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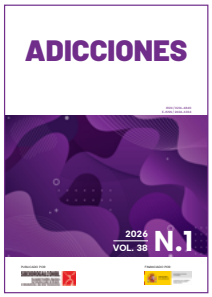
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EDITORIAL

Language and social perception of cannabis: A debate on narrative constructions and their impact on Public Health

Lenguaje y percepción social del cannabis: Un debate sobre construcciones narrativas y su impacto en la Salud Pública

Víctor José Villanueva-Blasco*,**; Mercè Balcells-Olivero***,****; Clara Oliveras***,****; Manuel Isorna Folgar**,*****.

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Words do not merely describe reality; they also shape attitudes and behaviors. In the case of cannabis, media and social debate has become framed within an apparently simple dichotomy between "recreational cannabis" and "medical cannabis." This terminological limitation can bias risk perception regarding the use of this substance. The adjective "recreational" suggests harmlessness and leisure, whereas the adjective "medical" suggests benefit and safety. From a public health perspective, the use of these terms is not trivial, because the way a substance and its uses are named can normalize them, shift the focus away from the determinants of harm (frequency, quantity, potency, age of initiation) toward people's subjective interpretations, and hinder clear preventive messages (Sanchez et al., 2023).

Moreover, in several countries where legal markets have opened, cannabis has become part of an economy with commercial interests capable of influencing messages, research, and policies. This phenomenon is better understood within the framework of the commercial determinants of health: marketing strategies, product design, lobbying, or the funding of evidence, all oriented toward industry profit and potentially increasing population exposure to cannabis and the harms associated with its use (Kickbusch et al., 2016). Experience with this type of industry suggests that, as the market grows, so do the incentives to normalize the product and expand the consumer base (Adams et al., 2021; Young-Wolff et al., 2022). In this context, rebranding strategies have been described that seek to present cannabis as a "natural" product associated with self-care or wellness, as well as influence dynamics that may shift the agenda from public health toward market expansion (Isorna & Villanueva-Blasco, 2022). In parallel, the circulation of ambiguous information (post-truths, oversimplifications, and "fake news") may erode health literacy and hinder informed social debate about risks, benefits, and regulation (Isorna-Folgar et al., 2023; López-Pelayo et al., 2018).

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Importance of language in the use of the concept of risk in cannabis use

The body of scientific evidence converges on one central idea: cannabis is not a harmless substance, and the risk associated with its use increases when the amounts of psychoactive substance consumed increase, use becomes more frequent, initiation occurs earlier, or products with higher THC potency are used (Campeny et al., 2020; Hoch et al., 2024). In adolescent populations, the evidence links cannabis use to poorer cognitive and educational performance, especially in intensive and sustained patterns of use (Lorenzetti et al., 2020). An association has also been described between the use of high-potency cannabis and a greater risk of psychotic disorders, particularly in vulnerable individuals (Di Forti et al., 2019; Volkow et al., 2016).

That said, it is important to clarify that there is no universally accepted "safe dose" of cannabis within the scientific community (Fischer et al., 2022; Oliveras et al., 2024; Solmi et al., 2023). In practice, accurately estimating how much THC is consumed is difficult because cannabis products are not homogeneous: potency (THC percentage), form of presentation (flower, resins, concentrates, edibles, extracts), route of administration (smoked, vaporized, oral), and, consequently, the amount actually absorbed and the effects all vary (Casajuana Kogel et al., 2018). This heterogeneity is compounded by the absence of a widely implemented standard unit that would allow THC exposure to be quantified comparably across product types and contexts of use (Casajuana et al., 2016; Freeman & Lorenzetti, 2020; López-Pelayo et al., 2021). Precisely for this reason, defining "risky cannabis use" remains a work in progress that requires consensus (Balcells-Oliveró & Oliveras, 2023).

In Spain, a Delphi consensus has proposed (while acknowledging that there is no risk-free pattern of cannabis use) an operational definition of "high-risk cannabis use" and underscores its necessarily provisional and revisable nature as evidence advances. In summary, risk indicators include the use of more than 28 mg of THC (around 4 joints) per week, the use of high-potency products (>10% THC), combined use with alcohol or other substances, and use in vulnerable situations or profiles, including initiation at early ages (before age 21) (Oliveras et al., 2024).

In this context, speaking of a "safe dose" may reinforce the idea that, below a supposed threshold, use would be harmless. This oversimplification is encouraged by rebranding narratives and misleading messages that present cannabis as a "natural" product, one that promotes well-being, or one that entails trivial risks, thereby contributing to reduced risk perception and shifting attention away from the real determinants of harm (potency, quantity, frequency, age of initiation, polysubstance use, and individual vulnerabilities) (Isorna-Folgar et al., 2023; Isorna & Villanueva-Blasco, 2022; López-Pelayo et al., 2018). Therefore, language should avoid being framed in terms of safety and should instead help identify higher-risk patterns and communicate clearly that "lower exposure" does not equal "zero risk," especially in adolescents and in people with vulnerability factors (Balcells-Oliveró & Oliveras, 2023; Casajuana et al., 2016).

In this regard, three terminological adjustments are proposed:

1. **Stop using the terminology "recreational cannabis" and use "non-medical use" instead.** Referring to non-therapeutic use as "recreational" introduces a leisure-related connotation that does not always reflect reality. Beyond leisure motives, many users report using cannabis to cope with negative emotions, to sleep, or as an established habit, and these motivations are associated with a higher likelihood of problematic use (Casajuana-Kögel et al., 2021). Likewise, the term "recreational" does not convey the determinants of risk (frequency, quantity, potency, age of initiation, polysubstance use, route of administration). For this reason, it is preferable to refer to "non-medical cannabis use" or "cannabis use for psychoactive purposes," which are more descriptive and neutral terms and allow the key element—the risk level of the pattern of use—to be incorporated into prevention and clinical approaches (Sanchez et al., 2023).
2. **Stop using the term "low risk" and use "lower risk" instead.** At present, when referring to cannabis use, we believe the most honest approach is to speak of "high risk" and "lower risk," the latter in a harm-reduction framework. In comparison with alcohol, for this legal substance there are consensuses on indicative low-risk thresholds, with the warning that zero risk does not exist (Córdoba-García et al., 2021; Ministerio de Sanidad, 2020). In cannabis, directly transferring that model is premature due to THC variability and the lack of dose standardization (Freeman & Lorenzetti, 2020; López-Pelayo et al., 2021), in addition to territorial variability in the legal and regulatory status of cannabis (Observatorio Español de las Drogas y las Adicciones (OEDA); Delegación del Gobierno para el Plan Nacional sobre Drogas (DGPNSD), 2026). As a precaution, it is more useful to prioritize the identification of high-risk patterns and, in parallel, offer harm-reduction recommendations—that is, "lower-risk" recommendations—eliminating the use of terms such as "low risk" or "safe use." In this line, Canada's Lower-Risk Cannabis Use Guidelines propose evidence-based recommendations to reduce harms in non-medical use (Fischer et al., 2022).
3. **From "medical cannabis" to "cannabis medicines" and "prescribed cannabinoids."** In colloquial language, the term "medical cannabis"

is used for very different realities, ranging from standardized pharmaceuticals to the use of flower or artisanal extracts with therapeutic intent. This ambiguity may increase the perception of safety and encourage self-medication. Evidence supports benefits in specific indications for certain cannabinoids or standardized preparations, whereas for many popular uses the evidence is insufficient or still preliminary (Hoch et al., 2024; Solmi et al., 2023). In addition, cannabis is not a homogeneous product; it contains multiple cannabinoids and other compounds, with potentially different effect profiles (Casajuana Kogel et al., 2018). Therefore, it is proposed to differentiate between: (a) "cannabis medicines" or "cannabinoid-based medicines," for standardized products evaluated for specific indications (Sordo & Gual, 2022); and (b) "prescribed cannabinoids," when there is an indication, dosage, follow-up, and pharmacovigilance, avoiding equating prescription with unregulated use (Bueno et al., 2024). This proposal is consistent with epidemiological surveillance, as conducted in drug surveys, in which prescribed and non-prescribed use of hypnotic-sedatives is distinguished, thereby facilitating risk interpretation and intervention planning (OEDA, 2025).

A call for scientific, political, and social consensus

An effective change in the social perception of cannabis—and, by extension, in the way it is used and its different uses are regulated—depends on a collaborative and sustained approach involving public health, the education system, the media, researchers, addiction professionals, and policymakers. Scientific evidence should guide the direction of the debate, but the way that evidence is translated into the public sphere is equally decisive. When language is oversimplified, introduces connotations of safety, or shifts attention toward subjective intent, cognitive biases are reinforced and health literacy is weakened (Sanchez et al., 2023), health literacy being people's ability to access, understand, evaluate, and communicate information about their health (Higgins et al., 2009).

This consensus must explicitly include the media. Their role is not limited to merely 'informing,' as their actions also help shape the public's interpretive frameworks regarding social issues. Their involvement is therefore essential to prevent language from functioning as a shortcut that downplays risks ("recreational") (Campeny et al., 2020; Hoch et al., 2024), magnifies limited evidence ("medical") (Solmi et al., 2023), or facilitates the instrumental use of narratives by industry and political agendas not aligned with public health (Isorna & Villanueva-Blasco, 2022; Kickbusch et al., 2016; López-Pelayo et al., 2018).

Accordingly, if the goal is to improve health literacy and reduce the inappropriate use of cannabis-related terminology, four simple recommendations are proposed:

1. Replace "recreational" with "non-medical use" and describe, where appropriate, a "high-risk pattern of use."
2. Reserve "cannabis medicines" or "prescribed cannabinoids" for standardized products used under supervision and refer to other uses as "unregulated therapeutic use."
3. Incorporate risk-determining variables whenever possible, such as quantity of psychoactive substance, frequency, THC potency, and route of administration, while acknowledging that dose standardization remains an unresolved challenge (Casajuana et al., 2016; Freeman & Lorenzetti, 2020; López-Pelayo et al., 2021).
4. Maintain an approach sensitive to the regulatory context. Many measures (advertising, labeling, access) are specific to regulated markets. However, in settings without a legal market, as is the case in Spain (Observatorio Español de las Drogas y las Adicciones (OEDA); Delegación del Gobierno para el Plan Nacional sobre Drogas (DGPNSD, 2026), the priority is evidence-based prevention, harm reduction, and epidemiological surveillance.

In this way, terminological consensus is not a minor semantic debate: it is a public health tool. Precise language reduces misinformation, improves the detection of high-risk cannabis use, and enables the development of clearer and more effective preventive messages.

Conflicts of interest

M.B.O. has received travel grants from Lundbeck and Camurus, and honoraria related to continuing medical education (CME) from Novo Nordisk, all outside the scope of this article. C.O. has received travel grants from Lundbeck, outside the scope of this text.

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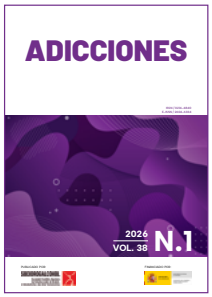
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ORIGINAL

Receptivity to persuasive narratives in juvenile offenders who use cannabis: Influence of motivational variables and engagement

Receptividad a narrativas persuasivas en menores con infracciones que consumen cannabis: Influencia de variables motivacionales y engagement

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Abstract

Persuasive narratives have been shown to be effective in influencing health behaviors. However, their impact on at-risk populations, such as justice-involved juveniles who use cannabis, has received limited attention. This study analyzes the response of 93 juveniles serving court-ordered sentences in detention centers to persuasive video-based narratives. These narratives were developed in accordance with the Health Action Process Approach (HAPA) and were gender-adapted. Additionally, variables influencing receptivity to the persuasive message, assessed in terms of favorability, were examined. Prior to exposure to the narrative, motivational variables such as risk perception, outcome expectancies (both positive and negative) of cannabis non-use, and self-efficacy for action were measured. Following the viewing, generated thoughts (cognitive responses) and engagement with the narrative, focusing on identification with the protagonist and narrative transportation, were assessed. The results revealed that the thoughts generated focused on the message content and personal experiences, with favorable thoughts predominating. No significant sex differences were observed, although the analyses did not allow conclusions to be drawn on equivalence between groups. Furthermore, narrative transportation acted as a significant mediator between risk perception and message favorability. This study provides empirical evidence on the effect of persuasive narratives in this population, indicating that their design, based on health behavior change theories, enhances receptivity. The findings support their integration into prevention programs within the context of juvenile justice.
Keywords: persuasion, audiovisual narrative, motivation, engagement, juvenile offenders, cannabis use, prevention

Resumen

Las narrativas persuasivas han demostrado ser efectivas para influir en los comportamientos de salud. Sin embargo, su impacto en poblaciones en riesgo, como menores en conflicto con la ley que consumen cannabis, ha sido poco explorado. Este estudio analiza la respuesta de 93 menores que cumplen medidas judiciales en centros de internamiento ante narrativas persuasivas en formato video. Estas narrativas se elaboraron conforme al modelo del Proceso de Acción en Salud (*Health Action Process Approach*, HAPA) y adaptadas por género. Asimismo, se investigaron las variables que influyen en la receptividad al mensaje persuasivo, evaluada en términos de favorabilidad. Antes de la exposición a la narrativa, se midieron variables motivacionales como percepción del riesgo, expectativas (positivas y negativas) de resultados del no consumo de cannabis y autoeficacia para la acción. Tras la visualización, se analizaron los pensamientos generados (respuestas cognitivas) y el *engagement* narrativo, a través de la identificación con el/la protagonista y el transporte narrativo. Los resultados revelaron que los pensamientos se centraron en contenido del mensaje y en experiencias personales, predominando aquellos de carácter de favorable. No se observaron diferencias significativas por sexo, si bien los análisis no permiten concluir equivalencia entre grupos. Además, el transporte narrativo actuó como mediador significativo entre la percepción del riesgo y la favorabilidad. Este estudio aporta evidencia empírica sobre el efecto de las narrativas persuasivas en esta población, demostrando que su diseño, basado en teorías de cambio de conducta de salud, favorece la receptividad. Los hallazgos respaldan su integración en programas de prevención en el contexto de la justicia juvenil.
Palabras clave: persuasión, narrativa audiovisual, motivación, engagement, menores con infracciones, consumo de cannabis, prevención

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Within the field of health communication, the use of narrative messages to promote healthy behaviours and reduce risk has become established as an effective strategy (de Graaf et al., 2016; Hinyard & Kreuter, 2007; Igartua et al., 2021; Miller-Day & Hecht, 2013; Perrier & Martin-Ginis, 2018; Petraglia, 2009). Various studies indicate that these narratives have the capacity to influence beliefs, attitudes, intentions, and behaviours (Braddock & Dillard, 2016; de Graaf et al., 2016; Perrier & Martin-Ginis, 2018), making them a promising tool in addiction prevention (Herrera-Sánchez et al., 2019; Miller-Day & Hecht, 2013).

However, the application of these strategies in at-risk youth populations, such as minors who have committed offences (hereafter MO), has not been explored. Adolescents in the juvenile justice system show high rates of psychiatric comorbidity, trauma exposure, and substance use (Chassin et al., 2016; Feldstein & Ginsburg, 2006). Within this group, cannabis stands out as one of the most commonly used illegal substances, characterised by earlier initiation and more problematic patterns of use compared with minors without a history of problems with the law (Tolou-Shams et al., 2021a). These factors not only increase their vulnerability but may also reduce the effectiveness of interventions targeted at this population (Kemp et al., 2023). In this regard, it is essential to examine how this population responds to persuasive messages in a context where psychoactive substance use is highly prevalent.

This study aims to contribute to the understanding of persuasive communication in the prevention of cannabis use, specifically targeting MO as an at-risk population. To this end, the effects of a narrative audiovisual intervention are designed and examined, based on a theoretical model that integrates the processes associated with narrative persuasion within the framework of narrative engagement and the motivational variables that drive behaviour change.

Narrative persuasion, resistance, and engagement

Narrative persuasion is a form of communication that conveys messages through structured stories, aiming to influence audiences and generate changes in attitudes and behaviours. Unlike more direct approaches, such as expository discourse that presents data and logical arguments, persuasive content is embedded within a story in which characters are portrayed with clear intentions to achieve goals (Igartua et al., 2021) and engage in events within a dynamic setting shaped by conflict, transformation, and resolution (Braddock & Dillard, 2016). These events may be presented non-chronologically; however, the underlying structure follows patterns of cause and effect or action and reaction, linking situations and characters into a coherent narrative (de Graaf et al., 2016). These elements give narratives their distinctiveness and facilitate the audience's ability to infer more complex relationships between events (Bilandzic & Busselle, 2013).

The immediate impact of a persuasive message is related to information processing, that is, the ability to critically analyse the implicit persuasive content. This process of scrutiny or detailed analysis of the message is known as elaboration (Petty & Cacioppo, 1986). Bilandzic and Busselle (2013) conceptualise elaboration, within the narrative context, in a broader way, as reflection on the topic without necessarily evaluating argument quality. From this perspective, elaboration encompasses both the persuasive message content and the plot and characters. In this study, two key processes linked to message elaboration are addressed: resistance to persuasion and narrative engagement.

Resistance to persuasion is the phenomenon whereby individuals question or refute the messages they receive, thereby opposing attitude change (Bilandzic & Busselle, 2013). Attitudes refer to the favourable or unfavourable evaluation a person holds toward an object, person, or idea, which in turn influences behaviour. This resistance can take various forms. Petty et al. (2004) describe it across four dimensions: (1) as an outcome, that is, the absence of attitude change following persuasion, which may involve no change or change in a direction opposite to the persuasive content; (2) as motivation, implying the desire to avoid modifying one's attitude, which may or may not lead to a resistant outcome; (3) as a process, referring to the specific cognitive and behavioural mechanisms used to resist the message, including counterarguing; and (4) as a quality, whereby resistance is not an action in itself but an inherent characteristic of individuals' prior attitudes that makes them difficult to modify, for example, the more certain a person is about their attitude, the more resistant they are to change.

This study adopts the perspective of Ratcliff and Sun (2020), which places resistance within the cognitive domain. According to these authors, resistance is a motivated response triggered by the perception of an attempt at influence, manifested with the aim of disregarding the persuasive intention and/or content. From this perspective, it is considered an immediate process that occurs during message processing and may precede or influence subsequent changes in attitude or behaviour.

Accordingly, a critical component is cognitive resistance, which is expressed through the generation of counterarguments, that is, thoughts that oppose the persuasive position of the received message, thereby reducing the audience's willingness to accept the arguments presented. In this study, cognitive resistance is assessed using the polarity index derived from the thought-listing technique (Igartua, 1998). This indicator makes it possible to quantify the orientation of cognitive responses to the

persuasive message, reflecting greater resistance when unfavourable thoughts predominate, or greater receptivity or openness when favourable thoughts prevail.

Within research on narrative persuasion, processes have been identified that help reduce this questioning of the message and enhance its receptivity. Among these, identification with the story's protagonist and narrative transportation stand out (Green & Brock, 2000; Moyer-Gusé, 2008; Moyer-Gusé & Nabi, 2010; Perrier & Martin-Ginis, 2018; Slater & Rouner, 2002). Both processes form part of the broader concept of narrative engagement, understood as audience involvement with both the plot and its characters, and encompassing perceived similarity, empathy, and immersion in the story (Kim et al., 2012).

Identification with a c haracter refers to perceived similarity (cognitive) and empathic responses (emotional) toward a character in the narrative, typically the story's protagonist. It indicates that the viewer adopts the character's feelings, perspectives, and goals (Cohen, 2001). When this occurs, the character's attitudes and beliefs are more likely to be adopted, which may increase receptivity to the persuasive message.

On the other hand, narrative transportation refers to deep immersion in the plot, involving a temporary detachment from the real world and a stronger focus on the story (Green & Brock, 2000). This experience engages the audience cognitively, affectively, and visually, which may produce a temporary disconnection from one's own beliefs and prior knowledge. This process can affect how the persuasive narrative is processed and responded to. By fostering greater immersion, critical processing of the message is reduced, thereby decreasing resistance (Green & Brock, 2000; Moyer-Gusé & Nabi, 2010; Slater & Rouner, 2002).

The role of familiarity and gender in narrative persuasion

Adolescent audiences, like other groups exposed to persuasive strategies, process messages in accordance with their values, beliefs, norms, and attitudes. Meta-analytic evidence has shown that persuasive narratives can produce significant changes (Braddock & Dillard, 2016), particularly when the audience perceives the content as relevant to their context. In this regard, familiarity with the content and characters may enhance effectiveness (de Graaf et al., 2016). When narrative content is perceived as close and recognisable, adolescent audiences are more likely to view the actions and decisions taken by the protagonist as applicable to their own lives.

Familiarity can be assessed by considering the similarity between the character and the audience, whether in terms of demographic or psychological characteristics (Igartua et al., 2021) or prior experiences related to the plot (Bilandzic & Busselle, 2013). Greater gender congruence between protagonist and audience has been proposed to facilitate identification and absorption. Likewise, the alignment of prior experiences strengthens the persuasive effect. However, the scientific evidence is inconclusive, highlighting the need for further research in this field (de Graaf et al., 2016).

Meta-analytic studies have found that the relationship between narrative engagement and resistance tends to be stronger in samples with a higher proportion of women (Ratcliff & Sun, 2020), which may suggest that certain narrative content aligns more closely with this population. However, this difference may be attenuated when there is gender similarity between the narrative protagonist and the audience (de Graaf et al., 2016; Igartua et al., 2021). In this study, narratives were designed so that the protagonist's gender matched that of the MO population, ensuring that the narrative content and context realistically reflected their experiences, language, and social environment. This strategy aims to maximise receptivity and reduce potential gender-related differences and is proposed as an exploratory hypothesis in a population for which no prior studies exist.

The role of motivational factors in narrative persuasion

A key component in high-risk groups is motivation, as it may promote or interfere with the cessation of health-compromising behaviours. Theories grounded in sociocognitive models identify risk perception (the subjective evaluation of the potential harm associated with specific behaviours), outcome expectancies (positive or negative contingencies between behaviour and its consequences), and self-efficacy (confidence in performing an action) as antecedent variables of change (Bandura, 2001; Schwarzer, 2008). Recent evidence indicates that these three factors are consistently associated with the intention to modify health-related behaviours. Higher risk perception has been linked to a lower likelihood of engaging in unhealthy behaviours, whereas positive expectancies toward such behaviours tend to increase their likelihood of adoption. Self-efficacy, in turn, has been shown to be one of the most robust predictors of change intention, as confirmed by the meta-analysis by Zhang et al. (2019), which reported consistent effects across different contexts and health behaviours.

In this study, we examine whether these motivational factors, present prior to exposure to the narrative, may influence the audience's willingness to accept or reject persuasive messages, since, as noted by Moyer-Gusé (2008), audiences do not approach narrative messages in a neutral manner but rather bring prior values, norms, and attitudes that shape their motivation to adopt healthy behaviours. It is therefore likely that MO who, before exposure to a persuasive message, report higher risk perception, more

positive expectations toward non-use and greater self-efficacy, as well as fewer negative expectations, will show more favourable cognitive responses to the narrative message.

Given the central role of these motivational factors in readiness for change, it is essential that narratives integrate them to enhance their effectiveness. For this reason, when narrative persuasion is used to promote healthy behaviours, it is recommended that story characters display a transition from an undesired behaviour to a positive one, obtaining benefits during the process (Bilandzic & Busselle, 2013; de Graaf et al., 2016; Moyer-Gusé, 2008). In line with behaviour change theories, this implies that the narrative incorporates risk perceptions, outcome expectancies, and self-efficacy as narrative drivers that support the character's progression.

