Xeplion 150 mg suspensión inyectable de liberación prolongada: PVL: 433,56 €; PVP: 484,47 €; PVP (IVA): 503,85 €. **Condiciones de prescripción y dispensación.** Con receta médica. Aportación reducida. Con visado de inspección para pacientes mayores de 75 años. **6.6. Precauciones especiales de eliminación.** La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él, se realizará de acuerdo con la normativa local. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN.** Janssen-Cilag International NV. Turnhoutseweg 30. B-2340 Beerse. Bélgica. **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN.** Xeplion 50 mg: EU/1/11/672/002. Xeplion 75 mg: EU/1/11/672/003. Xeplion 100 mg: EU/1/11/672/004. Xeplion 150 mg: EU/1/11/672/005. **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN.** Fecha de la primera autorización: 04 de marzo de 2011. Fecha de la última revalidación: 22 de octubre de 2015. **10. FECHA DE LA REVISIÓN DEL TEXTO.** 12/2015. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu.

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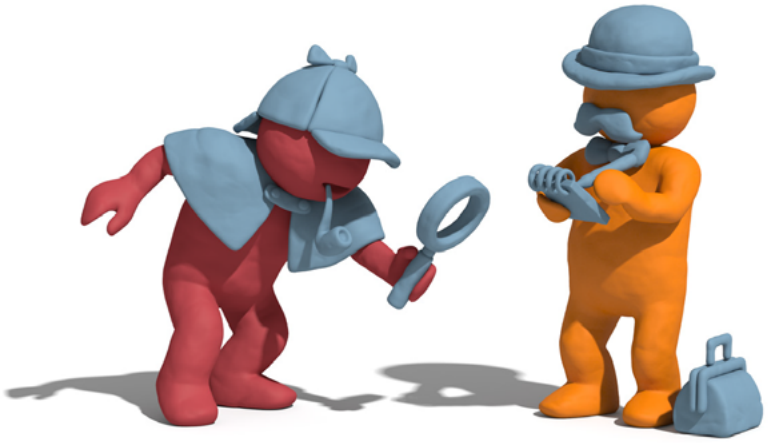

EFICACIA PARA SENTIRSE BIEN

FARMACOCINÉTICA[1, 2]

EFICACIA[1]

SIN SUPLEMENTACIÓN ORAL[3]

MONOTERAPIA[1, 4, 5]

TOLERABILIDAD CONTRASTADA[3, 7 *]

METABOLISMO HEPÁTICO LIMITADO[3]

CLARIDAD DE PENSAMIENTO[8]

FLEXIBILIDAD DE PAUTA POSOLÓGICA[3]

*Para más información sobre efectos adversos consultar apartado 4.8 de la Ficha Técnica

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PHARMACEUTICAL COMPANIES OF Johnson&Johnson

PHES/XEP/0315/0010(1) Abril 2016

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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.

Copyright y permisos. Los derechos de copyright de todos los artículos publicados en la revista Adicciones pasan a ser propiedad de la revista. La cesión de derechos será firmada por el autor o autores cuando envían su manuscrito para su consideración de publicación. Los autores se comprometen a acompañar el manuscrito de todos los permisos correspondientes para reproducir material previamente publicado que se va a incluir en el manuscrito, como texto, tablas, figuras, etc.