It can be understood that if the audience shares this readiness for change, they are more likely to identify with the character and perceive the story as relevant, thereby increasing receptivity to the desired behaviour. In this way, motivational factors would be related to narrative engagement, expressed through identification with the character and narrative transportation. Consequently, a greater predisposition to change combined with a higher level of immersion will tend to favour cognitive responses consistent with the persuasive message.

In turn, this narrative engagement may function as an indirect and mediating factor in persuasive outcomes. The literature suggests that the effectiveness of persuasive communication develops through these mediating processes (Igartua & Frutos, 2017; Slater & Rouner, 2002). In the case of MO, exposure to narratives that present conflicts similar to their own and depict a credible change process—where protagonists overcome barriers and obtain benefits—may facilitate message acceptance and increase readiness to modify unhealthy behaviours. Thus, the influence of motivational factors on cognitive responses is likely to be channelled through narrative engagement.

To examine the effect of narrative persuasion among MO who have already initiated cannabis use, the following objectives were proposed:

1. To examine how MO respond to a persuasive message based on behaviour change narratives designed specifically for this population, identifying their cognitive responses.
2. To analyse the role of gender, motivational variables (risk perception, positive and negative outcome expectancies, and self-efficacy for action), and narrative engagement (identification with the character and narrative transportation) in receptivity to the persuasive message, measured through the polarity index or favourability of thoughts toward the message.

For this second objective, the following hypotheses were formulated based on the reviewed literature:

H1. No significant differences will be observed between males and females in the polarity index after viewing a narrative featuring protagonists of the same gender.

H2. MO who, prior to exposure to the message, report higher levels of risk perception, more positive expectancies regarding cannabis non-use, and greater self-efficacy for action, as well as lower levels of negative expectancies regarding non-use, will be significantly associated with a polarity index more favourable to the message.

H3. Motivational variables (risk perception, positive and negative expectancies, and self-efficacy for action) and narrative engagement variables (identification with the protagonist and narrative transportation) will jointly explain a significant proportion of the variance in the polarity index.

H4. Narrative engagement variables (identification and transportation) will mediate the effect of motivational variables on the polarity index.

Methods

Participants

This study forms part of a broader project aimed at analysing the effectiveness of a preventive intervention targeting problematic cannabis use among minor offenders. MO serving court-ordered sentences in Juvenile Offender Detention Centres (known in Spain as CIMI) participated between September 2021 and June 2022.

A purposive sampling strategy was used with the following inclusion criteria: (a) being aged between 14 and 18 years; (b) having used cannabis prior to admission to the centre; (c) having completed the observation phase in accordance with Decree 98/2015 regulating the organisation and functioning of CIMI (Junta de Andalucía, 2015); (d) being under closed, semi-open, or open regimes, with precautionary measures or a final judicial sentence; and (e) voluntarily agreeing to participate in the study. Exclusion criteria were: (a) a diagnosed psychopathological disorder; (b) receiving treatment for substance misuse; and (c) displaying disruptive behaviours that prevented participation.

Although the literature indicates that MO populations present high rates of psychiatric comorbidity and substance misuse, this study opted to work with a sample lacking a clinical diagnosis or active treatment for substance misuse. This decision is based on the need to obtain clear results not confounded by clinical symptomatology or ongoing therapeutic interventions. At the same time, detention as a legal measure constitutes a key moment for addressing substance-related problems in adolescents, as well as for prevention among those who have initiated harmful patterns of use. This may help prevent escalation of

use or support the maintenance of abstinence once the deprivation of liberty has ended. While both strategies are essential, treatment tends to predominate in these contexts, relegating preventive interventions to a secondary role (Funk et al., 2020; Sales et al., 2018). In this regard, the exclusion of these variables allows the findings to be interpreted within a framework of selective or indicated prevention targeting at-risk groups, rather than a strictly therapeutic approach.

A total of 103 MO were recruited from 5 of the 13 CIMI located in Andalusia (Spain). Overall, these centres provide 751 places. The final sample was reduced to 93; the main reasons for non-participation among initially recruited minors were disruptive behaviour or unwillingness to participate at the time of the study. The sample had a mean age of 16.34 years (SD = 0.96), with 80% males. The mean age of initiation of use was 12.35 years (SD = 1.86), with a mean duration of use of 3.98 years (SD = 2.03). The average duration of the detention measure was 14.26 months (SD = 6.83), while the mean length of stay in the centre was 6.16 months (SD = 5.54).

Procedure

Approval prior to the start of the study was obtained from the Research Ethics Committee of the Virgen Macarena and Virgen del Rocío University Hospitals of the Andalusian Health Service. The research was conducted in accordance with the ethical and legal regulations in force in Spain for research involving minors within the context of juvenile justice. In this regard, the rights established in Organic Law 5/2000 of 12 January, regulating the criminal responsibility of minors (Jefatura del Estado, 2000), and Decree 98/2015 (Junta de Andalucía, 2015) were guaranteed. Particular attention was paid to the protection of personal data, confidentiality of information, and the right to receive clear, accurate, and understandable information about participation. In addition, voluntary participation was ensured, guaranteeing that minors could refuse without any consequences for their legal status or detention regime.

Accordingly, the directors of each CIMI were contacted to present the study and agree on sample recruitment in line with the established criteria. Technical staff were responsible for recruitment and for obtaining informed consent from the minors and their legal guardians.

Participants initially completed a questionnaire assessing motivational variables. One week later, they viewed the audiovisual material described in the following section and subsequently completed a second questionnaire in which measures related to narrative engagement and cognitive responses to the message were obtained. Separate groups of males and females were established, each consisting of 4 to 6 participants, who viewed the narrative corresponding to their gender. To ensure confidentiality, the study was conducted in a designated space within the centre, with only the research team present.

Audiovisual material

An audiovisual tool was developed consisting of two fictional stories, featuring Laura and Manu, both minors in CIMI. Each story is divided into two sections. In the first, Laura or Manu recount their experience in the centre in the first person, with an emphasis on cannabis use. They describe their family and emotional context, the onset of use, and the problems that led to their detention. They also narrate their experience in the centre, sharing their transition from initial resistance to admission to the CIMI to assuming responsibility for having reached that situation. They reflect on their relationship with CIMI professionals, their desire for change, and how they gradually develop a sense of control over cannabis use once the custodial measure ends. In the second section, Laura's psychologist and Manu's psychologist provide their perspective on each MO's personal and family difficulties, describing the observed progression toward achieving control over cannabis use.

To develop this audiovisual material, the following steps were undertaken:

1. **Preliminary analysis of the context of cannabis use.** Statistical and epidemiological data on cannabis use from the Spanish Observatory on Drugs and Addictions were consulted, together with sociodemographic data on MO from the National Statistics Institute. This information was complemented with interviews with professionals from CIMI and other addiction treatment centres (49 in total).
2. **Analysis of life stories related to cannabis use among MO.** Twenty-two interviews were conducted with MO in the final phase of their detention measure in order to extract relevant information about their trajectories of use and experiences of change within the centre. This analysis enabled the creation of a chronology of key events before admission, during their stay, and in the period prior to the completion of the custodial measure.
3. **Story construction using the storytelling technique.** Two narratives centred on the characters Laura and Manu were created, integrating both the information gathered in the previous phase and the processes of change toward healthy behaviours. Their development drew on theoretical foundations of behaviour change (Perrier & Martin-Ginis, 2018; Petraglia, 2009), enabling the characters to be portrayed as models of transition toward healthier lifestyles (Bilandzic & Busselle, 2013; Moyer-Gusé, 2008). In particular, the narratives were designed following the principles of the Health Action Process

Approach (HAPA) model (Schwarzer, 2008), which clearly and distinctively specifies the mechanisms required to initiate and maintain behavioural change.

To enhance familiarity, efforts were made to create stories closely aligned with the reality of the target population (de Graaf et al., 2016; Igartua et al., 2021; Miller-Day & Hecht, 2013), including events, situations, and characters presented from a gender perspective. For example, Laura was serving a judicial measure for domestic violence, whereas Manu was serving one for theft. The testimonies were recorded in a setting that simulated a CIMI in order to achieve a higher degree of realism. An audiovisual technical team adapted the narrative language to the visual format, ensuring its suitability for the target population.

4. **Validation of the narratives.** CIMI professionals reviewed a first draft of the narrative script featuring Laura and Manu's stories and provided suggestions regarding both content and form to better adapt it to the MO profile and clearly incorporate the health behaviour change processes of the HAPA model. A second version was produced with improvements that included simplifying the language to enhance comprehension without losing realism, clarifying episodes related to family conflict and use, and more explicitly incorporating negative effects following use and during adaptation to the centre. Institutional routines were also added to increase the credibility of the narrative.

This second version was validated using an ad hoc questionnaire comprising several sections. The first assessed whether the script clearly reflected the model's behaviour change processes, such as risk perception, outcome expectancies, self-efficacy, and action planning. For example, one item asked whether "the story describes the negative consequences of smoking cannabis," corresponding to outcome expectancies. Subsequent sections focused on the credibility and coherence of the story, with items adapted from previous work on narrative realism (Cho et al., 2014; Hall, 2003). Questions were included for professionals to evaluate the story's ability to capture attention, be understandable, and generate empathic responses. Finally, two open-ended questions were added for an overall appraisal (what they did not like and how it could be improved).

The questionnaire was completed by 13 professionals from different CIMI, allowing for further adjustments. Overall, the script featuring Laura's story received 85.7% positive evaluations, while Manu's reached 80.8%. In their qualitative observations, professionals suggested refining certain aspects, such as removing behaviours that were not representative and increasing the prominence of support from professionals and significant figures. Taken together, this process strengthened content validity by integrating the core behaviour change components of the HAPA model and improving the narrative quality of the persuasive stories. The scripts of Laura and Manu's audiovisual narratives, indicating their correspondence with the theoretical components of the HAPA model and the links for viewing them, are available in the supplementary material of this article.

Variables and measurement instruments

Cognitive responses to the message

Thought listing. To identify cognitive responses to the message, the thought-listing technique was used (Igartua, 1998). This technique has proven suitable not only for analysing the content of thoughts but also for examining associated variables, such as perceived confidence in those thoughts (Horcajo et al., 2022). After exposure to the message, each participant was asked to write down the thoughts that arose while watching the video. Ten boxes were provided for recording one thought in each, and participants were required to write at least three. Two members of the research team independently coded the responses across two dimensions. First, by the origin of the thought, with three categories: (1) Message, thoughts referring directly to the message content and the story shown in the video (e.g., "the boy must have had a hard time"); (2) Experience, when referring to personal experiences (e.g., "I smoke when I have problems"); and (3) Irrelevant, when unrelated to the task (e.g., "I didn't think anything"). Second, by response polarity, classified as: (1) Favourable, thoughts supporting the content and source of the persuasive message or reinforcing it based on personal experience (e.g., "I liked when he started changing his goals and improving his relationship with his mother, not wanting to worry her"); (2) Unfavourable, thoughts opposing the content and source of the persuasive message or using personal experience to contradict it (e.g., "as soon as I'm released I'm going to smoke a joint"); (3) Reflective, when they evoke a more considered analysis of the issue without indicating a clear position for or against (e.g., "it reminded me of when I was on the street"); and (4) Irrelevant, when unrelated to the task (e.g., "it's a good centre"). In total, 449 thoughts were coded. Inter-rater agreement was 94.8% for coding thought origin and 93.9% for coding polarity. Discrepancies were resolved through discussion to reach consensus.

Polarity index. Based on the coding of response polarity obtained through the thought-listing procedure, the polarity index was calculated by subtracting the percentage of unfavourable thoughts from the percentage of favourable thoughts and dividing the result by 100. This procedure produces values ranging from −1 to +1, where −1 indicates that all thoughts are unfavourable to the message, +1 that all are favourable, and 0 that there is an equal proportion of favourable and unfavourable thoughts. Thus, the polarity

index indicates the extent to which favourable responses (greater receptivity) or unfavourable responses (greater resistance) toward the persuasive message predominate.

Motivational variables

Risk perception of cannabis use. Perceived vulnerability regarding cannabis use was measured with the question: How much risk to your health do you think you have if you use cannabis? Response options were: 1 (no risk), 2 (a small risk), 3 (moderate risk), 4 (great risk), in addition to the option "I don't know." This question was answered according to frequency of use (once or twice a month, once a week, once a day, or more than twice a day). The reliability of the scale was α = .86.

Outcome expectancies. Beliefs about the contingencies of cannabis non-use and its positive or negative consequences were assessed. To facilitate responses, an open-ended question was used so that participants could identify up to six consequences and rate their importance on a scale from 1 (not important) to 5 (very important). Responses were categorised into positive consequences (pleasant and favourable to non-use, such as "I have fewer problems") and negative consequences (unpleasant and unfavourable to non-use, such as "I can't sleep"). Two members of the research team participated in this categorisation to achieve inter-rater agreement, which reached 95.5%. Subsequently, two variables were generated: positive outcome expectancies regarding cannabis non-use and negative outcome expectancies regarding cannabis non-use. Both variables were calculated by considering the total number of positive or negative consequences weighted by the importance assigned.

Self-efficacy for action. Personal belief in the ability to carry out a specific action—here, abstaining from cannabis use after completion of the detention measure—was assessed with the question: "Are you sure that you will not use cannabis once the detention measure in the centre ends?" A response scale from 1 (not at all sure) to 4 (completely sure) was used.

Narrative engagement variables

Identification with the character. The five items selected by Tal-Or and Cohen (2010), based on Cohen (2001), were used. These items include statements concerning understanding of the character and events, experiencing similar feelings, the ability to take the character's perspective, and understanding their motivations. The statements were adapted to the type of study and the story's protagonist. A 7-point Likert scale was used (1 = strongly disagree, 7 = strongly agree). Reliability for this sample was α = .66.

Narrative transportation. The short version of the Transportation Scale by Appel et al. (2015) was used. It contains five items assessing the cognitive and emotional dimensions of narrative transportation. Items were adapted to the audiovisual format, as the original scale was designed for written narratives. A 7-point Likert scale was used (1 = strongly disagree, 7 = strongly agree). The reliability obtained was α = .81.

Data analysis

Before statistical analysis, missing values in the variables risk perception (5), positive expectancies (7), negative expectancies (8), and self-efficacy (4) were imputed using mean substitution. Data normality and homoscedasticity were assessed using the Kolmogorov–Smirnov and Levene tests, indicating that the data did not follow a normal distribution; therefore, non-parametric tests were employed.

To test H1, the Mann–Whitney U statistic was calculated using R (version 4.5.1), along with effect size using Cliff's δ and the corresponding confidence intervals. These values were interpreted following Romano et al. (2006), whereby an effect size of |0–0.147| is considered trivial, |0.147–0.33| small, |0.33–0.474| medium, and values greater than 0.474 large. For H2, correlation analyses were conducted using Spearman's rho coefficient. For H3, after confirming that model residuals met normality criteria, stepwise multiple linear regressions were applied, and effect size (f^2) was calculated using GPower 3.1. For H4, the PROCESS macro for SPSS was used with bootstrapping of 5,000 resamples with bias correction for mediation analysis (Model 4), which was accepted if the confidence interval (CI) was statistically significant, that is, if the 95% CI did not include zero (Hayes, 2022). The proportion mediated was calculated as the ratio between the indirect effect and the total effect ($ab/ab + c'$). The Sobel test (1982) was applied to confirm the mediation effect, calculating the ratio between the point estimate and its standard error. The mediation effect was considered statistically significant if the z value was greater than or less than ±1.96 for a two-tailed alpha of 0.05, or ±2.58 for a two-tailed alpha of 0.01.

Results

First, cognitive responses of MO to the persuasive narrative were identified. The analysis revealed that 52.03% of thoughts focused on the video content (message), whereas 46.90% evoked personal experiences. Regarding polarity, favourable thoughts predominated (60.5%) compared with unfavourable ones (19.45%), with 15.31% classified as reflective thoughts. See Table 1.

Table 2 presents the descriptive statistics of the variables used in the inferential analysis. Median values for the motivational variables indicate that, prior to viewing, MO showed a moderate perception of risk associated with cannabis use (9.00), as well as both positive (10.00) and negative (10.00) expectancies regarding cannabis non-use.

However, based on interquartile range values, responses for negative expectancies were somewhat more clustered than for positive expectancies. In addition, participants reported moderate confidence in their ability to remain abstinent after completing their detention measure (2.00).

Post-viewing measures indicated that scores for identification with the protagonist and narrative transportation were located in the upper range of their respective scales, with medians of 25.00 and 26.00, respectively. The interquartile range for both variables confirmed this tendency. Finally, the polarity index showed a positive median value (0.57), with a range from 0.07 to 0.83, suggesting a clearly favourable tendency toward the persuasive message.

To test H1, differences in the polarity index between males (n = 75) and females (n = 18) were examined. The Mann–Whitney U test showed no statistically significant differences between groups (U = 758; p = .42). Medians were similar (males: Mdn = .60, IQR = .21–.80; females: Mdn = .42, IQR = −.45–.88). The effect size estimated using Cliff's δ was small and non-significant (δ = 0.12, 95% CI [−0.22, 0.44]). As the confidence interval exceeded the predefined equivalence margins (±0.147), it was not possible to conclude either equivalence or non-inferiority between male and female groups in the polarity index (Table 3). Therefore, although the results appear consistent with the stated hypothesis, they do not allow a conclusive confirmation.

To assess H2, a bivariate correlation was conducted using Spearman's rho (Table 4). Results indicate that the polarity index was significantly and positively correlated with risk perception (r = .40, p < .001), positive outcome expectancies (r = .25, p < .05), and self-efficacy for action (r = .28, p < .01). In addition, a significant negative correlation was observed with negative outcome expectancies (r = −.26, p < .05). Therefore, it can be confirmed that the motivational variables of the HAPA model are related to the polarity index and, consequently, receptivity to the persuasive message increases when levels of risk perception, self-efficacy for action, and positive outcome expectancies are high, and negative outcome expectancies are low.

To test H3, after confirming that the residuals of the variables included in the analysis met normality criteria, a stepwise multiple linear regression was conducted in which

Table 1

Descriptive statistics of cognitive responses

Variables		N	%	Md [RIC]	Min	Max
Thoughts by Origin						
	Message	93	52.03	2 [1-4]	0	10
	Experience	93	46.90	2 [0-4]	0	10
	Irrelevant	93	1.07	0 [0-0]	0	1
Response polarity						
	Favourable	93	60.50	3 [2-4]	0	9
	Unfavourable	93	19.45	0 [0-1]	0	9
	Reflective	93	15.31	0 [0-1]	0	5
	Irrelevant	93	4.74	0 [0-0]	0	3

Note. Md= median; IQR = interquartile range (p25-p75); Min = minimum value; Max = maximum value.

Table 2

Descriptive statistics of study variables

Variables	N	Md [RIC]	Min	Max
Risk perception	93	9 [6-12]	2	16
Positive expectancies	93	10 [0-15]	0	30
Negative expectancies	93	10 [4-16.5]	0	30
Self-efficacy	93	2 [2-3]	1	4
Identification	93	25 [20-30]	10	35
Narrative transportation	93	26 [18.5-29.5]	5	35
Polarity index	93	.57 [.07-.83]	-1	1

Note. Md= median; IQR = interquartile range (p25-p75); Min = minimum value; Max = maximum value.

Table 3

Comparison of Polarity Index by Gender

	Males (*n*=75)	Females (*n*=18)			
	Mdn [RIC]	*Mdn* [RIC]	*U (W)*	*p*	*δ* Cliff [IC95%]
Polarity index	.60 [.21 - .80]	.42 [-.45 - .88]	758	.42	.12 [-.22 - .44]

Note. Mdn = median; IQR = interquartile range; U = Mann–Whitney (reported as W in R). Cliff's δ is interpreted as effect size: |0–0.147| = trivial, |0.147–0.33| = small, |0.33–0.474| = medium, >0.474 = large (Romano et al., 2006).

Table 4

Spearman correlations between motivational variables and the Polarity Index

Variables	**1**	**2**	**3**	**4**	**5**
1. Risk perception	—				
2. Positive expectancies	.42***	—			
3. Negative expectancies	-.31**	-.70***	—		
4. Self-efficacy	.32**	.33**	-.23*	—	
5. Polarity index	.40***	.25*	-.26*	.28**	—

* p <.05, ** p < .01, *** p < .001.

motivational and narrative engagement variables were included as explanatory variables of the polarity index. As shown in Table 5, in the first step only the narrative engagement variable narrative transportation showed a significant fit (R^2 = .25; R^2_{aj} = .24; SEE = .51; F (1, 91) = 29.96; p < .001). In the second step, the model added the motivational variable risk perception, resulting in a significant improvement (R^2 = .30; R^2_{aj} = .29; SEE = .50; F(2, 90) = 19.76; p < .001), as it generated an increase in non-redundant explained variance (ΔR^2 = .06; ΔF(1, 90) = 7.44; p = .008). In the final model (Table 6), narrative transportation was the strongest predictor (β = .40; B = 0.03, SE = 0.007; t = 4.29; p < .001; 95% CI [0.02, 0.05]), while risk perception contributed an additional positive effect (β = .26; B = 0.04, SE = 0.015; t = 2.73; p = .008; 95% CI [0.01, 0.07]). Diagnostic statistics suggested independence of errors (Durbin–Watson ≈ 1.95) and absence of multicollinearity (VIF ≈ 1.15). Overall, the final model shows a medium global effect size (f^2 ≈ .44) and supports that higher levels of narrative transportation and risk perception are associated with a higher polarity index, with narrative transportation as the main contributor and risk perception as a complementary predictor that significantly increases explanatory precision.

To explore H4, a mediation analysis was conducted using the PROCESS macro for SPSS. The results are consistent with partial mediation of narrative transportation in the association between risk perception and the polarity index. First, risk perception positively predicts narrative transportation (Path a), and narrative transportation positively predicts the polarity index while controlling for risk perception (Path b). The indirect effect differs from zero according to bootstrap estimates (ab = 0.023; 95% CI [.007, .044]; ab_{cs} = .147, 95% CI [.046, .265]), indicating that part of the effect of risk perception on the polarity index is transmitted through narrative transportation. However, the persistence of a significant direct effect (c′) suggests that the mediation is partial rather than complete. Approximately 36% of the total effect of the motivational variable risk perception on resistance to persuasion (polarity index) is mediated (ab/c ≈ .364), while the remainder remains direct (c′). In summary, greater risk perception is associated with higher narrative transportation, which in turn is associated with a higher polarity index, providing robust bootstrap evidence of partial mediation (Tables 7 and 8; Figure 1).

Discussion

This study provides relevant findings on how MO respond to narrative persuasion and which variables are associated with message acceptance. The analysis of cognitive responses, conducted using the thought-listing technique, showed that a slightly higher proportion of participants focused their attention on the content of the narrative material (message), and nearly half of the responses evoked personal experiences. This suggests that well-structured persuasive narratives can capture audience interest (de Graaf et al., 2016; Herrera-Sánchez et al., 2019; Miller-Day & Hecht, 2013; Thomas

Table 5

Summary of the stepwise multiple regression model for the effect of motivational and engagement variables on resistance to persuasion

Step	*R*	R^2	R^2_{aj}	SEE	F (*gl1,gl2*)	*p*	ΔR^2	*ΔF (gl1,gl2)*	*p(ΔF)*	f^2	Durbin-Watson
1: Transportation	.50	.25	.24	.51	29.96 (1.91)	<.001	.25	29.96 (1.91)	<.001	.33	-
2: +Risk perception	.55	.30	.29	.50	19.76 (2.90)	<.001	.06	7.44 (1.90)	.008	.44	1.95

Note. SEE = standard error of the estimate.

Table 6

Final model coefficients

Predictor	*B*	SE(B)	*β*	*t*	*p*	[IC95%] of *B*	*VIF*
(Constant)	-0.71	.186	-	*-3.83*	*<.001*	[-1.08, -0.34]	-
Transportation	0.03	.007	.40	4.29	*<.001*	[0.02, 0.05]	1.15
Risk perception	0.04	.015	.26	2.73	.008	[0.01, 0.07]	1.15

Note. SE(B) = standard error of B; VIF = variance inflation factor.

Table 7

Mediation of narrative transportation on the relationship between risk perception and resistance to persuasion. Path coefficients (PROCESS, Model 4)

						IC 95% *B*	
Path	***B***	**SE(*B*)**	***β***	***t***	***p***	**LL**	**UL**
a: RP-T	0.732	.197	.363	3.72	<.001	.341	1.122
b: T-PI (controlling RP)	0.032	.007	.404	4.29	<.001	.017	.046
c': RP-PI (controlling T)	0.041	.015	.257	2.73	.007	.011	.070
c: Total effect (RP-PI)	0.064	.015	.404	4.21	<.001	.034	.094
	z			***SE***	***p*¹**		
Sobel test	2.35			.01	.02		

Note. RP = risk perception; T = transportation; PI = polarity index; SE: standard error of the estimate; 95% CI: 95% confidence interval; LL: lower limit; UL: upper limit; p1: two-tailed probability.

Table 8

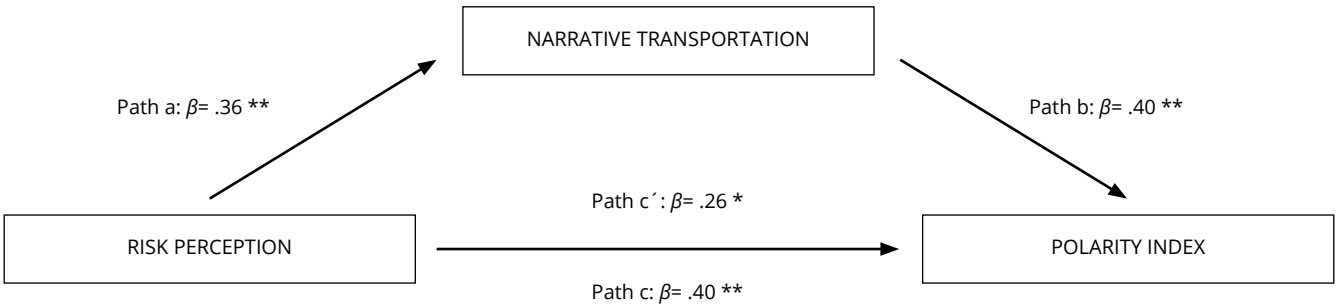
Indirect effect (Bootstrap = 5000; 95% CI percentile)

Effect	Estimate	BootSE	BootLLCI	BootULCI
ab (RP – T – PI)	0.023	.010	.007	.044
ab_{cs}	0.147	.057	.046	.265

Note. RP = risk perception; T = transportation; PI = polarity index; ab = unstandardized indirect effect; ab_{cs} = completely standardized indirect effect; 95% CI = 95% confidence interval; LLCI = Lower limit of the CI; ULCI = Upper limit of the CI; ab/c (mediation percentage) = .364 (36.4%).

Figure 1

Mediation model: Narrative transportation mediating the relationship between risk perception and the polarity index



Note. * p < .01; ** p < .001.

& Grigsby, 2024). In turn, the predominance of favourable over unfavourable thoughts can be interpreted as a positive reception of the persuasive message.

The presence of thoughts related to personal experiences is consistent with previous studies suggesting that memories evoked by a story may facilitate the validation of implicit messages (Hamby et al., 2017; Herrera-Sánchez et al., 2023). Reflective responses were also identified, indicating that reactions to a message are not limited to acceptance or rejection but may involve more elaborate critical processing (Herrera-Sánchez et al., 2023). A future line of research would be to examine how different forms of information processing, according to their origin and direction, influence the ways in which individuals respond to persuasive narratives. Additionally, the findings of this study could be complemented with more open discursive analyses that explore the nature of the discourse generated by the audience in greater depth.

Integrating a gender perspective is essential in this field. Previous research has documented differences between males and females in juvenile justice, both in legal characteristics and risk factors as well as in patterns and trajectories of substance use (Arteaga et al., 2021; Conrad et al., 2017). With this purpose, narrative material was developed to minimise gender effects through the creation of stories tailored to the reality of each group. Regarding H1, the results suggest a tendency toward similar responses between males and females, although without sufficient statistical strength to confirm this finding.

For this reason, these results should be interpreted with caution, as the study did not manipulate exposure to messages to compare groups and the sample included a higher proportion of males. The meta-analytic study by Ratcliff and Sun (2020) showed that the relationship between narrative engagement and resistance to persuasion was stronger in samples with a higher proportion of women, also indicating that effect size increased as the percentage of female participants rose. Therefore, the use of designs that allow for balanced samples in future research is recommended. Given that the juvenile offender population is predominantly male (Arteaga et al., 2021), it may also be appropriate to focus on analysing each group separately rather than conducting direct comparisons between males and females. This approach would allow for a better understanding of the particularities and specific factors influencing narrative persuasion and help avoid biases derived from the overrepresentation of one group. The ultimate goal is to expand research to, for example, examine how meanings of substance use are constructed according to gender and to develop sensitive interventions tailored to the specific needs of each group (Javdani & Allen, 2016; Tolou-Shams et al., 2021b).

The results of the bivariate correlation, showing significant associations between motivational variables and the polarity index, provided empirical support for H2. Specifically, MO who perceived greater risks associated with cannabis use and focused more on the benefits and less on the drawbacks of cannabis non-use tended to exhibit a more favourable cognitive response to the persuasive message. Likewise, those who reported higher self-efficacy tended to be more receptive to messages emphasising the capacity to refrain from use. These findings are consistent with those derived from sociocognitive models that highlight the role of motivational variables in the adoption of healthy behaviours (Schwarzer, 2008; Webb et al., 2010).

However, the stepwise multiple linear regression showed that only narrative transportation and risk perception were explanatory variables of the polarity index; therefore, H3 could only be partially confirmed. This result suggests that immersion in the story and perceiving cannabis use as a risk act as key factors in fostering a positive cognitive response to the persuasive message. The use of transition models in the narrative may explain why outcome expectancies and self-efficacy for action, initially associated with polarity, did

not emerge as significant predictors of message favourability. The character's progression within the story may have contributed to a process of natural alignment with MO experiences, facilitating receptivity without depending on individuals' prior readiness for change. Another possible explanation is that risk perceptions are beliefs that directly influence receptivity to messages. The influence of outcome expectancies and self-efficacy may be indirect, mediated by risk perceptions, which is also consistent with the HAPA model.

Likewise, identification with the character did not show a statistically significant effect on the polarity index. One possible explanation lies in the limitations of the measure used, as the identification scale presented reliability below .70. In addition, this study employed only a global score without analysing the effect of its components separately (e.g., perspective taking), which may have resulted in the loss of relevant information. There is agreement on addressing identification as a multidimensional construct, but there is no consensus on how these components are defined and measured (Huang & Fung, 2024). Future studies should consider the differentiated assessment of these components using scales better suited to the characteristics of this population. Finally, meta-analytic studies have indicated that similarity influences identification, with stronger effects when based on shared experiences (psychological similarity) rather than more objective characteristics such as age (Huang et al., 2024). In this study, the characters were designed to reflect the reality of the target population, which limits the possibility of determining precisely their impact on identification and, consequently, on narrative persuasion. Future research is recommended to explicitly manipulate psychological and objective similarity in order to examine more thoroughly their influence on resistance to persuasive messages in this specific population.

Regarding H4, the results showed that narrative transportation partially mediated the relationship between risk perception and the polarity index. This is consistent with previous analyses highlighting the role of narrative transportation in reducing resistance to persuasion (Bilandzic & Busselle, 2013; Green & Brock, 2000; Slater & Rouner, 2002; Thomas & Grigsby, 2024). However, the study by Cohen et al. (2015) identified a moderating rather than mediating role, suggesting that narrative transportation may operate differently depending on the context. In this study, risk perception may be interpreted as a motivational facilitator that intensifies receptivity to the persuasive message, while narrative transportation optimises its cognitive and emotional integration, thereby reducing resistance to persuasion.

In the present study, narrative engagement was addressed through identification with the protagonist and narrative transportation. Although identification did not emerge as a significant predictor, both variables were selected due to their strong theoretical grounding, evidence of their role in facilitating persuasion, and feasibility of measurement in the MO context. However, this construct has been defined in multiple ways, incorporating different cognitive and emotional components. Busselle and Bilandzic (2009) define narrative engagement as an experience that integrates four interrelated processes: narrative understanding, attentional focus (absence of distraction), emotional engagement (feeling for and with characters), and narrative presence (the sensation of entering the narrative world). Weiss (2022) even suggested that self-referencing (thinking about one's own life and experiences in relation to the story) could be considered part of the engagement process. From the Narrative Engagement Theory perspective, Miller-Day and Hecht (2013) conceptualise narrative engagement as the extent to which audiences become cognitively involved with a story and propose that it can be measured through audience interest in the narrative, perceived realism, and identification with characters. From a perspective more focused on the emotional dimension of engagement, Hamby and Jones (2022) argue that engagement depends not only on the intensity of emotions generated by the narrative but also on their nature (discrete emotions) and the cognitive appraisals that give rise to them. Although these variables were not assessed in the present study, their relevance is acknowledged. Future research in this context should expand the measurement of engagement to achieve a more comprehensive understanding of the mechanisms through which narratives reduce resistance.

It is important to consider that the results of this study are based on a specific sample, which limits their generalisability. Despite including participants from several centres, the absence of contextual or institutional data—such as the characteristics of intervention programmes at each centre—prevented assessment of potential nesting effects among participants. Therefore, future studies are encouraged to use mixed-effects models to estimate variability attributable to both individual factors and contextual variables. Another relevant limitation is that the study focuses on immediate cognitive responses to the persuasive message without measuring its effect on changes in attitudes or behaviours. Although the study provides evidence regarding the processes associated with this response, it is not sufficient to determine whether favourable reception translates into sustained change. In addition, the variables examined, such as identification with the character and narrative transportation, were not experimentally manipulated, which restricts the ability to establish direct causal relationships. Finally, the inclusion of ad hoc questions to assess risk perception and self-efficacy, as well as the use of a single item for the latter variable, may have affected the precision of the estimates. This methodological decision is justified by the lack of validated scales for this specific population and the need to minimise participants' cognitive burden given the judicial

context of the study. Future research could address these limitations through longitudinal designs that, using validated scales, allow evaluation of changes in receptivity and their relationship with changes in attitudes and behaviours. Experimental designs, in turn, would facilitate comparison of narrative persuasion with other communication strategies.

Despite these limitations, this study makes an original contribution to the field of persuasive communication by exploring how narrative persuasion may influence MO with a history of cannabis use, a group that might be expected to show greater resistance to influence attempts. The findings suggest that persuasive narrative is also effective with this audience profile, highlighting its potential for interventions targeting this population.

Furthermore, this work addresses a limitation identified by Perrier and Martin-Ginis (2018) in the development of persuasive materials by integrating components of a behaviour change theory into the narrative construction, ensuring a clear and structured progression in the behaviour change process that is readily understood by the audience. In addition, validation of the material by professionals guarantees fidelity to the underlying theoretical principles, strengthening its rigour and applicability in these intervention contexts.

This study is grounded in the psychoeducational principles of persuasive communication to improve the health of MO in CIMI. Beyond their sanctioning function, these centres implement educational and psychosocial intervention programmes. In general terms, these interventions include health education as a key component and, more specifically, incorporate prevention and treatment actions for addictions adapted to the characteristics of the minor population (Junta de Andalucía, 2023). The narrative material developed for this study could be integrated as a complement to preventive actions implemented in these centres. The study findings, showing a predominantly favourable reception, support its potential usefulness in strengthening selective and indicated prevention programmes for cannabis use in this context.

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Conflict of interest

All authors declare that they have no conflict of interest.

Data availability

The data used for this article are available at https://hdl.handle.net/11441/182046 or at https://doi.org/10.12795/11441/182046.

Supplementary material

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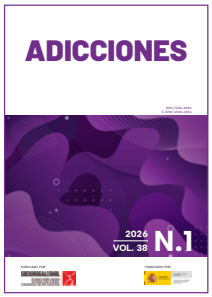
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ORIGINAL

Hepatitis C therapy with pangenotypic direct-acting antivirals: Drug-drug interactions in drug-using HCV patients and antipsychotic-treated HCV patients

Tratamiento de hepatitis C con antivirales pangenotípicos de acción directa: Interacciones farmacológicas en pacientes que consumen drogas y tratados con antipsicóticos

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Abstract

People who use drugs (PWUD) are at high risk of hepatitis C virus (HCV) infection, and HCV patients often have psychiatric disorders requiring nervous system drugs, including antipsychotics. These medicines can interact with HCV treatment-related metabolic pathways producing DDIs (drug-drug interactions). This analysis focused on potential DDIs between direct-acting antivirals (DAAs) and concomitant medications used in PWUD/antipsychotics-treated HCV patients, alongside associated adverse events (AEs) and clinical interventions in Spain. Electronic medical records (BIG-PAC® database) were used to analyse adult HCV patients treated with glecaprevir/pibrentasvir (GLE/PIB) or sofosbuvir/velpatasvir (SOF/VEL) between 2017-2020. The study included 1,620 HCV patients, 985 identified as PWUD and 187 as antipsychotic users, 75% of whom were also PWUD. In the PWUD cohort, cardiovascular (CV) comorbidities were the most frequent; 22.7% patients were at risk of DDIs with CV, with the risk being higher in GLE/PIB-treated (36.8%) versus SOF/VEL (13.7%) (p<0.001). Cardiovascular AEs were more common in the GLE/PIB group. In the antipsychotic cohort, quetiapine was the most prescribed antipsychotic comedication (26.2%), followed by paliperidone (17.6%) and olanzapine (17.1%). Fifty-one per cent of those on GLE/PIB were at risk of DDIs versus 23% on SOF/VEL (p<0.001). Two AEs were reported in the GLE/PIB group (n=37): one patient on quetiapine at a dose <300mg/day experienced extrapyramidal symptoms, leading to DAA discontinuation, and another paliperidone-treated experienced sedation, necessitating a dose reduction. The findings highlight DDIs risks in HCV patients on antipsychotics or with substance addiction, particularly with GLE/PIB. Comprehensive clinical follow-up is essential to optimise treatment and improve patient safety.

Keywords: Hepatitis C virus, people who use drugs, drug-drug interactions, antipsychotic medication, direct-acting antivirals

Resumen

Los usuarios de drogas (UD) tienen un alto riesgo de infección por el virus de la hepatitis C (VHC), y muchos pacientes con VHC presentan trastornos psiquiátricos que requieren medicación del sistema nervioso, incluidos antipsicóticos. Estos medicamentos pueden interactuar con los antivirales de acción directa (AAD), produciendo interacciones farmacológicas (IF). En este estudio, nos centramos en las potenciales IF entre AAD y medicaciones concomitantes utilizadas en estos pacientes, así como en los eventos adversos (EA) asociados e intervenciones clínicas en España. El estudio, basado en registros electrónicos de BIG-PAC®, analizó a adultos tratados con glecaprevir/pibrentasvir (GLE/PIB) o sofosbuvir/velpatasvir (SOF/VEL) entre 2017 y 2020. Se incluyeron 1.620 pacientes con VHC, 985 UD y 187 usuarios de antipsicóticos, de los cuales el 75% también eran UD. En la cohorte UD, las comorbilidades cardiovasculares fueron más frecuentes; el 22,7% presentaba riesgo de IF con medicación cardiovascular, mayor con GLE/PIB que con SOF/VEL (36,8% vs.13,7%, p<0,001). Los EA cardiovasculares fueron más frecuentes en GLE/PIB. En la cohorte de antipsicóticos, quetiapina fue el más prescrito (26,2%), seguida de paliperidona (17,6%) y olanzapina (17,1%). El 51% de los tratados con GLE/PIB presentó riesgo de IF, frente al 23% con SOF/VEL (p<0,001). Se reportaron dos EA en GLE/PIB: un paciente con quetiapina (<300 mg/día) presentó síntomas extrapiramidales y otro con paliperidona sufrió sedación, que requirió suspensión o ajuste. Los resultados subrayan el riesgo de IF en estas cohortes, especialmente en pacientes con GLE/PIB, destacando la necesidad de un seguimiento clínico estrecho para optimizar la seguridad del tratamiento.

Palabras clave: virus de la Hepatitis C, usuarios de drogas, interacciones farmacológicas, antipsicóticos, antivirales de acción directa

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Chronic hepatitis C virus (HCV) infection affects an estimated 50 - 58 million individuals worldwide (POLARIS, 2024; World Health Organisation, 2023). The primary treatment for HCV are pangenotypic direct-acting antiviral agents (DAAs). Between 2014 and 2022, 13.2 million patients worldwide were treated for HCV using DAAs, 82% in sofosbuvir-based regimens (Voeller et al., 2023). DAAs are usually well tolerated; however, patients often present comorbidities that require concomitant medications, and these medications may cause potential drug-drug interactions (DDIs) that must be considered when choosing a DAA (European Association for the Study of the et al., 2020). These potential DDIs can either result in drug toxicity or reduced efficacy of either the DAA or the concomitant medications (Gao et al., 2021). Therefore, meticulous patient management is crucial for DAAs to achieve optimal treatment outcomes (Dick et al., 2016). Modern DAA based regimens, such as sofosbuvir/velpatasvir (SOF/VEL) and glecaprevir/pibrentasvir (GLE/PIB) present lower risk of DDIs than first-generation DAAs (Schulte et al., 2020). Despite this, around 40% of HCV patients present DDIs, commonly related to interactions of DAAs and the metabolic pathways involved in the patient's comedications (Moore et al., 2019; Schulte et al., 2020).

People who use drugs (PWUDs) have a higher risk of contracting HCV infection (Pineda et al., 2020). According to a recent systematic review, worldwide, more than 50% of PWUDs are positive for HCV antibodies (Degenhardt et al., 2017). Indeed, in England, PWUDs represent around 80% of all HCV infections, which reflects the disproportionate burden of disease in this group (Di Marco et al., 2022). Additionally, HCV infection is 3 to 20 times more common in patients with severe mental illness, who are often treated with nervous system drugs (Fiore et al., 2023). Historically, interferon-based HCV treatment caused neuropsychiatric side effects, which led to the exclusion of these patients from therapy and from clinical trials (Fiore et al., 2023; Rifai et al., 2010). Barriers such as poor adherence, limited healthcare access, stigma, and vulnerability further hindered treatment efficacy (Gutierrez-Rojas et al., 2023).

Despite these facts, few studies have comprehensively evaluated the use of comedication and the risk of DDIs in PWUDs with HCV who are treated with DAA (Hintz et al., 2021; Nava et al., 2023). None of these have studied adverse events (AEs) related to DDIs. These limited studies have also shown that the use of antipsychotics is frequent among PWUD, even among those who are not infected with HCV (Hintz et al., 2021; Nava et al., 2023; Rifai et al., 2010).

We recently assessed DDIs' clinical impact, including AEs and efficacy, in HCV patients treated with SOF/VEL and GLE/PIB, the two most widely used DAAs (Turnes et al., 2024). We found that 77.5% of HCV patients were on ≥2 comedications, with almost 10% at risk of multiple DDIs (≥2 DDIs). To shed some light on two of the most vulnerable groups of patients, we conducted a sub-analysis to assess the incidence and severity of DDIs in PWUDs and antipsychotic users treated with DAAs within a real-life cohort in Spain.

Methods

Study design and data collection

We conducted a sub-analysis of a database compiled for our recently published retrospective observational study on HCV patients treated with DAAs (Turnes et al., 2024). Briefly, anonymised patient electronic medical records (EMR) were obtained from the BIG-PAC® database (representative of the Spanish population), which compiles primary data from public primary care centres and hospitals across seven autonomous communities in Spain (Sicras-Mainar et al., 2019). EMR confidentiality (anonymous and dissociated) was respected according to the European General Data Protection Regulation (2016/679) and Organic Law (3/2018) on Data Protection and Guarantee of Digital Rights.

Study population

The study included HCV patients who initiated treatment with SOF/VEL or GLE/PIB between 2017 and 2020. The index date was the date of treatment initiation. Diagnosis of HCV and treatment selection were based on criteria and clinical judgment of attending physicians, reflecting routine clinical practice. A detailed explanation of inclusion/exclusion criteria and other aspects of the study can be found in Turnes et al. 2024.

Study Cohorts

Two cohorts were defined. The number of patients and study flow is shown in Figure 1:

i. Individuals with a history of drug use, including chronic alcoholism, prescribed opioids, sedatives/anxiolytics, cannabis, cocaine, or heroin (referred to as "PWUD cohort").
ii. Individuals using antipsychotic medication, considering both PWUD and those who do not (referred to as "Antipsychotic cohort")

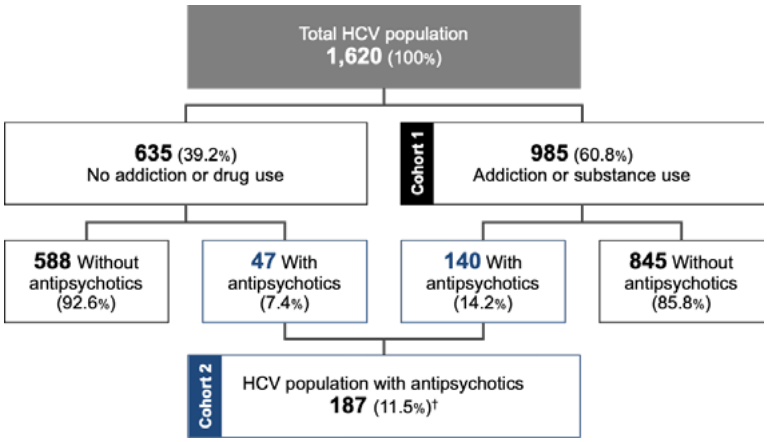
Objectives, Variables, and Assessments

Baseline demographic and clinical characteristics, concomitant medication, and potential DDIs associated with the most frequent comorbidity were described for both cohorts (PWUD cohort and antipsychotic cohort), whether as an adjunct to opioid substitution therapy (OST) or for the management of mental illness.

Patients receiving a protease inhibitor as DAA treatment (GLE/PIB) with those not (SOF/VEL) in terms of

Figure 1

Study diagram and patient populations stratified by addiction and use of antipsychotics



Note 1. † Percentage relative to the overall population. 75% (140/187) of patients with antipsychotics belonged to the population with addiction or substance use vs. 25% of the population without addictions or substance use (47/635), p<0.001.
Note 2. HCV = hepatitis C virus.

comorbidities, concomitant medications, and potential DDIs were compared. Additionally, AEs associated with these pharmacological interactions and the corresponding actions taken for their management were assessed.