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Este medicamento está sujeto a seguimiento adicional, lo que agilizará la detección de nueva información sobre su seguridad. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas. Ver la sección 4.8, en la que se incluye información sobre cómo notificarlas. **1. NOMBRE DEL MEDICAMENTO** Selincro 18 mg comprimidos recubiertos con película. **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA** Cada comprimido recubierto con película contiene 18,06 mg de nalmefeno (como dihidrato de hidrocloruro). Excipiente con efecto conocido: cada comprimido recubierto con película contiene 60,68 mg de lactosa. Para consultar la lista completa de excipientes, ver sección 5.1. **3. FORMA FARMACÉUTICA** Comprimido recubierto con película (comprimido). Comprimido recubierto con película de color blanco, ovalado, biconvexo, de 6,0 x 8,75 mm y grabado con "S" en una cara. **4. DATOS CLÍNICOS 4.1 Indicaciones terapéuticas** Selincro está indicado para la reducción del consumo de alcohol en pacientes adultos con dependencia del alcohol que presentan un nivel de consumo de alcohol de alto riesgo (NCR), sin síntomas de abstinencia físicos y que no requieran una desintoxicación inmediata. Selincro solo se debe prescribir junto con apoyo psicosocial mantenido dirigido a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. El tratamiento con Selincro se debe iniciar únicamente en los pacientes que mantienen un NCR alto dos semanas después de la evaluación inicial. **4.2 Posología y forma de administración** Posología En la visita inicial, se deben evaluar el estado clínico, la dependencia del alcohol y el nivel de consumo de alcohol del paciente (según el paciente). Por lo tanto, se debe solicitar al paciente que registre su consumo de alcohol durante aproximadamente dos semanas. En la siguiente visita, se puede iniciar el tratamiento con Selincro en los pacientes que mantienen un NCR alto, durante este periodo de dos semanas, junto con una intervención psicosocial dirigida a incrementar la adherencia al tratamiento y a reducir el consumo de alcohol. Durante los ensayos clínicos pivotales la principal mejoría se observó durante las 4 primeras semanas. Se debe evaluar la respuesta del paciente al tratamiento y la necesidad de mantener farmacoterapia con regularidad (p. ej., mensualmente). El médico debe seguir evaluando la evolución del paciente en cuanto a la reducción del consumo de alcohol, el funcionamiento general, la adherencia al tratamiento y los posibles efectos adversos. Se dispone de datos clínicos para el uso de Selincro en condiciones controladas y aleatorizadas para un periodo de 6 a 12 meses. Se recomienda precaución al prescribir Selincro durante más de 1 año. Selincro se toma a demanda: cada día que el paciente perciba un riesgo anticipado de consumo de alcohol debe tomar un comprimido, preferiblemente 1-2 horas antes del momento de consumo. Si el paciente ha empezado a beber alcohol sin haber tomado Selincro, el paciente debería tomar un comprimido lo antes posible. La dosis máxima de Selincro es un comprimido al día. Selincro se puede tomar con o sin alimentos. *Poblaciones especiales* Población de edad avanzada (≥ 65 años de edad) No se recomienda el ajuste de la dosis para este grupo de pacientes (ver sección 4.4). Insuficiencia renal No se recomienda el ajuste de la dosis para los pacientes con insuficiencia renal leve o moderada (ver sección 4.4). Insuficiencia hepática No se recomienda el ajuste de la dosis para los pacientes con insuficiencia hepática leve o moderada (ver sección 4.4). Población pediátrica No se ha establecido la seguridad y eficacia de Selincro en niños y adolescentes de < 18 años. No se dispone de datos. Forma de administración Selincro es un medicamento que se administra por vía oral. El comprimido recubierto con película se debe tragar entero. El comprimido recubierto con película no se debe dividir ni aplastar porque el nalmefeno puede provocar sensibilización cutánea en contacto directo con la piel. **4.3 Contraindicaciones** Hipersensibilidad al principio activo o a alguno de los excipientes incluidos en la sección 5.1. Pacientes en tratamiento con agonistas opioides (como analgésicos opioides, opioides para terapia de sustitución con agonistas opioides (por ejemplo metadona) o agonistas parciales (por ejemplo buprenorfina)) (ver sección 4.4). Pacientes con una actual o reciente adicción a opiáceos. Pacientes con síntomas agudos de abstinencia de opiáceos. Pacientes con sospecha de uso reciente de opiáceos. Pacientes con insuficiencia hepática grave (clasificación de Child-Pugh). Pacientes con insuficiencia renal grave (eGFR < 30 ml/min por 1,73 m^2). Pacientes con historia reciente de síndrome de abstinencia del alcohol agudo (incluyendo alucinaciones, convulsiones y delirium tremens). **4.4 Advertencias y precauciones especiales de empleo** Selincro no está indicado en pacientes cuyo objetivo terapéutico sea la abstinencia inmediata. La reducción del consumo de alcohol es un objetivo intermedio en el camino hacia la abstinencia. Administración de opiáceos En una situación de urgencia en la que se deban administrar opiáceos a un paciente que toma Selincro, la cantidad de opiáceo