Demographic variables, including age, sex, body mass index (BMI), comorbidities, and comedications of the study population, were collected at the entry to the study (index date). Patient comorbidities were recorded using the International Classification of Diseases, 9th edition, Clinical Modification (ICD-09-CM), and characterised by the Charlson comorbidity index (CCI) (Charlson et al., 1987). Comedications were categorised based on the Anatomical Classification (ATC) System, using data retrieved from prescription records in line with medical practice (World Health Organization, 2022). Comedications and possible DDIs were classified according to the strength of interaction and the predicted clinical outcome.

DDIs analysis

Potential DDIs between comedication taken by patients population (recorded in their medical record) and either SOF/VEL or GLE/PIB treatment were identified at the index date using the University of Liverpool's HEP Drug Interaction Checker (The University of Liverpool, 2024) (accessed November 2020 for PWUD cohort and May 2022 for antipsychotic cohort). The HEP Drug Interaction Checker, recommended by reputable medical associations including European Association for the Study of the Liver (EASL) (European Association for the Study of the et al., 2020), the American Association for the Study of Liver Diseases and the Infectious Disease Society of America (AASLD-IDSA) (AASLD, 2022; Bhattacharya et al., 2023) and the National Prisons Hepatitis Network (NPHN) (Winter et al., 2023), is an essential tool for evaluating potential DDIs before initiating new DAA therapy. It categorises interactions based on drug type, pharmacokinetic effects, and strength, aiding in identifying contraindications and significant interactions requiring monitoring or dosage adjustments. DDIs were classified as i) contraindications (drugs that should not be coadministered); ii) potential clinically significant interactions (requires additional monitoring, alteration of drug dosage, or timing of administration); iii) weak interactions (additional action is unlikely); or iv) no interaction expected. The effects of the DDIs were categorised as (i) an increase in plasma concentration of comedication, (ii) an increase in plasma concentration of DAAs, or (iii) a decrease in plasma concentration of DAAs. Multiple DDIs patients were those receiving ≥2 comedications with potential DDIs with the DAA. Those AEs that were probably connected to DDIs were described for the PWUD cohort and the antipsychotic cohort during the DAA treatment period. The comedications associated with AEs and their classification were recorded. We also analysed the actions taken by physicians during the DAA treatment regarding comedication with potential DDIs associated with AEs.

Statistical analysis

Data collected from the BIG-PAC® database were validated by Structured Query Language (SQL) commands and reviewed using an exploratory analysis to ensure quality and consistency (Sicras-Mainar et al., 2019). A descriptive univariate statistical analysis was performed, and absolute and relative frequencies were calculated for qualitative data. Quantitative data were expressed using means, standard deviations (SD), medians, and interquartile ranges (IQR). Bi-variant statistical analyses were carried out using the variance analysis (ANOVA) and Chi-squared tests for independent groups. The statistical software IBM/SPSS was used for analyses. Values of $p<0.05$ were considered statistically significant.

Results

Overall study population

In a previous study of 1,620 HCV patients treated with DAAs, 60.8% had a history of drug use (PWUD cohort), of whom 450 received SOF/VEL, and 535 received GLE/PIB (Turnes et al., 2024). Additionally, 11.5% were prescribed

antipsychotics (Antipsychotic cohort), the majority treated with SOF/VEL (80.2%). Among antipsychotic users, 75% also reported drug use, representing 14.2% of the PWUD cohort (Figure 1).

PWUD cohort

Baseline characteristics

Demographic and clinical characteristics of the PWUD cohort are summarised in Table 1. Substance use patterns varied across the cohort, with cannabis (44%), cocaine (26.2%), and chronic alcoholism (21.8%) being the most prevalent.

When comparing PWUD by group of treatment, individuals in the SOF/VEL group were significantly older, had higher comorbidity burden, and presented more advanced liver disease, including a greater prevalence of fibrosis stages F3 and cirrhosis (F4). Differences in substance use profiles were also observed, with higher rates of opioid and sedative–anxiolytic use in the SOF/VEL group.

Concomitant medication and DDI risk in the PWUD cohort

Concomitant medication use in the PWUD cohort is summarised in Table 2. A total of 2,888 active ingredients (AIs) were prescribed (mean 2.9 per patient), with SOF/VEL patients receiving nearly twice as many concomitant drugs as those on GLE/PIB. Cardiovascular (12%) and nervous system (40%) medications accounted for a substantial proportion of prescriptions. Hypertension was the most frequent comorbidity, renin-angiotensin inhibitors and diuretics were the main cardiovascular drugs (Figure 2), while psycholeptics and analgesics dominated nervous system prescriptions. Enalapril and quetiapine were the most common cardiovascular and antipsychotic agents, respectively.

Potential DDIs involving all prescribed AIs were more frequent in GLE/PIB than in SOF/VEL (15.2% vs 10.8%). The predicted severity of potential DDIs and associated clinical consequences are detailed in Table 3. Cardiovascular medications were particularly relevant in this regard: 22.7% were estimated to have DDIs in the overall population, with a higher proportion in GLE/PIB compared to SOF/VEL (13.7% vs 36.8%, $p<0.001$). Lipid-lowering agents and cardiac therapy medication had the highest potential interaction. Statins were a frequent source of clinically significant interactions in GLE/PIB, while interactions were less common in SOF/VEL. Renin-angiotensin inhibitors and eplerenone also showed clinically relevant risks in GLE/PIB.

AEs linked to comedications with potential DDIs by DAA

Adverse events (AEs) linked to potential DDIs in the PWUD cohort are detailed in Table 4. Five events were identified (two in SOF/VEL, three in GLE/PIB), most of which were associated with cardiovascular medications, particularly statins and renin–angiotensin system inhibitors. In the subgroup of renin–angiotensin system inhibitors, no AEs were reported with SOF/VEL, whereas GLE/PIB was associated with a respiratory adverse event requiring dose adjustment.

Lipid-lowering agents accounted for most of the remaining AEs. In patients treated with GLE/PIB, atorvastatin and simvastatin were associated with myalgia or myopathy, leading to discontinuation of either the statin or the antiviral. In the SOF/VEL group, statin-related AEs were less frequent and were managed with temporary cessation or clinical monitoring.

Antipsychotic cohort

Baseline characteristics

The antipsychotic cohort comprised HCV patients receiving antipsychotic medications, either as an adjunct to opioid substitution therapy or to manage mental illnesses. The median age was 53 years, although patients on GLE/PIB were slightly younger. Men represented 58.8% of the cohort, a lower proportion than in the PWUD cohort. Demographic and clinical characteristics are summarised in Table 5.

Metabolic comorbidities were common, including diabetes (20.9%), hypertension (19.8%), dyslipidaemia (19.3%), and obesity (17.1%). Depressive symptoms affected 13.4% of patients. Advanced fibrosis or cirrhosis was present in 44.4%. Drug use was also frequent (75%), predominantly cannabis (25.1%), sedatives–anxiolytics (21.4%), cocaine (14.4%), and alcohol (9.6%).

Concomitant medication and DDI risk

Concomitant medication pattern DDI risk of the PWUD cohort is shown in Table 6. A total of 963 AIs were prescribed (mean 5.1 per patient), with higher exposure in GLE/PIB compared to SOF/VEL (5.0 vs 5.9, $p<0.001$). Most patients (86.6%) received ≥2 AIs. Nervous system drugs accounted for 56.7% of prescriptions, with similar distribution across regimens (SOF/VEL: 58.4%; GLE/PIB: 50.7%). Psycholeptics, which include antipsychotics (quetiapine, paliperidone, olanzapine, aripiprazole, clotiapine, risperidone and clozapine), anxiolytics (diazepam, alprazolam and lorazepam) and sedative hypnotic agents (lormetazepam), were the most frequently prescribed (52.9%), followed by psychoanaleptics (15.4%), which include antidepressants and related agents (escitalopram and trazodone), analgesics (paracetamol, 14.7%) and antiepileptics (pregabalin, 11.7%). Analgesics were more common in GLE/PIB (19.1% vs 13.5%), while antiepileptics were more frequent in SOF/VEL (12.8% vs 7.3%). Quetiapine was the most commonly prescribed antipsychotic (Table 6).

Table 1

Demographic and clinical characteristics and concomitant medications of PWUD cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N, %	**985 (100%)**	**450 (45.7%)**	**535 (54.3%)**	***p*-value†**
Demographic characteristics				
Age in years; mean (SD)	51.6 (10.3)	53.3 (10.6)	50.2 (9.8)	<0.001
Median (P25-P75)	52 (45 - 58)	53 (46 - 59)	51 (44 - 57)	
Age groups, n (%)				
18 - 44 years	239 (24.3%)	86 (19.1%)	153 (28.6%)	
45 - 64 years	674 (68.4%)	316 (70.2%)	358 (66.9%)	
≥ 65 years	72 (7.3%)	48 (10.7%)	24 (4.5%)	<0.001
Gender (male)	641 (65.1%)	292 (64.9%)	349 (65.2%)	
Associated comorbidities, n (%)				
Arterial hypertension	151 (15.3%)	76 (16.9%)	75 (14%)	
Dyslipidaemia	114 (11.6%)	52 (11.6%)	62 (11.6%)	
Depressive syndrome	112 (11.4%)	61 (13.6%)	51 (9.5%)	0.048
Diabetes	92 (9.3%)	49 (10.9%)	43 (8%)	
Obesity	70 (7.1%)	35 (7.8%)	35 (6.5%)	
COPD	66 (6.7%)	34 (7.6%)	32 (6%)	
Asthma	62 (6.3%)	25 (5.6%)	37 (6.9%)	
Malignant neoplasms	40 (4.1%)	16 (3.6%)	24 (4.5%)	
Others‡	116 (11.8%)	78 (17.3%)	38 (7.1%)	
General comorbidity				
CCI; mean (SD)	0.9 (1.6)	1.2 (1.9)	0.7 (1.3)	<0.001
Hepatic-specific comorbidities n (%)				
Cirrhosis	52 (5.3%)	37 (8.2%)	15 (2.8%)	<0.001
Fibrosis prediction. FIB-4 score				<0.001
Without fibrosis (F0 - F1), <1.45 points	436 (44.3%)	178 (39.6%)	258 (48.2%)	
Intermediate (F2), 1.45 - 3.25 points	202 (20.5%)	84 (18.7%)	118 (22.1%)	
Fibrosis (F3 - F4), >3.25 points	347 (35.2%)	188 (41.8%)	159 (29.7%)	
Addictions, n (%)				
Cannabis	433 (44%)	198 (44%)	235 (43.9%)	
Sedatives-anxiolytics	276 (28%)	140 (31.1%)	136 (25.4%)	0.048
Cocaine	258 (26.2%)	116 (25.8%)	142 (26.5%)	
Chronic alcoholism	215 (21.8%)	110 (24.4%)	105 (19.6%)	
Heroin	157 (15.9%)	80 (17.8%)	77 (14.4%)	
Opioids	107 (10.9%)	60 (13.3%)	47 (8.8%)	0.022
Duration of treatment with DAA, in weeks: n (%)				
8 weeks	501 (50.9%)	0 (0.0%)	501 (93.6%)	
12 weeks	468 (47.5%)	445 (98.9%)	23 (4.3%)	
16 weeks	16 (1.6%)	5 (1.1%)	11 (2.1%)	

Note 1. † Only p-values <0.05 are shown. ‡ Others (Total n): peripheral arterial disease (33); ischemic heart disease (26); brain disease (25); renal insufficiency (20); heart failure (12).
Note 2. BMI = body mass index; CCI = Charlson Comorbidity Index; DAA = direct-acting antivirals; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; GLE/PIB = glecaprevir/pibrentasvir; HIV = Human immunodeficiency virus; P25-P75 = 25th percentile - 75th percentile; PWUD = People who use drugs; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Across therapeutic classes, potential DDIs were frequent between DAAs and nervous system comedications (12.8%), particularly psycholeptics (18.3%), analgesics (16.2%), and antiepileptics (6.2%). The proportion of nervous system prescriptions with potential DDIs was more than twice as high in GLE/PIB compared to SOF/VEL (22.7% vs 10.3%, $p<0.001$).

For antipsychotics, GLE/PIB showed a markedly higher DDI risk (51% vs 23%, $p< 0.001$) compared to SOF/VEL (Table 7); with quetiapine prescribed to only 14.2% of GLE/PIB patients, while 85.7% for SOF/VEL. Notably, all patients on GLE/PIB with quetiapine required clinical intervention (Figure 3).

AEs linked to comedications with potential DDIs by DAA

The AEs linked to potential DDIs in the antipsychotic cohort are summarised in Table 8. Two AEs were identified, both in the GLE/PIB group ($p=0.038$). One patient receiving quetiapine at <300 mg/day and GLE/PIB developed extrapyramidal symptoms that led to DAA discontinuation. No AEs were reported with quetiapine at any dose in the SOF/VEL group.

Table 2

Concomitant medication and number of potential interactions (DDIs) by number of comedications and therapeutic groups/subgroups involved in PWUD cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N (%)	**985 (100%)**	**450 (45.7%)**	**535 (54.3%)**	***p*-value†**
Concomitant medication				
Total number of prescribed medications (AI)	2.888	1.734	1.154	
Number of AI	625	337	288	
AI prescribed per patient, mean (SD)	2.9 (1.1)	3.9 (1.1)	2.1 (1.1)	<0.001
Patients with ≥ 2 AI, n (%)	749 (76%)	373 (82.9%)	376 (70.3%)	<0.001
According to % of total prescriptions and per group				
C - Cardiovascular system‡	348 (12.0%)	212 (12.2%)	136 (11.8%)	<0.001
C09 Renin-angiotensin agents	118 (33.9%)	64 (30.2%)	54 (39.7%)	
C03 Diuretics	66 (19.0%)	53 (25.0%)	13 (9.6%)	
C10 Lipid-lowering agents	55 (15.8%)	37 (17.5%)	18 (13.2%)	
C07 Beta blockers	55 (15.8%)	33 (15.6%)	22 (16.2%)	
C08 Calcium channel blockers	31 (8.9%)	18 (8.5%)	13 (9.6%)	
C01 Cardiac therapy	12 (3.4%)	4 (1.9%)	8 (5.9%)	
C02 Antihypertensives	11 (3.2%)	3 (1.4%)	8 (5.9%)	
N - Nervous system‡	1.152 (39.9%)	718 (41.4%)	434 (37.6%)	0.04
N05 Psycholeptics	500 (43.4%)	326 (45.4%)	174 (40.1%)	
N02 Analgesics	237 (20.6%)	143 (19.9%)	94 (21.7%)	
N06 Psychoanaleptics	203 (17.6%)	119 (16.6%)	84 (19.4%)	
N03 Antiepileptics	146 (12.7%)	96 (13.4%)	50 (11.5%)	
N07 Other nervous system drugs	66 (5.7%)	34 (4.7%)	32 (7.4%)	
According to main therapeutic group, (%)&				
C - Cardiovascular drugs				
Enalapril	43 (12.4%)	26 (12.3%)	17 (12.5%)	
Furosemide	28 (8.0%)	22 (10.4%)	6 (4.4%)	
Spironolactone	21 (6.0%)	20 (9.4%)	1 (0.7%)	
Bisoprolol	20 (5.7%)	11 (5.2%)	9 (6.6%)	
Propranolol	18 (5.2%)	15 (7.1%)	3 (2.2%)	
Amlodipine	18 (5.2%)	12 (5.7%)	6 (4.4%)	
N - Nervous system drugs				
Antipsychotics				
Quetiapine	39 (3.4%)	33 (4.6%)	6 (1.4%)	
Paliperidone	26 (2.3%)	22 (3.1%)	4 (0.9%)	
Others				
Alprazolam	118 (10.2%)	74 (10.3%)	44 (10.1%)	
Paracetamol	83 (7.2%)	52 (7.2%)	31 (7.1%)	
Diazepam	81 (7.0%)	47 (6.5%)	34 (7.8%)	
Potential drug-drug interactions, n (%)				
Patients with potential DDI	264 (26.8%)	149 (33.1%)	115 (21.5%)	<0.001
Total of active ingredients prescribed with potential DDI	363 (12.6%)	188 (10.8%)	175 (15.2%)	
Number of AI with potential DDI	68 (10.9%)	28 (8.3%)	40 (13.9%)	0.025
Patients with ≥ 2 comedications with potential DDI	68 (6.9%)	30 (6.7%)	38 (7.1%)	
DDIs by therapeutic groups (% relative to prescriptions per group and sub-group) &				
C - Cardiovascular comedication	79 (22.7%)	29 (13.7%)	50 (36.8%)	0.001
C10 Lipid-lowering agents	38 (69.1%)	23 (62.2%)	15 (83.3%)	
C01 Cardiac therapy	7 (58.3%)	2 (50.0%)	5 (62.5%)	
C09 Renin-angiotensin agents	23 (19.5%)	0	23 (42.6%)	
C02 Antihypertensives	2 (18.2%)	1 (33.3%)	1 (12.5%)	
C07 Beta blockers	7 (12.7%)	2 (6.1%)	5 (22.7%)	
C08 Calcium channel blockers	2 (6.5%)	1 (5.6%)	1 (7.7%)	
C03 Diuretics	2 (3.0%)	0	1 (7.7%)	

Note 1. † Only p-values <0.05 are shown. ‡ATC therapeutic group and sub-group (% of total prescriptions). & Percentage relative to the number of the therapeutic group.
Note 2. AI = active ingredient; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; PWUD = People who use drugs; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Table 3

Strength of potential DDIs and predicted clinical outcomes of patients in PWUD cohort

PWUD cohort: patients addicted to substances (cardiovascular comedication)		
Therapeutic Group / **DAA**	**SOF/VEL**	**GLE/PIB**
Patients with CV medication, *n*	**212**	**136**
Patients with CV DDIs, *n* (%)	**29 (13,7%)**	**50 (36,8%)***
Renin-angiotensin agents (n/N [%])	Enalapril (26/64 [40.6%])	↑ Enalapril (17/54 [31.5%])
	Irbesartan (0/64 [0%])	↑ Irbesartan (2/54 [3.7%])
	Olmesartan (2/64 [3.1%])	↑ Olmesartan (3/54 [5.6%])
	Telmisartan (2/64 [3.1%])	↑ Telmisartan (1/54 [1.9%])
Diuretics (n/N [%])	Eplerenone (1/53 [1.9%])	↑ Eplerenone (1/13 [7.7%])
Beta Blockers (n/N [%])	↑ Carvedilol (2/33 [6.1%])	↑↑ Carvedilol (5/22 [22.7%])
Lipid Lowering Agents (n/N [%])	↑ Atorvastatin (12/37 [32.4%])	↑ Atorvastatin (5/18 [27.8%])
	↑ Simvastatin (7/37 [18.9%])	↑ Simvastatin (4/18 [22.2%])
	Ezetimibe (2/37 [5.4%])	↑ Ezetimibe (1/18 [5.6%])
	Gemfibrozil (0/37 [0%])	↑↑ Gemfibrozil (1/18 [5.6%])
	Pitavastatin (0/37 [0%])	↑ Pitavastatin (2/18 [11.1%])
	Pravastatin (1/37 [2.7%])	↑ Pravastatin (1/18 [5.6%])
	↑ Rosuvastatin (3/37 [8.1%])	↑ Rosuvastatin (1/18 [5.6%])
	↓ Colestyramine (1/37 [2.7%])	Colestyramine (0/18 [0%])
Calcium Channel Blockers (n/N [%])	↑↑ Diltiazem (n=1/18 [5.6%])	↑ Diltiazem (1/13 [7.7%])
Cardiac therapy (n/N [%])	Amiodarone (0/4 [0%])	↑ Amiodarone (4/8 [50.0%])
	↑ Digoxin (2/4 [50.0%])	↑ Digoxin (1/8 [12.5%])
Antihypertensives (n/N [%])	↑ Prazosin (1/3 [33.3%])	↑ Prazosin (0/8 [0%])

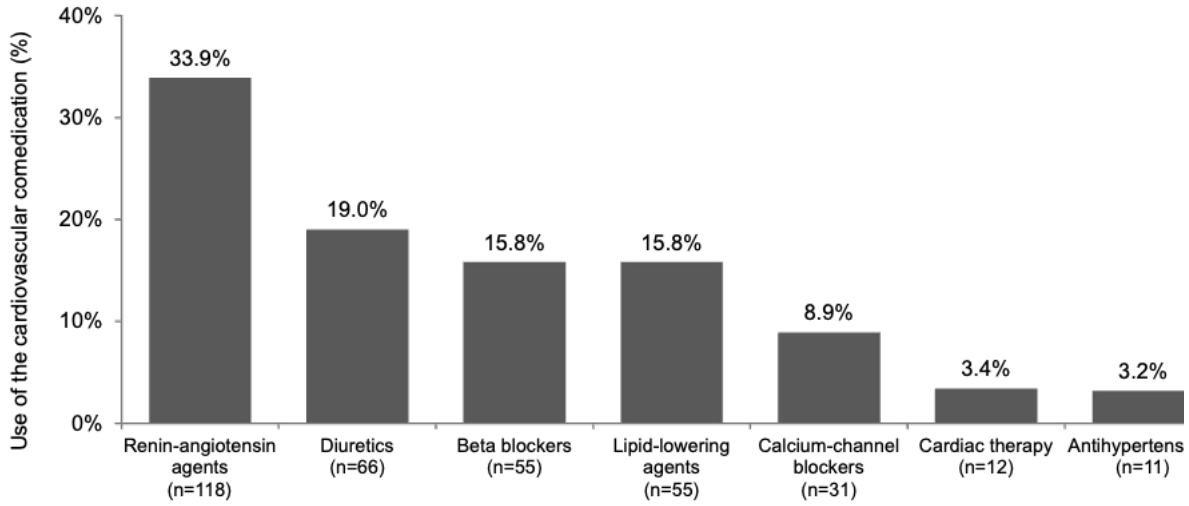
Strength of interaction

Contraindicated	**Significant interaction**	**Weak interaction**	**No interaction**

Note 1. *p <0.001.
Note 2. (↑) = increase in comedication. (↑↑) = increase in comedication + increase in DAA. (↓) = decrease in DAA. n = number of patients on treatment with the corresponding comedication within a therapeutic group (TG). (N) = total number of patients by TG. Percentages were estimated by dividing n (drug prescribed with DDI)/N (total prescribed DDI per subgroup).
Note 3. AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; PWUD = People who use drugs; SOF/VEL = sofosbuvir/velpatasvir.

Figure 2

Cardiovascular comedications prescribed to the PWUD cohort



Note 1. PWUD = People who use drugs.

Table 4

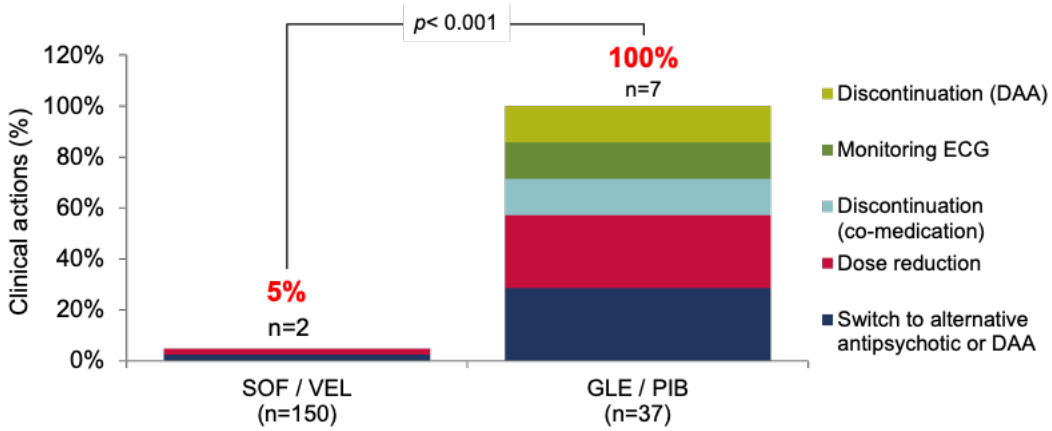
Adverse events (AE) linked to comedications with potential DDIs by DAA in PWUD cohort

AEs linked to cardiovascular medication with potential DDIs by DAA in PWUD cohort (*n*=985)		
DAA	SOF / VEL	GLE / PIB
Number of patients with CV medication, n	212	136
Number of patients with CV DDIs, n (%)	29 (13.7%)	50 (36.8%)*
Adverse Events reported, AE n (%)	2 (0.9%)	3 (2.2%)
Renin-angiotensin agents associated with AE		
Enalapril†	0% AE (0 AE/ 26), [Sin AA] *(No Action)*	5,9% (1 AE / 17), [Respiratory] *(Dose Reduction)*
Lipid Lowering agents		
Atorvastatin†	8.3% AE (1 AE/ 12), [Myalgia/myopathy] *(Statin discontinued)*	20% (1 AE/ 5),), [Myalgia/myopathy] *(DAA discontinued)‡*
Simvastatin†	14.3% (1 AE/ 7), [Myalgia/myopathy] *(Clinical monitoring)**	25% (1 AE/ 4),), [myalgia/myopathy] *(Statin discontinued)‡*

Note 1. * $p < 0.001$.
Note 2. † Results expressed as %AE (#AE/ patients), [AE description], (action required due to AE). ‡ New treatment with DAA was required within 6 months after the end of treatment with SOF/VEL or GLE/PIB, which was considered an indirect indicator of lack of efficacy of the DAA regimen.
Note 3. The colours green or orange represent the strength of interaction. % = The percentage of adverse events associated with medication was calculated by dividing the number of patients with AE between the total patients treated with the corresponding medication by DAA group.
Note 4. AE = adverse events; AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions GLE/PIB = glecaprevir/pibrentasvir; n = number; PWUD = People who use drugs; SOF/VEL = sofosbuvir/velpatasvir.

Figure 3

Clinical actions reported in patients of the antipsychotic cohort prescribed quetiapine



DAA	SOF/VEL	GLE/PIB	*p*-value
Total patients taking quetiapine, N (%)	42 (100%)	7 (100%)	
Total clinical actions in patients taking quetiapine, N (%)	2 (4.8%)	7 (100%)	<0.001
<300 mg quetiapine	0	5 (71.4%)	
>300 mg quetiapine	2 (100%)	2 (28.6%)	

Note 1. DAA = direct-acting antivirals DDI = direct-drug interaction; ECG = electrocardiogram; GLE/PIB = glecaprevir/pibrentasvir; SOF/VEL = sofosbuvir/velpatasvir.

Table 5

Demographic and clinical characteristics and concomitant medication in the antipsychotic cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N, %	**187 (100%)**	**150 (80.2%)**	**37 (19.8%)**	***p*-value[†]**
Demographic characteristics				
Age in years; mean (SD)	52 (10.8)	52.5 (9.4)	50.1 (15.3)	
Median (P25-P75)	53 (46 - 57)	53 (46 - 56)	48 (36 - 61)	
Age groups, n (%)				
18 - 44 years	44 (23.5%)	28 (18.7)	16 (43.2%)	
45 - 64 years	125 (66.8%)	110 (73.3)	15 (40.5%)	
≥ 65 years	18 (9.6%)	12 (8.0%)	6 (16.2%)	0.001
Gender (male)	110 (58.8%)	88 (58.7%)	22 (59.5%)	
Associated comorbidities (Top 6), n (%)				
Diabetes	39 (20.9%)	31 (20.7%)	8 (21.6%)	
Arterial hypertension	37 (19.8%)	30 (20%)	7 (18.9%)	
Dyslipidaemia	36 (19.3%)	29 (19.3%)	7 (18.9%)	
Obesity	32 (17.1%)	26 (17.3%)	6 (16.2%)	
Depressive syndrome	25 (13.4%)	20 (13.3%)	5 (13.5%)	
COPD	18 (9.6%)	15 (10.0%)	3 (8.1%)	
Others [‡]				
CCI, mean (SD)	1.0 (1.0)	1.0 (1.1)	0.9 (0.9)	
Specific comorbidities, n (%)				
Cirrhosis	10 (5.3%)	8 (5.3%)	2 (5.4%)	
Fibrosis prediction. FIB-4 score				
Without fibrosis (F0 - F1), <1.45 points	64 (34.2%)	49 (32.7%)	15 (40.5%)	
Intermediate (F2), 1.45 - 3.25 points	40 (21.4%)	35 (23.3%)	5 (13.5%)	
Fibrosis (F3 - F4), >3.25 points	83 (44.4%)	66 (44.0%)	17 (45.9%)	
Addictions				
Chronic alcoholism	18 (9.6%)	14 (9.3%)	4 (10.8%)	
Opioids	13 (7.0%)	10 (6.7%)	3 (8.1%)	
Sedatives-anxiolytics	40 (21.4%)	32 (21.3%)	8 (21.6%)	
Cannabis	47 (25.1%)	38 (25.3%)	9 (24.3%)	
Cocaine	27 (14.4%)	22 (14.7%)	5 (13.5%)	
Heroin	15 (8.0%)	12 (8.0%)	3 (8.1%)	
Duration of treatment with DAA, in weeks: n (%)				
8 weeks	30 (16.0%)	0 (0.0%)	30 (81.1%)	
12 weeks	155 (82.9%)	149 (99.3%)	6 (16.2%)	
16 weeks	2 (1.14%)	1 (0.7%)	1 (2.7%)	

Note 1. [†] Only *p*-values <0.05 are shown. [‡] Others (Total n) = renal insufficiency (9); brain disease (8); heart failure (8); asthma (8); peripheral arterial disease (6); malignant neoplasms (5); ischemic heart disease (4).
Note 2. BMI = body mass index; CCI = Charlson Comorbidity Index; DAA = direct-acting antivirals; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; GLE/PIB = glecaprevir/pibrentasvir; HIV = Human immunodeficiency virus; P25-P75 = 25th percentile - 75th percentile; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Table 6

Concomitant medication, number of potential interactions (DDIs) by number of comedications and therapeutic groups/subgroups involved in the antipsychotic cohort

DAA group	**Total**	**SOF/VEL**	**GLE/PIB**	
N (%)	**187 (100%)**	**150 (80.2%)**	**37 (19.8%)**	***p*-value[†]**
Concomitant medication				
Total active ingredients prescribed (%)	963	746	217	
Number of AI	337	217	120	
Active ingredients prescribed: Mean (SD)	5.1 (1.2)	5.0 (1.2)	5.9 (1.2)	**<0.001**
Patients with ≥ 2 active ingredients (%)	162 (86.6%)	130 (86.7%)	32 (86.5%)	**0.98**
Concomitant medication (% of total prescriptions and per group)				
C - Cardiovascular system[‡]	81 (8.4%)	59 (7.9%)	22 (10.1%)	**0.30**
C09 Renin-angiotensin agents	27 (33.3%)	20 (33.9%)	7 (31.8%)	
C03 Diuretics	17 (21.0%)	13 (22.0%)	4 (18.2%)	
C10 Lipid lowering agents	11 (13.6%)	9 (15.3%)	2 (9.1%)	
C07 Beta blockers	11 (13.6%)	9 (15.3%)	2 (9.1%)	
C08 Calcium channel blockers	8 (9.9%)	6 (10.2%)	2 (9.1%)	
C01 Cardiac therapy	4 (4.9%)	1 (1.7%)	3 (13.6%)	
C02 Antihypertensives	3 (3.7%)	1 (1.7%)	2 (9.1%)	
N - Nervous system[‡]	546 (56.7%)	436 (58.4%)	110 (50.7%)	**0.04**
N05 Psycholeptics	289 (52.9%)	230 (52.8%)	59 (53.6%)	
N06 Psychoanaleptics	84 (15.4%)	68 (15.6%)	16 (14.5%)	
N02 Analgesics	80 (14.7%)	59 (13.5%)	21 (19.1%)	
N03 Antiepileptics	64 (11.7%)	56 (12.8%)	8 (7.3%)	
N07 Other nervous system drugs	29 (5.3%)	23 (5.3%)	6 (5.5%)	
Main concomitant medication by the main therapeutic group, (%) [&]				
N: Nervous system drugs				
Antipsychotics				
Quetiapine	49 (9.0%)	42 (9.6%)	7 (6.4%)	
Paliperidone	33 (6.0%)	28 (6.4%)	5 (4.5%)	
Olanzapine	32 (5.9%)	26 (6.0%)	6 (5.5%)	
Aripiprazol	14 (2.6%)	11 (2.5%)	3 (2.7%)	
Risperidone	9 (1.6%)	6 (1.4%)	3 (2.7%)	
Clozapine	3 (0.5%)	3 (0.7%)	0 (0.0%)	
Potential drug interactions, n (%)				
Patients with potential DDI	92 (49.2%)	65 (43.3%)	27 (73%)	**0.001**
Total of AI prescribed with potential DDI	141 (14.6%)	95 (12.7%)	46 (21.2%)	**0.001**
Number of AI with potential DDI	40 (11.9%)	18 (8.3%)	22 (18.3%)	**<0.001**
Patients with ≥ 2 comedications with DDI potentials	32 (17.1%)	23 (15.3%)	9 (24.3%)	
DDIs by therapeutic groups (% relative to prescriptions per group and sub-group)				
N - Nervous system	70 (12.8%)	45 (10.3%)	25 (22.7%)	**<0.001**
N05 Psycholeptics	53 (18.3%)	34 (14.7%)	19 (32.2%)	**0.002**
N02 Analgesics	13 (16.2%)	8 (13.6%)	5 (23.8%)	
N03 Antiepileptics	4 (6.2%)	3 (5.4%)	1 (12.5%)	

Note 1. [†] Only p-values <0.05 are shown. ǂ ATC therapeutic group and sub-group (% of total prescriptions). & Percentage relative to the number of the therapeutic group.
Note 2. AI = active ingredient; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; SD = standard deviation; SOF/VEL = sofosbuvir/velpatasvir.

Table 7

Strength of potential DDIs and predicted clinical outcomes in the antipsychotic cohort

Antipsychotic cohort: Patients treated with antipsychotics (AP)		
Therapeutic Group / **DAA (*n*)**	**SOF/VEL (150)**	**GLE/PIB (37)**
No Patients with AP DDIs, n (%)	**34 (23%)**	**19 (51%)***
Antipsychotics (n/N [%])	Quetiapine (42/150 [28.0%])	↑ Quetiapine (7/37 [18.9%])
	↑ Paliperidone (28/150 [18.7%])	↑ Paliperidone (5/37 [13.5%])
	Aripiprazole (11/150 [7.3%])	↑ Aripiprazole (3/37 [8.1%])
	Clotiapine (9/150 [6.0%])	↑ Clotiapine (1/37 [2.7%])
	↑ Risperidone (6/150 [4.0%])	↑ Risperidone (3/37 [8.1%])
	Clozapine (3/150 [2.0%])	↑ Clozapine (0/37 [0%])

Strength of interaction

Contraindicated	**Significant interaction**	**Weak interaction**	**No interaction**

Note 1. *p <0,001.
Note 2. (↑) = increase in comedication. (↓) = decrease in DAA. n = number of patients on treatment with the corresponding comedication within a therapeutic group (TG). (N) = total number of patients by TG. Percentages were estimated by dividing n (drug prescribed with DDI)/N (total prescribed DDI per subgroup).
Note 3. AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions; GLE/PIB = glecaprevir/pibrentasvir; SOF/VEL = sofosbuvir/velpatasvir.

Table 8

Adverse events (AE) linked to comedications with potential DDIs by DAA in the antipsychotic cohort

AEs linked to antipsychotics with potential DDIs by DAA in antipsychotic cohort (n=187)		
DAA	**SOF / VEL**	**GLE / PIB**
Number of patients with AP medication, n	150	37
Number of patients with AP DDIs, n (%)	34 (23%)	19 (51%)*
Adverse Events reported, AE, n (%)	0	2 (5.4%)**
Antipsychotics associated with AE		
Quetiapine†&	0% AE (0 AE/ 42);); [No AE] *(No Action)*	14% (1AE / 7); [Extrapyramidal] *(DAA discontinued)*
Paliperidone†	0% AE (0 AE/ 28) [No AE] *(No Action)*	20% (1 AE/ 5); [Sedation] *(Dose Reduction)*

Note 1. * p <0.001; ** p = 0.038.
Note 2. † Results expressed as %AE (#AE/ patients), [AE description], (action required due to AE). ‡New treatment with DAA was required within 6 months after the end of treatment with SOF/VEL or GLE/PIB, which was considered an indirect indicator of lack of efficacy of the DAA regimen. & The dose of quetiapine was <300 mg/day.
The colours green or orange represent the strength of interaction. % = The percentage of adverse events associated with medication was calculated by dividing the number of patients with AE between the total patients treated with the corresponding medication by DAA group.
Note 3. AE = adverse events; AP = antipsychotic; CV = cardiovascular; DAA = direct-acting antivirals; DDI = drug-drug interactions GLE/PIB = glecaprevir/pibrentasvir; n = number; SOF/VEL = sofosbuvir/velpatasvir.

Paliperidone was prescribed more frequently in the SOF/VEL group, with no associated AEs. In contrast, in the GLE/PIB group, paliperidone use was associated with sedation in 20% of cases, requiring a dose reduction. Although other antipsychotics showed significant or weak interaction potential, no AEs were reported, and no clinical actions were needed.

Clinical actions reported in patients prescribed quetiapine at the prescribed dose

Clinical actions included dose adjustments, switching to an alternative antipsychotic, modifying the DAA regimen, or temporarily interrupting treatment, depending on the nature and severity of the predicted DDI. There were 49 patients treated with quetiapine, the majority with SOF/VEL (85.7% vs 14.2%). The study evaluated the need for clinical interventions for quetiapine dosages below and above 300 mg/day when combined with DAA regimens

(Figure 3). All patients on GLE/PIB taking quetiapine at doses of ≤300 mg /day or >300 mg/day required clinical actions. For SOF/VEL, no interventions were needed at quetiapine doses ≤300 mg, and interventions were necessary for only two patients at higher doses.

Discussion

To our knowledge, this is the first study to examine potential DDIs associated with pangenotypic DAAs specifically in Spanish patients with chronic HCV infection who either use drugs or receive antipsychotic treatments, using real-world data. The findings indicate that DDI risk is particularly relevant in these two vulnerable groups, and that GLE/PIB is associated with a higher frequency of potential interactions and related clinical actions than SOF/VEL.

DDIs in PWUD

Consistent with studies from Germany and Italy (Hintz et al., 2021; Nava et al., 2023) PWUD in our cohort exhibited a complex multimorbidity profile and substantial exposure to polypharmacy, particularly involving cardiovascular therapies. Hypertension and dyslipidaemia were the most frequent comorbidities, reflecting a clinically vulnerable population in which the risk of DDIs is an important therapeutic consideration (Nava et al., 2023). Use of nervous system medications was also common, with approximately 40% of PWUD receiving ATC class N agents, closely mirroring proportions reported in German cohorts (Hintz et al., 2021).

Patients treated with SOF/VEL were generally older, had more comorbidities and higher CCI scores, and were exposed to a broader range of comedications than those treated with GLE/PIB. Despite this greater polypharmacy, potential DDIs were more frequently identified among GLE/PIB recipients, consistent with the interaction profile of protease inhibitor–based regimens (Hintz et al., 2021). This pattern suggests that DDI risk in PWUD is driven primarily by the pharmacological properties of the antiviral agent rather than by the overall number of concomitant medications.

Statins were a frequent source of interaction risk. Atorvastatin and simvastatin, which are contraindicated for co-administration with GLE/PIB, were still prescribed in some patients and were associated with clinically significant DDIs. These findings highlight gaps in real-world medication optimisation and underline the need for systematic review of concomitant therapies. Consistent with previous Spanish evidence, patients on GLE/PIB showed a higher proportion of clinically relevant cardiovascular and nervous system interactions (Turnes et al., 2024).

Overall, these observations support the preferential use of regimens with fewer interaction risks, such as SOF/VEL, in PWUD with complex clinical and therapeutic profiles. They also reinforce the importance of multidisciplinary medication assessment at treatment initiation.

Patients receiving antipsychotic treatment

Patients on antipsychotics were typically receiving more than five concomitant active ingredients, and approximately half of them presented potential DDIs, which is consistent with previous evidence showing high levels of polypharmacy and frequent psychotropic DDIs in psychiatric populations (Pinkoh et al., 2023). SOF/VEL was more frequently prescribed in these patients, which is consistent with its favourable interaction profile and its suitability for individuals with multiple comorbidities (Fagiuoli et al., 2023; Hintz et al., 2021). In contrast, GLE/PIB was associated with a higher proportion of clinically significant interactions that required therapeutic actions, particularly in patients treated with quetiapine or paliperidone. These observations align with the expected DDI profile of protease inhibitor-based regimens and underline the importance of selecting antiviral therapy according to the patient's psychiatric and comedication burden.

Overall, these findings highlight the need for close coordination between hepatology, psychiatry, and pharmacy services when treating HCV in patients receiving antipsychotics. A careful review of psychotropic medication at the time of DAA initiation may help anticipate interactions and reduce the risk of avoidable adverse events. These findings may also inform future updates of clinical practice guidelines and contribute to public health strategies aimed at enhancing HCV micro-elimination in vulnerable populations.

Limitations

This study has several limitations. First, the clinical overlap between antipsychotic use and drug use makes it difficult to separate the contribution of each factor to the observed DDIs. Second, the Liverpool interaction checker does not consider the cumulative effects of multidrug regimens or combinations with overlapping toxicity profiles, which are common in patients receiving psychotropic medication or opioid substitution therapies (Andersen et al., 2021; Davidson et al., 2022). Third, the retrospective design may lead to incomplete recording of diagnoses, prescriptions, or adverse events, and documentation practices may differ between healthcare centres (Gonzalez-Colominas et al., 2023). These limitations are unlikely to have affected the comparison between DAA groups, but they should be considered when interpreting the results. Additionally, a potential prescription bias should also be acknowledged, as patients receiving SOF/VEL presented a higher burden of comorbidities and polypharmacy, which may have influenced clinicians' preference for this regimen and partially contributed to the differences observed between treatment groups. On the other hand, the BIG-

PAC database only includes information from the Spanish National Health System; therefore, treatments prescribed in private healthcare were not captured. Finally, the interaction assessment was based on the November 2022 version of the Liverpool tool, and subsequent updates may modify the predicted relevance of some DDIs.

Despite the limitations in this study, our findings suggest that, in real clinical practice in Spain, HCV patients treated with antipsychotics and those addicted to substances have a high risk of potential DDIs, particularly if treated with GLE/PIB. Potential interactions between DAAs and comedications require a comprehensive approach to their clinical follow-up to optimise their treatment and improve their safety by choosing the available DAA with less potential DDIs.

Conclusion

Our findings indicate that HCV patients who use drugs or antipsychotic treatment face a high risk of potential DDIs, particularly with GLE/PIB. These interactions may compromise treatment safety, requiring close clinical monitoring and therapy adjustments. Given the high prevalence of comorbidities and polypharmacy in these patients, optimising DAA selection is crucial. SOF/VEL appears to have a more favourable safety profile in this context. A multidisciplinary approach, integrating pharmacists and clinicians, is essential to minimise risks and ensure effective treatment. Future prospective studies should validate these findings and explore strategies to mitigate DDIs, including AI-driven tools for early detection and personalised treatment optimisation. Given the high level of polypharmacy observed in both cohorts, the participation of clinical pharmacists is crucial for optimising treatment, identifying potential DDIs at baseline, and reducing avoidable adverse events during antiviral therapy.

Institutional Review Board Statement

The study was approved by the Research Ethics Committee of Consorci Sanitari de Terrassa, Barcelona, Spain.

Informed Consent Statement

Patient consent was not necessary, according to Article 5 of Royal Decree 957/2020, of November 3rd, which regulates observational studies with medicines for human use (MINISTERIO DE SANIDAD, 2020).

Data Availability Statement

The data supporting this study are based on patient records, and no link is available; the info is aggregated upon study request. The data supporting this study's findings is not available due to the nature of the data (from patients belonging to the National Health System).

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Author Contributions

Ignacio Hernández, Cándido Hernández and Marinela Méndez conceived the study. Ignacio Hernández, Cándido Hernández and Marinela Méndez participated in and contributed to its design. Ignacio Hernández collected data and performed statistical analysis. Alfonsina Trento wrote the first draft. Juan Turnes, Antonio García-Herola, Marinela Méndez, Cándido Hernández, Alfonsina Trento, Ramón Morillo-Verdugo, Francisco Pascual and Ignacio Hernandez interpreted the results and critically reviewed and approved the final version of the manuscript.

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Conflicts of Interest

Authors have received funding not conditional on results for their participation as Speaker/consultant/research: Juan Turnes (AbbVie, Gilead Sciences, MSD), Antonio García-Herola (AbbVie, Gilead Sciences), Ramón Morillo-Verdugo (AbbVie, Gilead Sciences, Janssen, MSD, ViiV Healthcare), Francisco Pascual (Gilead). Cándido Hernández and Marinela Méndez are employees of Gilead Sciences, Spain. Ignacio Hernández and Alfonsina Trento are employees of Atrys Health, a contract research organisation that received funds from Gilead to conduct this study. The sponsor, including both the pharmaceutical company and its local affiliate, had no role in the data analysis or interpretation. The authors retained full editorial control and responsibility for the final content.

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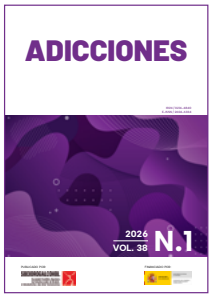
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ORIGINAL

Emotion regulation strategies mediate the relationship between excessive alcohol use and suicidal behaviour

Las estrategias de regulación emocional median en la relación entre el consumo excesivo de alcohol y la conducta suicida

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Abstract

Alcohol is one of the most widely consumed substances worldwide. It is hypothesized that people who use alcohol have poor emotional regulation strategies, something shared by individuals who have engaged in suicidal behaviour or those who have died by suicide. Therefore, the aim of this work is to study the mediational effect of coping strategies and distress tolerance in the relationship between excessive alcohol use and suicidal risk. A sample of 1014 participants (33.82% male, 66.17% female; M = 33.0, SD = 15.15) were assessed using a custom sociodemographic questionnaire, the Alcohol Use Disorders Identification Test (AUDIT), the Coping with Stress Questionnaire (CSQ), *Distress Tolerance Stress (DTS),* and Suicide Risk (RS). Two mediation models were performed in which AUDIT scores were used as the independent variable, RS score as the dependent and sex as a covariate. In the first model the mediating variable was the CSQ scores and in the second the DTS scores. The relationship was mediated positively by Negative Auto-Focused, Appraisal and Absorption, and negatively by Tolerance. Emotional regulation is a transdiagnostic strategy that can reduce not only alcohol consumption, but also suicidal risk. Given these results, there is a pressing need to develop preventive programs centered on adaptive emotion regulation strategies. Emotional regulation plays a key role in the relationship between excessive alcohol use and suicidal risk.