requerida para lograr el efecto deseado puede ser superior a la habitual. El paciente se debe someter a un estricto control para detectar síntomas de depresión respiratoria como consecuencia de la administración de opiáceos, así como otras reacciones adversas. Si se precisan opiáceos en una urgencia, la dosis siempre se debe ajustar de forma individual. Si se requieren dosis excepcionalmente altas, será necesaria una estrecha observación. El tratamiento con Selincro se debe interrumpir temporalmente 1 semana antes del uso previsto de opiáceos (p. ej., cuando se vayan a utilizar analgésicos opioides en una intervención quirúrgica programada). El médico prescriptor deberá advertir a los pacientes de la importancia de informar a su médico de la última toma de Selincro en caso de que sea necesario el uso de opiáceos. Se debe tener precaución cuando se utilicen medicamentos que contengan opiáceos (p. ej., antitusígenos, analgésicos opioides (ver sección 4.5)). Comorbilidad Trastornos psiquiátricos Se han registrado efectos psiquiátricos en estudios clínicos (ver sección 4.8). Si los pacientes presentan síntomas psiquiátricos no asociados al inicio del tratamiento con Selincro, y/o que no son transitorios, el médico prescriptor deberá considerar otras causas de los síntomas y valorar la necesidad de continuar el tratamiento con Selincro. Selincro no se ha investigado en pacientes con enfermedad psiquiátrica inestable. Se debe proceder con precaución al prescribir Selincro a pacientes con comorbilidad psiquiátrica presente como el trastorno depresivo mayor. Trastornos convulsivos Se dispone de experiencia limitada en pacientes con antecedentes de trastornos convulsivos, incluidas las convulsiones por abstinencia de alcohol. Se recomienda precaución si se inicia un tratamiento para reducir el consumo de alcohol en estos pacientes. Insuficiencia renal o hepática Selincro se metaboliza principalmente en el hígado y se elimina predominantemente por la orina. Por lo tanto, se debe tener precaución cuando se prescriba Selincro a pacientes con insuficiencia renal o hepática leve o moderada, por ejemplo, realizando controles más frecuentes. Se debe proceder con precaución al prescribir Selincro a pacientes con valores altos de ALAT o ASAT (> 3 veces el LSN), ya que estos pacientes fueron excluidos del programa de desarrollo clínico. Pacientes de edad avanzada (≥ 65 años de edad) Se dispone de datos clínicos limitados sobre el uso de Selincro en pacientes ≥ 65 años de edad con dependencia del alcohol. Sea debe tener precaución al prescribir Selincro a pacientes ≥ 65 años de edad (ver sección 4.2). Otras Se recomienda precaución si Selincro se administra conjuntamente con un inhibidor potente de la enzima UGT2B7 (ver sección 4.5). Lactosa Los pacientes con intolerancia hereditaria a galactosa, insuficiencia de lactasa de Lapp o problemas de malabsorción de glucosa o galactosa no deben tomar este medicamento. **4.5 Interacción con otros medicamentos y otras formas de interacción** No se han llevado a cabo estudios de interacción farmacológica *in vivo*. Según estudios *in vitro*, no se prevén interacciones clínicamente relevantes entre el nalmefeno, o sus metabolitos, y medicamentos administrados simultáneamente metabolizados por las enzimas más comunes CYP450 y UGT o transportadores de membrana. La administración conjunta con medicamentos que sean inhibidores potentes de la enzima UGT2B7 (p. ej., diclofenaco, fluconazol, acetato de medroxiprogesterona, ácido meclofenámico) puede aumentar significativamente la exposición a nalmefeno. Es improbable que esto suponga un problema con el uso ocasional, pero si se inicia un tratamiento a largo plazo simultáneo con un inhibidor potente de la UGT2B7, no se puede descartar la posibilidad de un aumento en la exposición a nalmefeno (ver sección 4.4). Por el contrario, la administración conjunta con un inductor de la UGT (p. ej., dexametasona, fenobarbital, rifampicina, omeprazol) puede dar lugar a concentraciones plasmáticas subterapéuticas de nalmefeno. Si se toma Selincro de manera simultánea con agonistas opioides (p. ej., algunos tipos de antitusígenos y antigripales, determinados antidiarreicos, y analgésicos opioides), puede que el paciente no se beneficie del agonista opioide. No existe ninguna interacción farmacocinética clínicamente relevante entre el nalmefeno y el alcohol. Se produce un pequeño deterioro en la función cognitiva y psicomotora tras la administración de nalmefeno. No obstante, el efecto de la combinación de nalmefeno y alcohol no superó la suma de los efectos de cada uno de ellos por separado. El consumo simultáneo de alcohol y Selincro no previene los efectos de la intoxicación del alcohol. **4.6 Fertilidad, embarazo y lactancia** Embarazo No hay datos o estos son limitados (menos de 300 resultados en embarazos) relativos al uso de nalmefeno en mujeres embarazadas. Los estudios en animales han mostrado toxicidad en la reproducción. No se recomienda Selincro durante el embarazo. Lactancia Los datos farmacodinámicos/toxicológicos disponibles en animales muestran que nalmefeno/metabolitos se excretan en la leche. Se desconoce si nalmefeno se excreta en la leche materna. No se puede excluir el riesgo en recién