Keywords: alcohol, suicide, emotion regulation, tolerance of distress, coping skills

Resumen

El alcohol es una de las sustancias más consumidas en todo el mundo. Se hipotetiza que las personas que consumen alcohol tienen pobres estrategias de regulación emocional, algo que comparten las personas que se suicidan. Por ello, el objetivo de este trabajo es estudiar el efecto mediacional de las estrategias de afrontamiento y la tolerancia a la angustia en la relación entre el consumo excesivo de alcohol y el riesgo suicida. En una muestra de 1014 participantes (33,82% hombres, 66,17% mujeres; M = 33,0, DE = 15,15) se aplicó un cuestionario sociodemográfico personalizado, el Test de Identificación de Trastornos por Consumo de Alcohol (AUDIT), el Cuestionario de Afrontamiento del Estrés (CSQ), la escala de Tolerancia al Distrés (DTS) y el de Riesgo Suicida (RS). Se realizaron dos modelos de mediación en los que se utilizaron las puntuaciones del AUDIT como variable independiente, la puntuación del RS como dependiente y el sexo como covariable. En el primer modelo la variable mediadora fueron las puntuaciones CSQ y en el segundo las puntuaciones DTS. La relación fue mediada positivamente por Autoenfoque Negativo, Valoración y Absorción, y negativamente por la Tolerancia. La regulación emocional es una estrategia transdiagnóstica que puede reducir no sólo el consumo de alcohol, sino también el riesgo suicida. Dados estos resultados, existe una necesidad imperiosa de desarrollar programas preventivos centrados en estrategias adaptativas de regulación emocional. La regulación emocional juega un papel clave en la relación entre el consumo excesivo de alcohol y el riesgo suicida.

Palabras clave: alcohol, suicidio, regulación emocional, tolerancia a la angustia, habilidades de afrontamiento

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Alcohol is one of the most widely consumed psychoactive substances worldwide. A cross-sectional study found that the average lifetime prevalence of alcohol consumption across countries surveyed by the World Health Organization (WHO) was 80% (Glantz et al., 2020). In Spain, alcohol remains the most commonly used psychoactive substance, with a prevalence of 76.5% by 2024, slightly higher in males (Spanish Ministry of Health, 2025). The widespread consumption of alcohol carries significant social and health problems (Rehm et al., 2017). Regarding social problems, heavy drinking has been linked to interpersonal difficulties, with studies showing that excessive alcohol use is significantly associated with problems in peer relationships (Fletcher, 2019) and a feeling of loneliness (Waesche et al., 2016). Moving on to health problems, alcohol use is associated with several diagnoses (Griswold et al., 2018; Rehm et al., 2017), and global morbidity and mortality, accounting for approximately three million deaths annually (Kranzler & Soyka, 2018; WHO, 2019), being the leading cause of death among individuals with substance use disorders (Wilcox et al., 2004) and found that 33% of suicide victims tested positive for alcohol, with 63% meeting criteria for alcohol intoxication based on blood alcohol levels (Krug et al., 2002).

Suicide is a complex and multifactorial phenomenon that affects everyone and kills one person every 40 seconds (WHO, 2021), so there are several theories to understand and reduce it. One of them is the Interpersonal Theory of Suicide (Joiner, 2005; Van Orden et al., 2010) which suggests that suicidal behavior arises from the interaction of thwarted belongingness, perceived burdensomeness, and the capability for suicide. Thwarted belongingness refers to feelings of social disconnection and isolation, while perceived burdensomeness involves the belief that one is a liability to others and that one's death would be more beneficial than one's existence. When both factors are present, suicidal ideation may develop. However, an individual must also acquire the capability for suicide—through repeated exposure to painful or provocative experiences, such as self-harm or substance use—to overcome the natural fear of death and act on their suicidal thoughts. Therefore, emotional regulation is an essential axis in this theory.

However, as recent research has emphasized, suicidal behaviour cannot be fully understood through linear or exclusively individual models of risk. The field has progressively shifted toward developmental, psychosocial, and contextual perspectives that integrate emotional, cognitive, and environmental determinants (Al-Halabí & Fonseca-Pedrero, 2024). These approaches highlight that suicidal behaviour emerges from the dynamic interaction between personal vulnerabilities and social contexts—such as isolation, stigma, or socioeconomic stressors—that shape individual distress and coping responses.

In this broader framework, addictive and suicidal behaviours are understood as interconnected processes that share common underlying mechanisms—particularly emotional dysregulation, impulsivity, and maladaptive coping—which mutually reinforce one another (Fonseca-Pedrero & Al-Halabí, 2024). Empirical evidence in Spanish adolescents supports this interaction: alcohol consumption has been linked to self-injurious, pointing to developmental pathways where substance use both reflects and exacerbates emotional distress (Bousoño et al., 2021). Moreover, individuals who present with self-harm have a very elevated risk of suicide (Hawton et al., 2015).

Within more integrative theoretical frameworks, Rory O'Connor's Integrated Motivational–Volitional (IMV) model underscores that the transition from suicidal thinking to action is moderated by volitional factors such as impulsivity, exposure to self-harm, and planning capacity, rather than being solely the result of static risk factors (O'Connor & Kirtley, 2018). There are several ways to prevent suicide behaviour and, despite of Hawton et al. (2024) also highlights that restricting access to lethal means remains among the most effective population-level suicide prevention measures, not always is posible.

Another way is improving emotion regulation. Emotion regulation has been conceptualized as processes through which individuals modulate their emotions consciously and nonconsciously (Rottenberg et al., 2005). Thus, can be divided into maladaptive or adaptive depending on the damage to our health. Maladaptive strategies may include behaviours aimed at regulating emotional distress, such as excessive alcohol consumption or suicidal behaviour. For example, individuals who struggle with regulating negative emotions may use alcohol as a maladaptive coping mechanism to alleviate distress (Aldao et al., 2010) and, when they cannot tolerate higher levels, increase the risk of suicide (Vujanovic et al., 2017). Conversely, adaptative emotion regulation strategies can mitigate the harmful effects of excessive alcohol use by reducing impulsive reactions to distressing situations and reducing suicidal behaviour. Emotional regulation encompasses different strategies, such as coping-strategies or distress tolerance. Thus, while coping-strategies are strategies used to manage stressors and unpleasant emotions (Romero et al., 2020), distress tolerance is a metaemotional construct that refers to the ability to withstand and manage negative psychological states associated with stress (Melli et al., 2021). However, both are emotional regulation strategies and with an improvement of these adaptative strategies, suicidal behaviour could be reduced.

From a clinical and preventive perspective, strengthening adaptive emotional regulation processes has been proposed as a key pathway to mitigate both substance misuse and

suicidality. According to Al-Halabí & Fonseca-Pedrero, (2023) y Fonseca-Pedrero & Al-Halabí (2024), effective interventions should not only address individual symptoms but also humanize care and integrate social determinants—such as connection, meaning, and equity—into prevention and treatment programs.

The present work aims to study the possible mediating effect of emotional regulation (coping-strategies and tolerance of distress) on the relationship between excessive use of alcohol and the risk of suicide.

Methods

Sample and procedure

This study employed a cross-sectional observational design. Data collection took place between August 2022 and September 2023 using an online methodology via the SurveyMonkey platform. On average, participants required approximately 30 minutes to complete the assessment. The only exclusion criterion was being under 18 years of age. The study was reviewed and approved by the Research Ethics Committee of the Principality of Asturias under the number 2022.193, ensuring adherence to ethical standards and research integrity.

Over the 13-month data collection period, a total of 1,763 individuals initiated the survey; however, only 1,014 participants (57.7% of the total sample) completed it in its entirety. Incomplete responses were excluded from the final analysis. The final sample comprised 1,014 individuals, with 33.82% identifying as male and 66.17% as female. Participants' ages ranged from 18 to 75 years (M = 33.0, SD = 15.15). Further details regarding sample characteristics are presented in Table 1.

Table 1

Sociodemographic characteristics of the sample

	Sample (n = 1014)	
	n	**%**
Sex		
Male	343	33.83
Female	671	66.17
Age		
18-25 years	546	53.85
26-39 years	164	16.17
40-59 years	265	26.13
60+ years	39	3.85
Marital status		
Single	343	33.83
Married	312	30.77
Divorced	183	18.05
Unmarried couple	161	15.88
Widower	15	1.48
Educational Level		
Basic education	184	18.15
Secondary education	184	18.15
Bachelor's Degree	423	41.72
University studies	223	21.99
Socioeconomic level		
Low	136	13.41
Medium	618	60.95
Medium-high	254	25.05
High	6	0.59

Instruments

Ad-hoc sociodemographic questionnaire. the ad-hoc sociodemographic questionnaire designed for this study comprises a series of key questions that seek to collect comprehensive information on various social and demographic aspects of the participants' lives. Categories assessed include age, gender, marital status, presence of family history of mental health problems, and socioeconomic status.

Alcohol Use Disorders Identification Test (AUDIT) (Pérula de Torres et al., 2005; Saunders et al., 1993) is a self-administered instrument developed by the World Health Organization, providing classifications of alcohol consumption and dependence. The internal consistency was acceptable (a = 0.78).

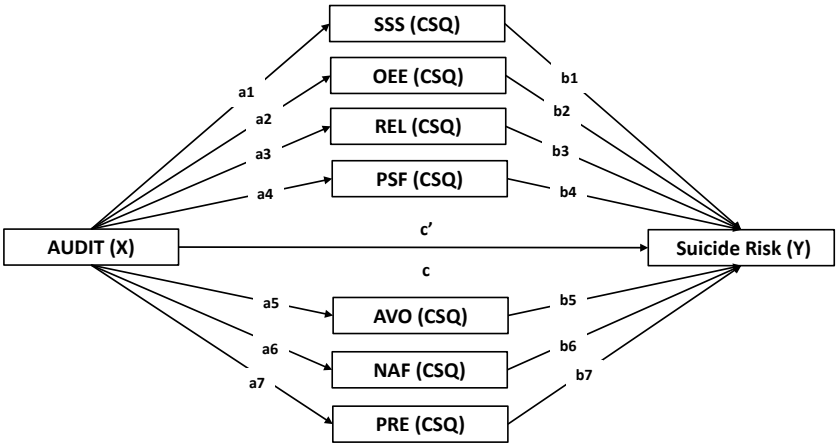
The Coping with Stress Questionnaire (CSQ) (Sandín & Chorot, 2003) is a 42-item self-report measure that assesses various forms of coping with stress. It consists of seven dimensions: focus on problem solving (FSP), positive reappraisal (PRE), seeking social support (SSS), negative self-focus (NAF), open emotional expression (OEE), avoidance (AVO) and religion (REL). A higher score on each of the scales indicates a higher use of that strategy. Internal consistency was good for the scales (α=.72-.90).

The *Distress Tolerance Stress (DTS)* (Simons & Gaher, 2005; Spanish validation: Sandín et al., 2017) is a 15-item self-report scale that assesses an individual's ability to tolerate stress. It is composed of 4 subscales: tolerance of distressing emotions (TOL), rating of experienced ability and distress (APP), absorption in one's own negative emotions (ABS) and ability to regulate emotions (REG). Participants rate these items on a 5-point Likert anchor scale (1=strongly disagree; 5=strongly agree). The DTS is scored by calculating the mean score for each of the four subscales and a higher score indicates a greater ability to tolerate distress. The DTS demonstrated good internal consistency across the sample for the different subscales (α=.81-.89).

Risk of Suicide (RS) Scale (Plutchik & Van Praag, 1989; Spanish validation: Rubio et al., 1998). . It is a self-administered instrument that provide a score that indicate risk of suicide The scale offers the possibility of

Figure 1

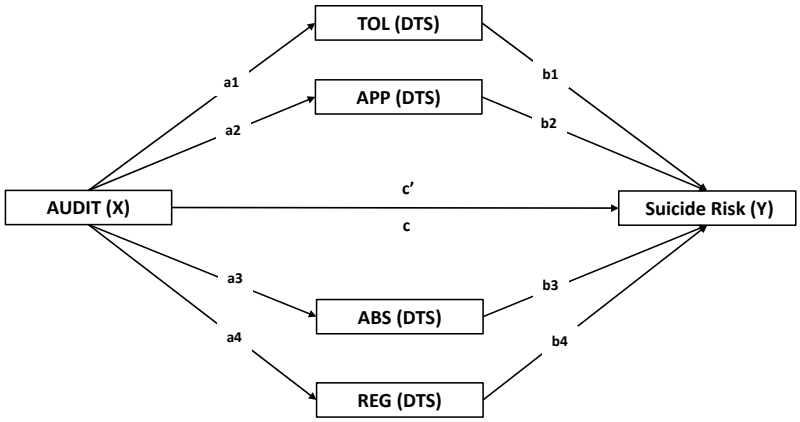
Hypothetical mediation model with CSQ



Note. CSQ: Coping Questionnaire Stress; SSS: seeking social support; OEE: open emotional expression; REL: religion; PSF: problem-solving focus; AVO: avoidance; NAF: negative self-focus; PRE: positive reappraisal. Gender as entered as covariate.

Figure 2

Hypothetical mediation model with DTS



Note. DTS: Distress Tolerance Stress; TOL: tolerance; VAL: valence; APP: appraisal; REG: emotion regulation. Gender as entered as covariate.

answering "yes" or "no" to 15 questions. Each affirmative answer is scored as 1 point indicating a higher final score, a higher suicidal risk. The internal consistency was good (a = 0.82).

Analysis

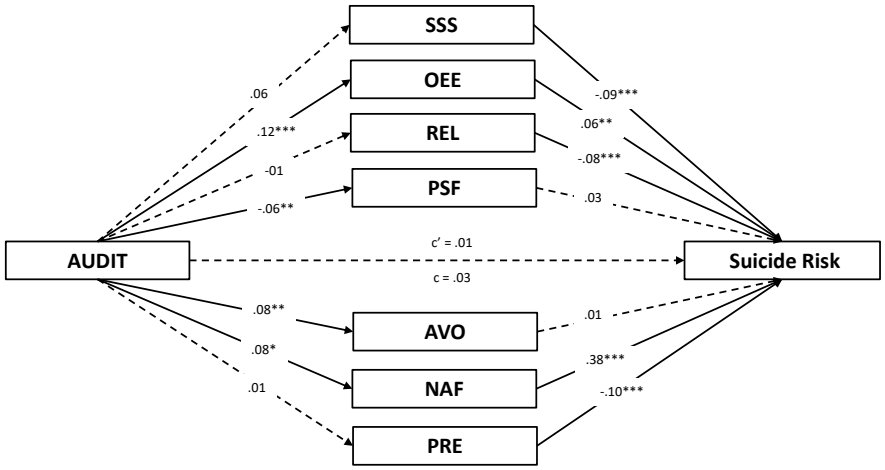
First, the Statistical Package for Social Sciences (SPSS v.28) data analysis software was used to manage data and descriptive analyses. Secondly, using, R (4.3.3) multivariate mediation analysis models were performed. Two different models were estimated, the independent variable (X) and the dependent variable (Y) were held constant, but the mediators (Me) were modified. In the first model, the Me were the 7 coping strategies listed in the CSQ: Seeking Social Support, Open Emotional Expression, Religion, Focus on Problem Solving, Avoidance, Negative Self-Focus and Positive Reappraisal. In the second model, the 4 stress tolerance scales of the DTS were introduced as Mediators: Tolerance, Appraisal, Absorption and Regulation. In all models, sex and age were introduced as covariates to control for their possible effects on the results.

In both multivariate mediation models, 95% confidence intervals were estimated using 5.000 bootstrap samples. The direct effects of the variable X on the mediators (a_i), the direct effects of the mediators (Me) on the variable Y (bi), the direct effect (c'), the total effect (c), and the indirect effect of X on Y through the different mediators were examined. In all figures, direct and indirect effects are reported in standardized β to improve comparability.

Additionally, given that this is a cross-sectional study, and considering that the directionality proposed in the hypotheses may raise some doubts despite its

Figure 3

Mediation model with CSQ



Note. *p < .05, **p < .01, *** p < .001; CSQ: Coping Questionnaire Stress; SSS: seeking social support; OEE: open emotional expression; REL: religion; PSF: problem-solving focus; AVO: avoidance; NAF: negative self-focus; PRE: positive reappraisal. Gender as entered as covariate.

theoretical justification, an inverse mediation model was also calculated. In this alternative model, suicidal risk was entered as the independent variable and alcohol consumption as the dependent variable. The aim of this analysis was to verify whether the inverse relationship was non-significant, thereby providing greater robustness to the proposed model. In the event that a significant relationship emerged, such bidirectionality would be considered as a potential line of future research.

The figures below show the proposed hypothetical multivariate mediation models (Figure 1 and 2).

Results

Mediation analysis with CSQ

The direct effects of AUDIT were significant for Open Emotional Expression (β = .12, [95% CI = .07, .18], p < .001), Avoidance (β = .08, [95% CI = .02, .14], p = .016), and Negative Self-Focus (β = .08, [95% CI = .01, .15], p = .020). In contrast, direct effects on Seeking Social Support, Religion, Focus on Problem Solving, and Positive Reappraisal were not significant (p > .05). Similarly, the direct and total effects of AUDIT on suicidal behaviour (RS) were also non-significant (p = .602 and p = .126, respectively; see Figure 3).

Regarding the direct effects of the different coping strategies (mediators), significant effects were observed for Seeking Social Support (β = −.09, [95% CI = −.13, −.06], p < .001), Seeking Social Support (β = .07, [95% CI = .00, .12], p = .035), Religion (β = −.08, [95% CI = −.13, −.04], p < .001), Negative Self-Focus (β = .39, [95% CI = .34, .44], p < .001), and Positive Reappraisal (β = −.10, [95% CI = −.15, −.05], p < .001) (see Figure 3).

Finally, concerning the indirect effects, only the pathway mediated through Negative Self-Focus was significant (β = .03, [95% CI = .01, .06], p = .022). The remaining indirect effects were not statistically significant (see Table 2). In the inverse model, where suicide risk was considered the independent variable, significant effects were observed for Open Emotional Expression (β = .032, p = .010), Problem-solving focus (β = .037, p = .013). However, the remaining coping strategies did not show significant effects (all p > .05) (see Table 2).

Mediation analysis with DTS

The direct effects of AUDIT were significant for Tolerance (β = .08, 95% CI [0.02, 0.13], p = .010), Appraisal (β = .15, 95% CI [0.03, 0.25], p = .011), and Absorption (β = .08, 95% CI [0.02, 0.14], p = .008), but not for Regulation (p = .811). The direct effect of AUDIT on suicidal behaviour was not significant (p = .469); however, the total effect was significant (β = .07, p = .031) (see Figure 4).

The direct effects of the different mediators (DTS dimensions) on suicidal behaviour were significant for all: Tolerance (β = −.18, 95% CI [−.27, −.09], p < .001), Appraisal (β = .26, 95% CI [.20, .31], p < .001), Absorption (β = .36, 95% CI [.26, .46], p < .001), and Regulation (β = −.12, 95% CI [−.22, −.02], p = .014) (see Figure 4).

Finally, the indirect effects of the model were significant through the mediators Tolerance (β = −.01, p = .033), Appraisal (β = .04, p = .017), and Absorption (β = .03, p = .012), but not through Regulation (p = .821) (Table 2). In the inverse model, where suicide risk was considered the independent variable, significant effects were observed for Regulation (β = −.046, p = .025), whereas the other variables did not show significant effects (all p > .05).

Table 2

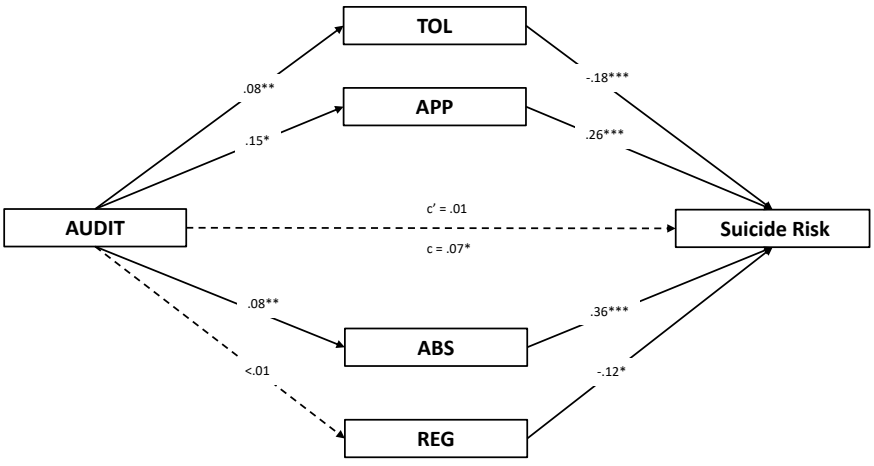
Estimates of indirect effects of the multivariate mediation analyses

		Main analyses (Models AUDIT→RS)		Sensitivity analyses (Models RS→AUDIT)	
Dependent Variable	**Mediator**	**Estimate effect (SE)**	p	**Estimate effect (SE)**	p
Suicide Risk	SSS	-.006 (.005)	.206	-.010 (.012)	.397
	OEE	.008 (.004)	.068	**.032 (.012)**	**.010**
	REL	.001 (.003)	.854	.002 (.003)	.553
	PSF	-.002 (.002)	.412	**.037 (.015)**	**.013**
	AVO	-.001 (.002)	.779	.004 (.004)	.323
	NAF	.031 (.013)	.022	.005 (.031)	.873
	PRE	-.001 (.004)	.055	-.027 (.016)	.092
Suicide Risk	TOL	-.014 (.007)	.033	.033 (.023)	.163
	APP	.037 (.016)	.017	.068 (.053)	.199
	ABS	.029 (.012)	.012	.013 (.041)	.752
	REG	-.001 (.003)	.821	-.046 (.021)	.025

Note. SSS: social support seeking; OEE: overt emotional expression; REL: religion; PSF: problem solving focus; AVO: avoidance; NAF: negative auto-focused; PRE: positive reappraisal; DTS: Distress Tolerance Stress; TOL: tolerance; APP: appraisal; ABS: absortion; REG: emotion regulation. The β coefficients of the indirect effects are standardized.

Figure 4

Mediation model with DTS



Note. *p < .05, **p < .01, *** p < .001; DTS: Distress Tolerance Stress; TOL: tolerance; VAL: valence; APP: appraisal; REG: emotion regulation. Gender as entered as covariate.

Discussion

This study jointly examined emotion regulation processes (coping strategies and distress tolerance) as mediators between excessive alcohol use and suicidal behaviour. In the first model, coping strategies were tested as mediators in the relationship between excessive alcohol use and suicidal behaviour. Results indicated that this relationship was significantly mediated only through the Negative Self-Focus strategy, while the remaining coping strategies did not show significant indirect effects. In particular, higher alcohol use predicted greater reliance on Negative Self-Focus, which in turn was associated with increased suicidal behaviour. In the second model, distress tolerance dimensions were explored as mediators of the relationship between excessive alcohol use and suicidal behaviour. The results showed that this association was positively mediated by Appraisal and Absorption, and negatively mediated by Tolerance.

Regarding the inverse model these results indicate that while some associations in the inverse direction reached statistical significance, the overall pattern of mediation was less consistent and theoretically less coherent. Therefore, the results of the inverse model do not contradict the directionality proposed in the original hypotheses but rather reinforce the robustness of the initially hypothesized model.

Previous studies have reported mixed findings regarding the relationship between distress tolerance and suicidality. For instance, Anestis et al. (2011) found discrepancies between self-reported and behavioural measures of distress tolerance, while Vujanovic et al. (2017) and Antuña-Camblor et al., (2024) observed that lower distress tolerance and specific subcomponents (Appraisal, Absorption, and Tolerance) are linked to suicidal behaviour. These inconsistencies underscore the importance of examining both subjective and behavioural indicators to clarify how distress tolerance contributes to vulnerability.