nacidos/lactantes. Se debe decidir si es necesario interrumpir la lactancia o interrumpir/abstenerse de iniciar el tratamiento con Selincro tras considerar el beneficio de la lactancia para el niño y el beneficio del tratamiento para la madre. Fertilidad En estudios de fertilidad en ratas, no se observaron efectos de nalmefeno sobre la fertilidad, el apareamiento, el embarazo o los parámetros espermáticos. **4.7 Efectos sobre la capacidad para conducir y utilizar máquinas** No se ha estudiado la influencia de nalmefeno sobre la capacidad para conducir y utilizar máquinas. Selincro puede provocar reacciones adversas como náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, relacionadas con el inicio del tratamiento y tuvieron una corta duración. La influencia de Selincro sobre la capacidad para conducir y utilizar máquinas es nula o insignificante. **4.8 Reacciones adversas** Resumen del perfil de seguridad Más de 3.000 pacientes han sido expuestos a nalmefeno en estudios clínicos. En general, el perfil de seguridad concuerda en todos los estudios clínicos realizados. Las frecuencias de las reacciones adversas en la Tabla 1 se calcularon basándose en tres estudios aleatorizados, a doble ciego y controlados con placebo en pacientes con dependencia del alcohol (1.144 pacientes expuestos a Selincro a demanda y 797 expuestos a placebo a demanda). Las reacciones adversas más frecuentes fueron náuseas, mareo, insomnio y cefalea. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración. En los estudios clínicos se comunicaron estados confusionales y, en raras ocasiones, alucinaciones y disociación. La mayoría de estas reacciones fueron leves o moderadas, estuvieron relacionadas con el inicio del tratamiento y tuvieron una corta duración (de unas pocas horas a unos pocos días). La mayoría de estas reacciones adversas se resolvieron con el tratamiento continuo y no recurrieron con la administración repetida. Si bien estos acontecimientos tuvieron generalmente una corta duración, podrían tratarse de psicosis alcohólica, síndrome de abstinencia alcohólica o enfermedad psiquiátrica comórbida. Tabla de reacciones adversas Las frecuencias se definen como: muy frecuentes (≥1/10), frecuentes (≥1/100 a <1/10), poco frecuentes (≥1/1.000 a <1/100), raras (≥1/10.000 a <1/1.000), muy raras (<1/10.000) o frecuencia no conocida (no puede estimarse a partir de los datos disponibles). Notificación de sospechas de reacciones adversas Es importante notificar sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del sistema Español de Farmacovigilancia de medicamentos de Uso Humano: https://www.notificaram.es. **4.9 Sobredosis** En un estudio en pacientes diagnosticados de ludopatía, se investigaron dosis de nalmefeno de hasta 90 mg/día durante 16 semanas. En un estudio en pacientes con cistitis intersticial, 20 pacientes recibieron 108 mg/día de nalmefeno durante más de 2 años. Se ha registrado la toma de una dosis única de 450 mg de nalmefeno sin cambios en la tensión arterial, la frecuencia cardiaca y respiratoria o la temperatura corporal. No se ha observado un patrón atípico de reacciones adversas en estos contextos, si bien la experiencia es limitada. En caso de sobredosis, se recomienda realizar un tratamiento sintomático y someter al paciente a observación. **5. DATOS FARMACÉUTICOS 5.1 Lista de excipientes** Núcleo del comprimido Celulosa microcristalina Lactosa anhidra Crospovidona, tipo A Estearato de magnesio Recubrimiento del comprimido Hipromelosa Macrogol 400 Dióxido de titanio (E171) **5.2 Incompatibilidades** No procede. **5.3 Periodo de validez** 3 años. **5.4 Precauciones especiales de conservación** Este medicamento no requiere condiciones especiales de conservación. **5.5 Naturaleza y contenido del envase** Blísters transparentes de PVC/PVdC/aluminio en cajas de cartón. Tamaños de envases de 7, 14, 28, 42, 49 y 98 comprimidos recubiertos con película. Puede que solamente estén comercializados algunos tamaños de envases. 5.6 Precauciones especiales de eliminación La eliminación del medicamento no utilizado y de todos los materiales que hayan estado en contacto con él se realizará de acuerdo con la normativa local. **6. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN** H. Lundbeck A/S Ottiliavej 9 DK-2500 Valby Dinamarca **7. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN** EU/1/12/815/001 7 comprimidos. EU/1/12/815/002 14 comprimidos. EU/1/12/815/003 28 comprimidos. EU/1/12/815/004 42 comprimidos. EU/1/12/815/005 98 comprimidos. EU/1/12/815/006 49 comprimidos. EU/1/12/815/007 14 comprimidos, tarjeta. EU/1/12/815/008 28 comprimidos, tarjeta. **8. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN** Fecha de la primera autorización: 25 de Febrero de 2013. **9. PRESENTACIÓN Y PRECIO PVP (IVA)** Selincro 18 mg, envase con 14 comprimidos. P.V.P 63,04 € P.V.P iva 65,57 €. **10. CONDICIONES DE DISPENSACIÓN POR LA SEGURIDAD SOCIAL** Con receta médica. Especialidad reembolsable por el Sistema Nacional de Salud. Con visado de inspección. Cícero de aportación reducida. **11. FECHA DE LA REVISIÓN DEL TEXTO:** Mayo 2015. La información detallada de este medicamento está disponible en la página web de la Agencia Europea de Medicamentos http://www.ema.europa.eu/.