Considering our results, in the models studied, the relationship between excessive use of alcohol and risk of suicide attempts is positively mediated by Negative Self-Focus, Appraisal and Absorption, and negatively mediated by Tolerance. Therefore, they are according to the Interpersonal Theory of Suicide (Joiner, 2005; Van Orden et al., 2010), which proposes that suicidal behavior arises from the interaction of perceived burden, frustrated belongingness, and suicidality.

Our findings suggest that maladaptive emotion regulation strategies interact with alcohol use to increase vulnerability to suicidal behaviour. Specifically, alcohol may serve as a maladaptive coping mechanism that temporarily reduces negative affect but ultimately exacerbates self-focused rumination and emotional absorption. This myopic focus, amplified by alcohol's cognitive narrowing effects (Waesche et al., 2016), may heighten perceived burdensomeness and social disconnection—key components of the Interpersonal Theory of Suicide (Joiner, 2005; Van Orden et al., 2010). Individuals who rely on Negative Self-Focus and Appraisal distortions may experience intensified self-criticism and hopelessness, while low tolerance for distress diminishes their perceived ability to endure psychological pain. The convergence of these factors can create a critical pathway through which excessive alcohol use and poor emotional regulation increase the likelihood of suicidal behaviour.

From a preventive and clinical perspective, these results highlight the value of targeting emotion regulation and distress tolerance within addiction treatment programs. The findings showed that Negative Self-Focus, Absorption, and catastrophic Appraisal acted as positive mediators between excessive alcohol use and suicidal behaviour, whereas Tolerance functioned as a protective factor, mediating the relationship negatively. This pattern suggests that individuals who use alcohol as a means to regulate distress may become trapped in self-focused rumination and emotional absorption, amplifying hopelessness and suicidal vulnerability. Conversely, greater tolerance of distress appears to buffer the negative emotional impact of alcohol misuse.

Interventions such as Dialectical Behaviour Therapy (DBT) (Linehan, 1993) could strengthen adaptive coping, enhance distress tolerance, and reduce the appeal of alcohol as an emotion-regulation tool (Neacsiu et al., 2014). These findings are consistent with the proposals of Fonseca & Al-Halabí (2024) who emphasize that the co-occurrence of addictive and suicidal behaviours reflects shared underlying mechanisms—emotional dysregulation, impulsivity, and impaired coping processes—rather than independent disorders. Consequently, integrated approaches that simultaneously address substance use and suicidality are essential for prevention and treatment.

Moreover, as highlighted by Al-Halabí & Fonseca-Pedrero (2023), effective psychotherapies for suicidal behaviour share common components such as comprehensive assessment, a strong therapeutic alliance, work on emotional regulation, and inclusion of the individual's social context. Incorporating these principles into addiction-related interventions could enhance therapeutic efficacy and ensure continuity of care.

In line with the editorial perspective of Al-Halabí & Fonseca-Pedrero (2024), preventive programs should also adopt a humanizing and socially informed framework, addressing not only individual risk factors but also social determinants such as isolation, stigma, and inequality, which may exacerbate both alcohol misuse and suicidality. Prevention programs might therefore focus on enhancing social connectedness and emotional awareness, counteracting the effects of frustrated belongingness and self-perceived burdensomeness. Furthermore, brief motivational and cognitive-behavioural

interventions in substance-use settings could include modules that address maladaptive rumination and negative self-appraisal, aiming to reduce the emotional cascade that links excessive alcohol use to suicidal behaviour.

By integrating these evidence-based, prevention and treatment efforts can more effectively mitigate both substance misuse and suicidal behaviour, fostering resilience through improved emotional regulation and a more compassionate, person-centred model of care.

Limitations

Despite the novelty of this study and the valuable findings obtained, it is essential to acknowledge its limitations. First, the reliance on a cross-sectional design restricts the ability to establish causal relationships and determine the temporal sequencing between excessive use of alcohol, emotional regulation, and suicidal behaviour. Second, the use of self-report measures, such as questionnaires, introduces the possibility of response bias and social desirability effects, which may affect the accuracy of the data. Third, the sample's gender distribution was skewed, with a higher proportion of women than men, necessitating statistical control for this variable. Fourth, the study's sample may not fully represent the diversity of the Spanish population, potentially limiting the generalizability of the findings. Lastly, while no significant overlap was found between the suicidal behaviour scale and excessive alcohol use, and the scales demonstrated high specificity, some shared variance remains possible. Future studies should explore the specific and differential components that contribute to the decision to attempt suicide.

Future lines and conclusion

Future research should employ longitudinal and multi-method designs—including behavioural tasks, clinical interviews, and informant reports—to better clarify causal relationships and mitigate biases inherent to self-report. Expanding to more diverse and gender-balanced samples, including clinical populations, will enhance generalizability and allow examination of potential subgroup differences.

Overall, the present findings contribute to understanding the mechanisms linking excessive alcohol use, emotion regulation, and suicidal behaviour. The data suggest that maladaptive emotion regulation strategies—particularly Negative Self-Focus, catastrophic Appraisal, and low Tolerance—amplify the impact of alcohol use on suicidal vulnerability. Conversely, strengthening adaptive coping and distress tolerance may buffer this effect.

These insights underscore that interventions designed to enhance emotional regulation skills should be integrated into prevention and treatment programs for individuals with substance use problems. By improving tolerance of distress and promoting adaptive coping, such programs could reduce both alcohol misuse and suicidal behaviour, ultimately supporting more effective and compassionate clinical practice within the field of addictions.

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Authors' contributions

CAC: Conceptualization, investigation, writing – original draft, visualization, methodology, formal analysis, writing – review & editing.
GEC: Methodology, formal analysis, visualization, writing – original draft, writing – review & editing.
RMN: Conceptualization, Funding Acquisition, Writing – original draft, Writing – review & editing.

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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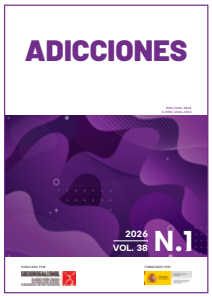
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ORIGINAL

Traditional gambling, betting in video games, and financial trading: Associations with gambling severity and associated harm in young adults

Juego tradicional, apuestas en videojuegos y trading financiero: Asociaciones con la gravedad del juego y el daño asociado en adultos jóvenes

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Abstract

The digitization of gambling has led to the proliferation of gambling-like products in areas such as video games and financial investment platforms. Although these practices share structural mechanisms and risk profiles with gambling, evidence on their relationship with associated harm and their joint role in predicting gambling severity remains limited. This study examined the association between recent participation (within the last 60 days) in these activities, along with traditional forms of gambling, and gambling severity (PGSI) and related harm (SGHS). The sample is derived from a randomized controlled trial (ClinicalTrials.gov ID: NCT06681103), from which only the pre-intervention baseline assessment data were utilized. A total of 1,889 young people aged 18–34 living in Spain were recruited, of whom 53.9% (n=1,018) had recently participated in gambling or similar activities, forming the sample analyzed. Both indicators were modelled using hierarchical ordinal regression, with adjustments made for overall involvement (frequency and number of activities) and sociodemographic factors. The associations with severity remained after all adjustments, with adjusted ORs (aORs) between 1.9 and 3.6 (p<0.01), with video game betting and commodity trading standing out, with magnitudes similar to those observed for slot machines, casinos, and sports betting. In the SGHS, only eSports betting and commodity trading (aOR=2.23, p<0.05) retained their association with a higher number of harms after sociodemographic adjustment, while lotteries showed inverse associations with both indicators (aOR=0.58 in PGSI, and aOR=0.56 in SGHS, p<0.05). The results emphasize the importance of incorporating these new forms of digital spending into the detection and prevention of gambling harm among young adults.

Keywords: gambling harms, problem gambling severity index, Esports betting, skin gambling, cryptocurrency, financial trading, young adults

Resumen

La digitalización del juego ha favorecido la expansión de productos análogos al juego de azar en espacios como los videojuegos y las plataformas de inversión financiera. Aunque estas prácticas comparten mecanismos estructurales y perfiles de riesgo con el juego de azar, la evidencia sobre su relación con el daño asociado y su papel conjunto en la predicción de la gravedad del juego sigue siendo limitada. Este estudio analizó si la participación reciente (últimos 60 días) en estas actividades, junto con las formas tradicionales de juego, se asocia con la gravedad del juego (PGSI) y el daño relacionado (SGHS). La muestra procede de un ensayo controlado aleatorizado (ClinicalTrials.gov ID: NCT06681103), del que se emplearon únicamente los datos de la evaluación inicial previos a la intervención. Se reclutaron 1.889 jóvenes de 18–34 años residentes en España, de los cuales el 53,9 % (n=1.018) había participado recientemente en actividades de juego o análogas, conformando la muestra analizada. Ambos indicadores se modelaron mediante regresión ordinal jerárquica ajustada por implicación global (frecuencia y número de actividades) y sociodemográficas. Las asociaciones con la gravedad se mantuvieron tras todos los ajustes, con OR ajustadas (ORa) entre 1,9 y 3,6 (p<0,01), destacando las apuestas en videojuegos y el trading de materias primas, con magnitudes similares a las observadas para máquinas tragaperras, casino y apuestas deportivas. En el SGHS, solo las apuestas en eSports y el trading de materias primas (ORa=2,23, p<0,05) conservaron su asociación con un mayor número de daños tras el ajuste sociodemográfico, mientras que las loterías mostraron asociaciones inversas con ambos indicadores (ORa=0,58 en PGSI, y ORa=0,56 en SGHS, p<0,05). Los resultados subrayan la necesidad de incorporar estas nuevas formas de gasto digital en la detección y prevención del daño asociado al juego entre jóvenes adultos.

Palabras clave: daño asociado al juego, índice de gravedad de problemas con el juego, apuestas en Esports, apuestas con skins, criptomonedas, trading financiero, adultos jóvenes

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The expansion of the gambling industry and the global increase in participation in gambling activities, particularly among younger populations, have become an emerging public health challenge (Reith et al., 2019; Tran et al., 2024; Wardle et al., 2024). Accumulating evidence increasingly indicates an association between gambling involvement, especially in online contexts, and multiple forms of harm that extend beyond financial impact (e.g., Browne, Tulloch et al., 2025; Davis et al., 2025; Marionneau et al., 2023; Riley et al., 2021; Suomi et al., 2023; Wall et al., 2025). Problem gambling has been linked to elevated levels of psychological distress, substance use, and an increased risk of suicidal behaviour (Dowling et al., 2015, 2017; Kristensen et al., 2024; Moreira et al., 2023), functioning both as a contributing factor to these problems and as a consequence of them (Cowlishaw & Kessler, 2016; Fonseca-Pedrero & Al-Halabí, 2024; Wardle et al., 2024). These effects tend to intensify in the presence of debt, although they may emerge even before financial harm is formally recognised (Håkansson & Widinghoff, 2020; Kristensen et al., 2024; Marko et al., 2023; Oksanen et al., 2018; Ronzitti et al., 2017).

The development of harm is not limited to individuals who meet clinical criteria for a gambling disorder, but extends across the entire risk spectrum, including people whose gambling involvement is considered low risk (Browne et al., 2017, 2018; Browne & Rockloff, 2017; Canale et al., 2016; Hwang et al., 2024; Wardle et al., 2024). Indeed, it has been documented that most harms, including some severe consequences such as job loss, relationship breakdown, or the need to sell personal belongings, are more frequent among those at lower levels of risk, who, due to their high population prevalence, account for the largest share of the overall burden of harm (Browne et al., 2017, 2018; Hwang et al., 2024; Tulloch et al., 2024). These findings reinforce the view that harm constitutes an inherent risk of gambling, regardless of severity level, which is particularly relevant given that these negative effects may persist beyond 12 months after cessation of gambling behaviour and affect not only the individual's life course but also their immediate social environment and even future generations (Dowling et al., 2025; Hing, Russell, et al., 2022; Rockloff et al., 2022; Suomi et al., 2023). From a public health perspective, these results also underscore the need to examine gambling-related harm not exclusively in terms of gambling severity, but by considering the contextual factors on which its emergence depends (Al-Halabí & Fonseca-Pedrero, 2024; Fonseca-Pedrero & Al-Halabí, 2024).

Although gambling can entail negative consequences across the population, young people constitute a particularly vulnerable group to the development of addictive disorders and the emergence of gambling-related harm (Gavriel-Fried et al., 2024; Grande-Gosende et al., 2020; Raisamo et al., 2015; Tran et al., 2024; Tulloch et al., 2024; Wardle et al., 2024). In Spain, in line with global trends (Tran et al., 2024), land-based gambling has declined since 2020, while online participation continues to increase, with an estimated prevalence of 6–7% in the general population. These figures rise to 7.4% among those aged 15–24 and to 8.8% among those aged 25–34, exceeding 13% among men in the latter age group (Spanish Observatory of Drugs and Addictions [OEDA], 2024). Furthermore, although disaggregated data simultaneously by age and gambling modality are not available, the Survey on Alcohol, Drugs and Other Addictions in Spain (Encuesta sobre Alcohol, Drogas y otras Adicciones en España, EDADES, EDADES; OEDA, 2024) shows that online gambling is associated with a higher prevalence of problem gambling (18.4%) than land-based gambling (4.3%), and that the 25–34 age group consistently presents one of the highest rates of problem gambling in recent years (OEDA, 2024).

This pattern of greater youth involvement in online gambling also extends to new forms of digital spending which, although not legally classified as gambling, reproduce many of its structural dynamics (Andrade & Newall, 2023; Coloma-Carmona, Carballo, Sancho-Domingo, et al., 2024; Griffiths, 2018). The digitalisation of gambling has facilitated the expansion of gamblified or gambling-analogous products across spaces such as video games, social media, and even financial investment platforms (Andrade & Newall, 2023; Brock & Johnson, 2021; Coloma-Carmona, Carballo, Sancho-Domingo, et al., 2024; Davies & Ferris, 2022; Macey & Hamari, 2024). Spending on these products has been linked in multiple studies to indicators of problem gambling (e.g., Coloma-Carmona, Carballo, Miró-Llinares, & C. Aguerri, 2025; Coloma-Carmona, Carballo, Sancho-Domingo, et al., 2024; Drummond et al., 2020; Greer et al., 2021, 2022, 2023; Johnson et al., 2023; Oksanen, Hagfors, et al., 2022; Wardle & Tipping, 2023), and an increase has also been observed in the number of individuals seeking help for difficulties arising from participation in these activities (Marionneau et al., 2024). Within the video game context, the purchase of loot boxes (packages containing randomised rewards that provide virtual items in exchange for real money) has been consistently associated with higher levels of problem gambling (González-Cabrera et al., 2022; King & Delfabbro, 2018; Raneri et al., 2022; Zendle, 2020; Zendle & Cairns, 2018). Other practices such as betting with skins or virtual items that hold economic value (skin betting), despite receiving less empirical attention, have shown an even stronger association with gambling severity and related harm, even after controlling for involvement in traditional forms of gambling (Greer et al., 2023; H. S. Kim et al., 2023; Wardle & Tipping, 2023).

In parallel with betting within video games, the use of financial trading platforms, particularly those oriented toward short-term strategies such as day trading or scalping, in which financial asset transactions are completed within the same day or even within hours, has also become increasingly popular among young adults (Andrade & Newall, 2023; Coloma-Carmona, Carballo, Miró-Llinares, et al., 2024; Roza et al., 2024). This activity is characterised by conducting financial operations in highly volatile markets, making decisions under conditions of uncertainty, and assuming a high risk of economic loss (Andrade & Newall, 2023; Coloma-Carmona, Carballo, Miró-Llinares, & C. Aguerri, 2025; Coloma-Carmona, Carballo, Miró-Llinares, C. Aguerri, et al., 2025; Delfabbro, King, & Williams, 2021; Guzmán et al., 2021; Oksanen, Mantere, et al., 2022; Roza et al., 2024). For this reason, it has been described as a gambling-like activity not only because of its structure and dynamics, but also because it shares profiles and psychological consequences similar to those observed among individuals involved in gambling (Coloma-Carmona, Carballo, Miró-Llinares, & C. Aguerri, 2025; Coloma-Carmona, Carballo, Sancho-Domingo, et al., 2024; Delfabbro, King, & Williams, 2021; Jain et al., 2025; Johnson et al., 2023; Mosbey et al., 2024). Recent studies have shown that frequent involvement in speculative trading is associated with a higher prevalence of problem gambling and with specific psychological, financial, and social harms, particularly among young people with risk profiles (Coloma-Carmona, Carballo, Miró-Llinares, C. Aguerri, et al., 2025; Jain et al., 2025; Johnson et al., 2023; Loscalzo et al., 2025; Mosbey et al., 2024). Moreover, individuals who combine trading with other gambling activities, especially those conducted online, share similar vulnerability profiles, including younger age, higher levels of impulsivity, gambling-related cognitive distortions, and substance use (Coloma-Carmona, Carballo, Miró-Llinares, & C. Aguerri, 2025; Delfabbro, King, Williams, et al., 2021).

Despite the growing evidence on the association between these emerging forms of digital spending and gambling-related harm, no study to date has jointly examined the extent to which participation in video-game related betting and financial trading, together with traditional forms of gambling, is associated with the severity of gambling-related harm. Moreover, the limited literature available on harm linked to trading has predominantly focused on cryptocurrencies, without considering the trading of other financial assets such as exchange-traded funds or foreign exchange markets, whose popularity has increased among the general population. This gap limits the understanding of the specific impact of each of these practices, particularly among young adults, where their prevalence is higher (Coloma-Carmona, Carballo, Miró-Llinares, et al., 2024).

Furthermore, although part of the literature suggests that gambling-related risk is more strongly determined by the overall level of involvement, that is, by the frequency and variety of activities undertaken (Baggio et al., 2017; Greer et al., 2021, 2023; LaPlante et al., 2013, 2014), other studies have shown that mere participation in specific modalities such as casino gambling, electronic gaming machines, and online gambling more broadly is already associated with greater risk, even after controlling for this level of involvement (Allami et al., 2021; Binde et al., 2017; Gainsbury et al., 2019; Gooding & Williams, 2024; Mazar et al., 2020; Nelson et al., 2018; Wardle & Tipping, 2026). However, this hypothesis has not yet been tested in relation to gambling-like practices, which makes it difficult to assess their relative contribution to gambling-related harm.

Accordingly, the present study aimed to examine among young adults (18–34 years): (1) the association between participation in different gambling activities, including traditional forms of gambling, betting integrated within video games, and financial asset trading, and both gambling severity and related harm; and (2) whether these associations remained after controlling for overall gambling involvement and sociodemographic factors.

Methods

Design and procedure

The sample analyzed in this study derives from a registered randomised controlled trial (ClinicalTrials.gov ID: NCT06681103), whose overall aim was to evaluate the effectiveness of a brief online intervention designed to promote intention to change and treatment-seeking among young adults with problematic behaviours related to gambling and financial investments. The detailed study protocol has been described elsewhere (Coloma-Carmona et al., 2026). Inclusion criteria were being aged between 18 and 34 years, residing in Spain, having participated at least once in the past 60 days in traditional forms of gambling, betting within video games, or financial asset trading, and providing informed consent.

The sample was recruited through an online panel managed by an external company specialised in quantitative and qualitative research. Data collection took place between December 2024 and January 2025. Each participant could access the survey only once via a personalised link. Invitations were sent exclusively to panel members who met the established age range (18–34 years), through the provider's email and mobile application. Those who agreed to participate completed a brief eligibility assessment to verify compliance with the inclusion criteria. Participation was voluntary and followed the provision of informed consent. Individuals who completed the questionnaire received non-monetary incentives (points redeemable for products), managed by the recruitment

company. For the analyses presented in this study, only data collected at baseline, prior to any exposure to the experimental conditions, were used.

The study was approved by the Research Ethics Committee of Miguel Hernández University of Elche (reference: DPS.ACC.150523) and complies with the ethical principles set out in the Declaration of Helsinki.

Participants

Of the 1,889 individuals who accessed the survey, 1,112 met the inclusion criteria. Given that the primary aim of the study was to analyse the relative contribution of emerging forms to gambling severity and gambling-related harm, in comparison with traditional gambling activities, participants whose involvement was limited exclusively to betting within video games or financial asset trading were excluded from the analyses (n = 94), resulting in a final sample of 1,018 participants.

Regarding the sociodemographic profile, the mean age of participants was 28.6 years (SD = 4.4), and 55.8% (n = 568) were women. The majority identified as single (82.5%, n = 840). More than half had completed university education (54.6%, n = 556), and 61.8% (n = 629) were employed full-time. The mean monthly income was €1,343 (SD = €890.9). Table 1 presents the full sociodemographic characteristics of the sample.

Table 1

Sociodemographic characteristics of the sample (N = 1,018)

Variables	Total sample (N = 1,018)
Age, M (SD; Range)	28.6 (4.4; 18-34)
Sex, % (n)	
Female	55.8 (568)
Male	44.2 (450)
Marital status, % (n)	
Single	82.5 (840)
Married	16.6 (169)
Divorced	0.9 (9)
Educational level, % (n)	
No formal education	0.8 (8)
Primary education	2.8 (28)
Secondary education	41.8 (426)
University education	54.6 (556)
Employment status, % (n)	
Employed full-time	61.8 (629)
Employed part-time	12.6 (128)
Student	15.9 (162)
Unemployed or on sick leave	8.3 (85)
Domestic worker	1.2 (12)
Retired	0.2 (2)
Monthly income (excluding extreme values), M (SD; Range)[a]	1,325.6€ (884.4; 0-8.000)
Monthly income (transforming extreme values), M (SD; Range)[b]	1,343€ (890.9; 0-8.000)

Note. [a] 23 responses were excluded due to extreme values (z > 3.29), with reported incomes between €15,000 and €45,000.
[b] Extreme values were considered possible reporting errors of annual income and were adjusted by dividing the value by 12 months to estimate the monthly income.
Abbreviations: n = frequency, M = mean, SD = standard deviation.

Variables and measures

Outcome variables

Gambling severity. This was assessed using the *Problem Gambling Severity Index*, Spanish version (PGSI; Ferris & Wynne, 2001; López-González et al., 2018), with a reference period of the past 12 months. Total scores range from 0 to 27, with higher values indicating greater gambling severity. For the analyses, the standard four-level categorisation of the scale was applied: non-problem gambling (PGSI = 0), low risk (PGSI = 1–2), moderate risk (PGSI = 3–7), and problem gambling (PGSI ≥ 8). The Spanish version of the PGSI has shown excellent internal consistency (ordinal α = 0.97) and good convergent validity with DSM-IV scores (r = 0.77). In the present sample, the internal consistency of the PGSI was ω = 0.94.

Gambling-related harm. This was measured using the *Short Gambling Harm Screen* (SGHS; Browne et al., 2018), also with a reference period of the past 12 months. The SGHS comprises 10 dichotomous items (yes/no) assessing harms associated with gambling involvement across financial, emotional/psychological, and social domains. Total scores range from 0 to 10, with higher scores indicating a greater accumulation of harms. In its original validation, the SGHS showed a unidimensional structure with high internal reliability (α = 0.93; ω = 0.83) and a strong correlation with the PGSI (r = 0.68) (Browne et al., 2018). For the analyses, the number of harms was categorised into four groups: 0 harms, 1–2 harms, 3–5 harms, and 6 or more (Boyle et al., 2022; Browne et al., 2022). In the present sample, the internal consistency of the SGHS was ω = 0.86.