Tabla 1: Frecuencias de las reacciones adversas

Sistema de clasificación de órganos	*Frecuencia*	*Reacción adversa*
Trastornos del metabolismo y de la nutrición	Frecuente	Apetito disminuido
Trastornos psiquiátricos	Muy frecuente	Insomnio
	Frecuente	Trastorno del sueño
		Estado confusional
		Inquietud
		Libido disminuida (incluida la pérdida de libido)
	No conocida	Alucinación (incluidas alucinaciones auditivas, alucinaciones táctiles, alucinaciones visuales y alucinaciones somáticas)
		Disociación
Trastornos del sistema nervioso	Muy frecuente	Mareo
		Cefalea
	Frecuente	Somnolencia
		Temblor
		Alteración de la atención
		Parestesia
		Hipoestesia
Trastornos cardiacos	Frecuente	Taquicardia
		Palpitaciones
Muy frecuente	Muy frecuente	Náuseas
	Frecuente	Vómitos
		Boca seca
Trastornos de la piel y del tejido subcutáneo	Frecuente	Hiperhidrosis
Trastornos musculoesqueléticos y del tejido conjuntivo	Frecuente	Espasmos musculares
Trastornos generales y alteraciones en el lugar de administración	Frecuente	Fatiga
		Astenia
		Malestar general
		Sensación anormal
Exploraciones complementarias	Frecuente	Peso disminuido

1. Ficha Técnica de Selincro®. Lundbeck España SA. En: http://www.emea.europa.eu/ema. **2.** François C, et al. PLoS One. 2015 Jun 8;10(6):e0129289.

*Rasca la zona plateada para descubrir el caso de **Álex**.*

Álex, 43 años.

Se siente cansado con facilidad y sufre fuertes resacas. Aumentó su consumo de alcohol debido a su alto grado de responsabilidad y estrés en el trabajo como consecuencia de la presión por incrementar los ingresos familiares tras el nacimiento de su hijo. El alcohol se ha convertido en su vía de escape de la realidad del día a día.

Empieza a beber desde que se levanta, ingiriendo un promedio de 5 cervezas diarias o más entre semana y a menudo una caja el fin de semana.

¿Qué haría en su lugar?

*Caso fictício.

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