Predictor variables

Participation in traditional gambling and betting activities. Participation (yes/no) in the past 60 days was assessed for eight gambling products included in the EDADES survey of the Spanish National Plan on Drugs (OEDA, 2024): (1) lotteries, coupons, football pools, scratch cards; (2) sports betting; (3) horse race betting; (4) slot machines, slots, electronic gaming machines; (5) card games (e.g., poker); (6) bingo; (7) casino games or gaming venues; and (8) contests involving a monetary stake (e.g.,

television contests). Access channels (online, land-based, or mixed) were not differentiated for each activity; however, participants were asked about their main form of gambling ("Overall, which would you say is your main way of gambling with money?"), with three response options: land-based (e.g., casinos, physical venues, betting shops), online (e.g., websites or mobile applications), or mixed (e.g., land-based and online equally).

Participation in gambling-like activities. Involvement (yes/no) in the past 60 days was recorded for activities with gambling-analogous components identified in recent literature (Zendle, 2020): (1) eSports betting, (2) betting for skins or in-game equipment upgrades (skin betting), (3) purchasing loot boxes, and (4) betting on players/characters during live video game streaming (e.g., Twitch). Participation in financial trading activities was also assessed across the following assets: (1) foreign exchange (Forex), (2) cryptocurrencies (e.g., Bitcoin, Ether, Ripple), (3) commodities (e.g., precious metals, agricultural products), (4) exchange-traded funds (ETFs), (5) contracts for difference (CFDs), (6) futures (contracts on assets exchanged at a future date), (7) options (contracts with the right, but not the obligation, to buy/sell an asset), and (8) stock markets (e.g., shares, stock indices, penny stocks, high-risk investment funds).

Control variables

Overall gambling involvement. In line with the proposal by LaPlante et al. (2014), two indicators were included to control for the level of gambling involvement: (1) the total number of activities in which each participant reported participation in the past 60 days, considering both traditional and gambling-like forms; and (2) the maximum frequency of participation during the past year in any of the reported activities, measured across five levels (once or twice a year, monthly, fortnightly, weekly, and more than once per week). The total number of activities was categorised into three groups (1–2, 3–4, 5 or more) for the regression analyses, following criteria used in previous studies (Wardle & Tipping, 2023, 2026).

Sociodemographic variables. Age, sex (male/female), marital status (single, married, divorced, widowed), educational level (no formal education, primary education, secondary education, university education), employment status (full-time employed, part-time employed, student, unemployed or on sick leave, domestic worker, retired), and monthly income (in euros, recorded as a numeric value) were collected. Following the strategy applied in previous studies (Wardle & Tipping, 2023, 2026), several variables were recategorized: monthly income was grouped into three ranges (≤ €499, €500–1,499, and ≥ €1,500), educational level into two categories (university education vs. no university education), and employment status into two groups (employed or student/in training vs. neither employed nor student/in training).

Data analysis

Statistical analyses were conducted using SPSS (version 27). Descriptive statistics (means, standard deviations, frequencies, and percentages) were calculated to describe the sociodemographic characteristics of the sample, and cross-tabulations were used to examine the distribution of gambling severity and gambling-related harm levels across each gambling and gambling-like activity. Outliers were examined for all variables, and for the monthly income variable 23 extreme values were identified ($z > 3.29$), corresponding to possible self-report errors. These responses, which included annual income figures ranging between €15,000 and €45,000, were corrected by dividing the reported value by 12 to estimate monthly income (Table 1). The mean income did not change substantially either when these cases were removed or when they were corrected; therefore, they were retained following correction.

Ordinal logistic regression models were used to examine the association between participation in gambling and gambling-like activities and the outcome variables: gambling severity (PGSI) and gambling-related harm (SGHS). Both variables were modelled as ordinal, using the four categories described in the Variables and measures section. Following procedures used in previous studies (LaPlante et al., 2014; Wardle & Tipping, 2026), three hierarchical models were estimated for each outcome variable: Model 1 (unadjusted) included only participation (yes/no) in each gambling and gambling-like activity over the past 60 days as predictor variables; Model 2 additionally adjusted for overall gambling involvement, including maximum participation frequency over the past 12 months and the number of different activities undertaken in the past 60 days; and Model 3 (fully adjusted) further incorporated sociodemographic variables (age, sex, marital status, educational level, monthly income, and employment or training status).

Adjusted odds ratios (aOR) and their 95% confidence intervals (CI) were calculated from the estimated coefficients. In ordinal logistic regression, coefficients are interpreted as common ORs for each predictor, assuming that the effect is constant across all thresholds of the outcome variable (the proportional odds assumption). To assess compliance with this assumption, the test of parallel lines was used. For the PGSI, the test indicated a violation of this assumption in adjusted Models 2 and 3 ($p < 0.001$). This result is common in contexts with multiple predictors, particularly when continuous variables are included and large samples are used (Brant, 1990; O'Connell, 2006), as in the present study. To evaluate the robustness of the findings, the analyses were replicated using multinomial logistic regression models, which do not require this assumption (McNulty, 2021). The observed associations were consistent in magnitude and direction with those obtained in the ordinal models;

therefore, the latter are presented due to their greater parsimony and comparability with previous studies that used the same analytical approach (e.g., Greer et al., 2023).

Model fit was evaluated using Nagelkerke's pseudo-R^2, with values around 0.20 considered indicative of satisfactory fit (Hosmer et al., 2013). Results from the fully adjusted models were illustrated using forest plot graphics generated with the *forestplot* package in R (version 05.1+513).

Results

Participation in gambling and gambling-like activities in the sample

In the total sample (N = 1,018), the most frequent activity was participation in lotteries and coupons (87.9%, n = 895), followed at a distance by bingo (19.0%, n = 193), sports betting (18.2%, n = 185), cryptocurrency trading (13.1%, n = 133) and stock market trading (10.4%, n = 106), and slot machine gambling (8.5%, n = 87). Other activities with prevalences between 6% and 7% included trading in exchange-traded funds (6.8%, n = 69) and commodities (6.5%, n = 66), as well as purchasing loot boxes (6.4%, n = 65) and betting for skins in video games (6.4%, n = 65). The remaining activities showed prevalences below 6% (Table 2).

Regarding combinations of activities, 66.8% of participants (n = 680) reported involvement exclusively in traditional modalities (e.g., lotteries, bingo, casino). A further 18.2% (n = 185) combined traditional gambling with financial asset trading, and 7.2% (n = 73) combined it with betting within video games. An additional 7.9% (n = 80) reported involvement in all three types of activity. Concerning mode of access, 49.6% (n = 223) considered land-based formats (i.e., casinos, betting shops, physical venues) to be their primary mode of access, whereas 42% (n = 189) reported online access (i.e., via websites or applications). A total of 8.4% (n = 38) indicated using both access formats equally. With respect to the maximum frequency of participation in any of these activities over the past 12 months, 59.6% (n = 607) reported participating at least monthly.

Mean gambling severity score (PGSI) among participants was 2 (SD = 4.3, range: 0–22), and 11.2% (n = 114) obtained scores indicative of possible problem gambling (PGSI ≥ 8). Regarding harm derived from gambling involvement, the mean score on the SGHS was 1.1 (SD = 2, range: 0–10). Most participants (68.5%, n = 697) reported no gambling-related harm, whereas 5.7% (n = 58) reported experiencing six or more harms (Table 2).

Distribution of gambling-related harm and gambling severity by activities undertaken

Figure 1 presents the distribution of gambling severity and Figure 2 the number of gambling-related harms reported by those who participated in each type of activity over the past 60 days. As multiple activities could be selected, the same participant may be represented in more than one category.

As shown in Figure 1, gambling-like activities, particularly those linked to high-risk financial asset trading (contracts for difference, futures, and options), concentrated the highest proportions of participants with scores indicative of problem gambling (PGSI ≥ 8), ranging between 61.4% and 69.4%. High percentages of problem gambling were also observed among those participating in gamblified video game–related activities, such as betting on players/characters in streaming contexts (60.3%), eSports betting (58.5%), skin betting (53.8%), and the purchase of loot boxes (46.2%).

Table 2

Participation in gambling and gambling-like activities and distribution of gambling severity (PGSI) and gambling-related harm (SGHS) in the sample (N=1,018)

Variables	Total sample (N = 1,018)
Traditional gambling, % (n)	
Lotteries, Coupons, Football pools, Scratchcards	87.9 (895)
Sports betting	18.2 (185)
Horse race betting	4.4 (45)
Slot machines, electronic gaming machines	8.5 (87)
Card games for money (e.g., poker, blackjack...)	7.2 (73)
Bingo	19 (193)
Casino or gaming hall games	11.7 (119)
Contests with monetary stake (e.g., television, radio, press...)	5.6 (57)
Betting within video games, % (n)	
eSports betting	5.2 (53)
Betting in video games for skins or equipment upgrades (skin betting)	6.4 (65)
Buying loot boxes in video games	6.4 (65)
Betting on players/characters during online game broadcasts on streaming platforms (e.g., Twitch)	5.7 (58)
Financial asset trading, % (n)	
Forex (foreign exchange)	4.3 (44)
Cryptocurrency (e.g., Bitcoin, Ether, Ripple...)	13.1 (133)
Commodities (precious metals -gold, silver-, agricultural products, etc.)	6.5 (66)
Exchange-traded funds (ETFs)	6.8 (69)
Contracts for difference (CFDs)	3.5 (36)
Futures (contracts on assets exchanged at a future date)	4.1 (42)
Options (contracts with the right, but not the obligation, to buy/sell an asset)	3.3 (34)
Stock market (e.g., stocks, stock market index, penny stocks, high-risk mutual funds...)	10.4 (106)

Table 2 (cont.)

Participation in gambling and gambling-like activities and distribution of gambling severity (PGSI) and gambling-related harm (SGHS) in the sample (N=1,018)

Variables	Total sample (N = 1,018)
Frequency of participation in the past 12 months, % (n)	
1 or 2 times a year	40.4 (411)
Monthly	23.5 (239)
Every two weeks	11.8 (120)
Weekly	18.8 (191)
More than once a week	5.6 (57)
Predominant access mode (self-reported)[a], % (n)	
Land-based	49.6 (223)
Online	42 (189)
Mixed (land-based and online equally)	8.4 (38)
Gambling severity (PGSI classification), % (n)	
Non-problem gambling (PGSI = 0)	65.9 (671)
Low-risk gambling (PGSI 1-2)	14.5 (148)
Moderate-risk gambling (PGSI 3-7)	8.3 (85)
Problem gambling (PGSI ≥ 8)	11.2 (114)
Total PGSI score, M (SD; Range)	2 (4.3; 0-22)
Gambling-related harm (SGHS classification), % (n)	
0 harms (SGHS = 0)	68.5 (697)
1-2 harms (SGHS = 1-2)	14.6 (149)
3-5 harms (SGHS = 3-5)	11.2 (114)
≥ 6 harms (SGHS = 6-10)	5.7 (58)
Total SGHS score, M (SD; Range)	1.1 (2; 0-10)

Note. [a] Given that the access mode (online or land-based) was not recorded for each specific activity, information from a general question regarding the primary mode of gambling reported by each participant was used.
Abbreviations: *n* = frequency, *M* = mean, *SD* = standard deviation, *PGSI* = Problem Gambling Severity Index, *SGHS* = Short Gambling Harm Screen.

Among traditional forms of gambling, horse race betting (64.4%), contests involving a monetary stake (59.6%), and playing card games with money (53.4%) also showed a high proportion of participants grouped in the problem gambling category. In contrast, participation in lotteries presented the lowest risk levels, with 69.3% of participants classified as non-problem gamblers (PGSI = 0) and the lowest rates of problem gambling (8.7%).

Figure 2 shows a similar pattern regarding perceived harm, with activities linked to speculative trading and betting within video games concentrating the highest percentages of participants who reported multiple gambling-related harms. The highest proportions of participants reporting at least one harm corresponded to contracts for difference (CFD) trading (83.3%), foreign exchange (Forex) markets (81.8%), futures (78.6%), options (79.4%), and betting on characters in streaming platforms (75.9%). In these five activities, more than one third of participants reported experiencing six or more harms, with contracts for difference (44.4%) and options (38.2%) being particularly notable.

High proportions were also observed in other gambling-like activities, such as eSports betting (37.7% with ≥ 6 harms), skin betting (32.3%), and betting on characters in streaming contexts (31%). Among traditional modalities, horse race betting, slot machine gambling, and card games played for money stood out, with proportions of participants reporting ≥ 6 harms ranging between 24.7% and 26.7%. In contrast, lotteries were the only activity in which more than 70% of participants reported no harm, followed by bingo (51.3%) and trading in exchange-traded funds (50.7%). Stock market trading (46.2%), cryptocurrencies (42.9%), and the purchase of loot boxes (41.5%) also showed a high proportion of participants without harm and relatively low rates of cases with ≥ 6 harms (≤ 15%). However, in the case of loot boxes, a polarised distribution was observed, as 21.5% of those participating in this activity also reported six or more harms.

Association between gambling severity (PGSI) and participation in gambling and gambling-like activities

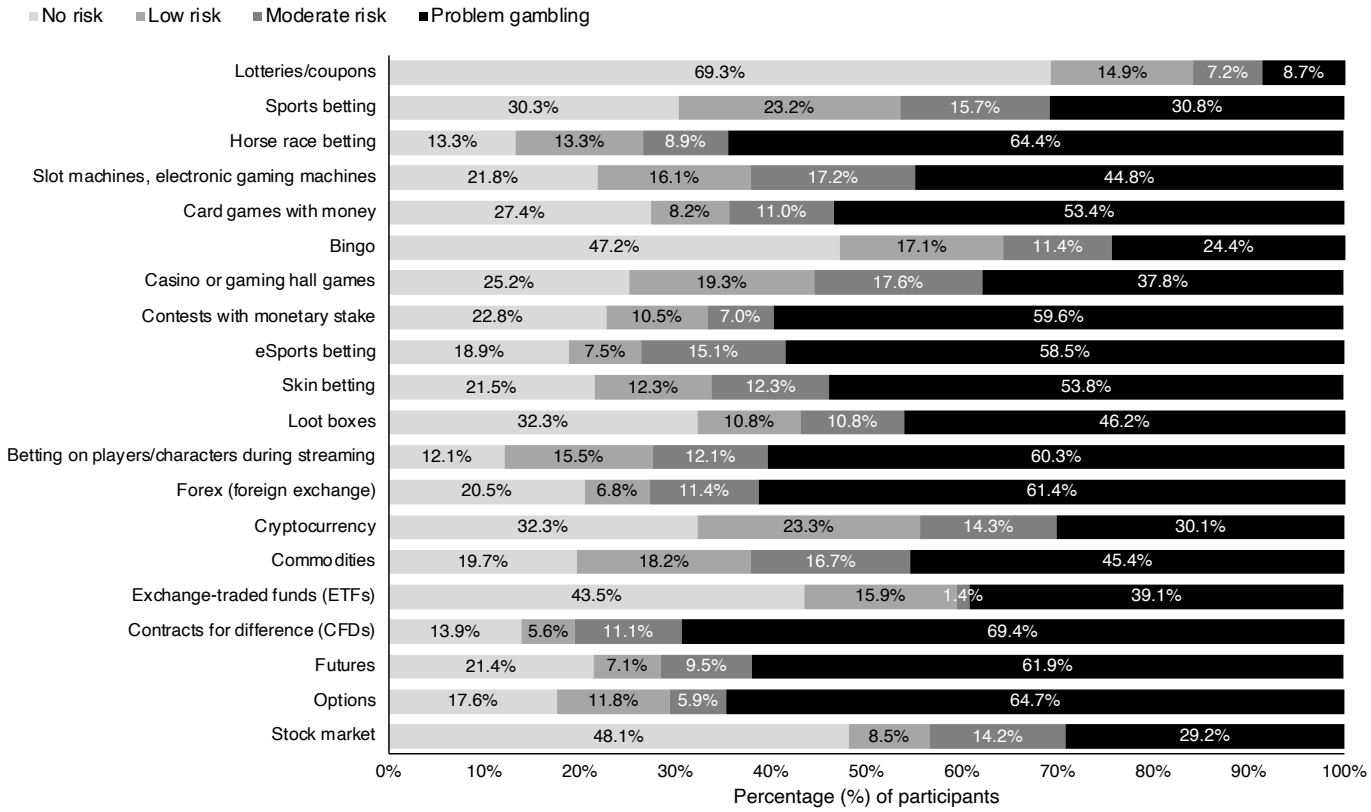
The majority of the associations observed in the unadjusted model (Model 1) remained after adjustment for overall gambling involvement (Model 2) and sociodemographic variables (Model 3), with no relevant changes in the direction of the effects. The only exception was for betting on players or on streamed matches, which was not statistically significant in the initial model (p = 0.074) but became significant after incorporating the control variables and remained significant in the final model.

In Model 3 (Nagelkerke R^2 = 0.418), the traditional activities associated with greater gambling severity were horse race betting (aOR = 3.61, 95% CI [1.65, 7.91]), slot machine gambling (aOR = 2.89, 95% CI [1.65, 5.06]), casino gambling (aOR = 2.17, 95% CI [1.30, 3.63]), and sports betting (aOR = 1.91, 95% CI [1.22, 2.98]). In contrast, participation in lotteries was inversely associated with PGSI (aOR = 0.58, 95% CI [0.36, 0.93]).

Among gambling-like activities, gambling severity was associated with all examined video game–related betting modalities, except for the purchase of loot boxes (p = 0.431). Individuals who had participated in eSports betting (aOR = 2.81, 95% CI [1.37, 5.76]), skin betting or betting on players (aOR = 2.43, 95% CI [1.28, 4.60]), or betting on streamed matches (aOR = 2.29, 95% CI [1.10, 4.77]) in the past 60 days were more likely to be classified in higher PGSI categories compared with those who did

Figure 1

Distribution of gambling severity (PGSI) among participants for each type of gambling activity



not participate in these activities. Similarly, participation in commodity trading (aOR = 2.86, 95% CI [1.52, 5.37]) and cryptocurrencies (aOR = 1.90, 95% CI [1.20, 3.00]) was also associated with greater gambling severity.

Regarding covariates, maximum frequency of participation in the reported activities over the past year was consistently associated with gambling severity. Compared with those who gambled only once or twice a year, any higher frequency of participation was linked to higher levels of severity, with the strongest associations observed for fortnightly participation (aOR = 3.08; 95% CI [1.89, 5.01]) and participation more than once per week (aOR = 3.25; 95% CI [1.76, 5.99]). In contrast, having a university education (aOR = 0.67; 95% CI [0.49, 0.91]) and being employed or in education/training (aOR = 0.51; 95% CI [0.32, 0.82]) were associated with lower gambling severity. No significant associations were found between PGSI levels and sex, age, marital status, or monthly income ($p > 0.05$).

Association between gambling-related harm (SGHS) and participation in gambling and gambling-like activities

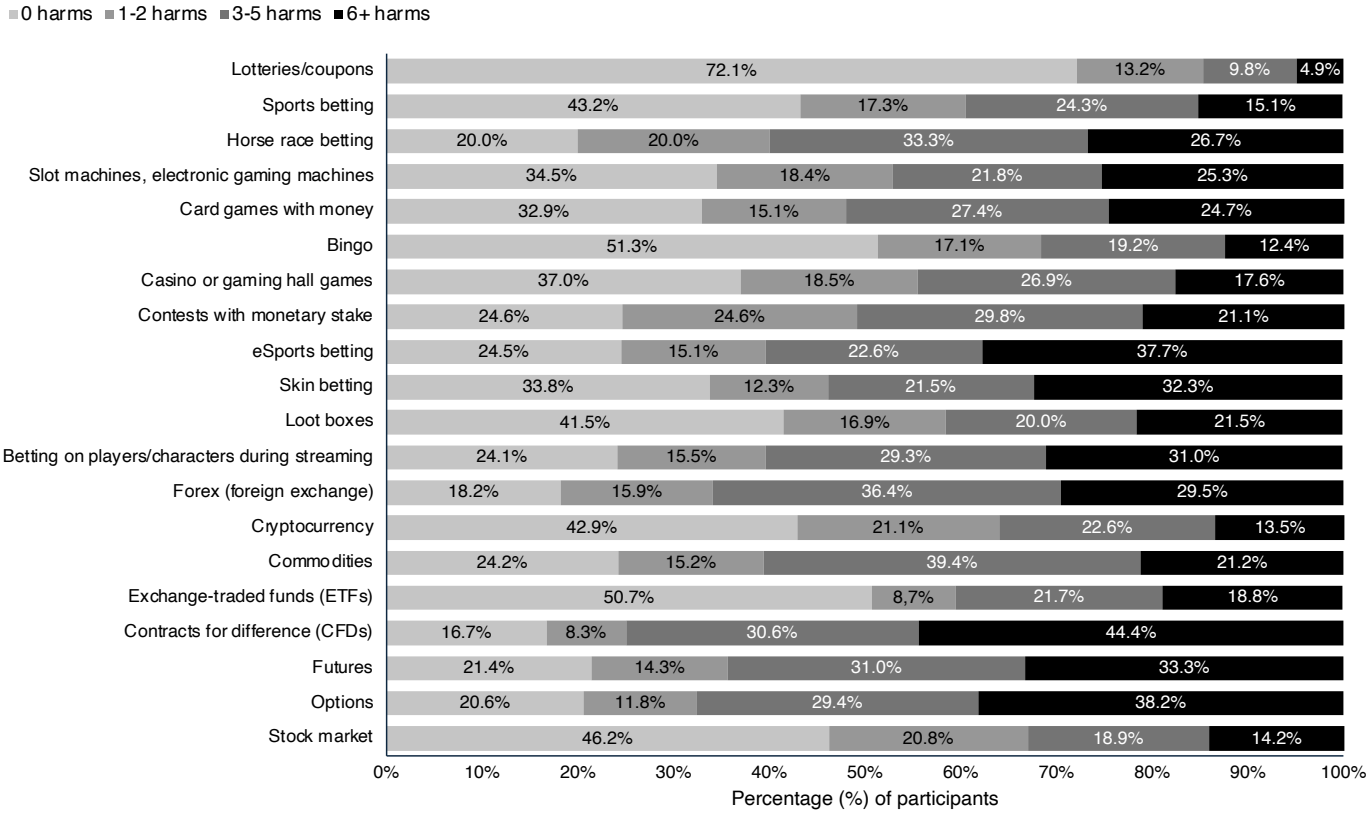
Sports betting, slot machine gambling, eSports betting, the purchase of loot boxes, and commodity trading were significantly associated ($p < 0.05$) with experiencing a higher number of harms in Models 1 and 2; however, these associations were no longer significant after incorporating sociodemographic variables in Model 3. In this fully adjusted model (Nagelkerke $R^2 = 0.296$), only eSports betting (aOR = 2.23, 95% CI [1.18, 4.22]) and commodity trading (aOR = 2.23, 95% CI [1.24, 4.02]) remained associated with a higher number of harms, whereas participation in lotteries showed an inverse association (aOR = 0.56, 95% CI [0.37, 0.86]).

Regarding covariates, individuals who had participated fortnightly (aOR = 1.52, 95% CI [1.02, 2.25]) or weekly (aOR = 2.13, 95% CI [1.32, 3.45]) in any of the reported activities over the past year were more likely to be classified in higher SGHS categories compared with those who participated only once or twice a year. Men also showed higher odds of accumulating a greater number of harms than women (aOR = 1.38, 95% CI [1.00, 1.89]). In contrast, having a university education was associated with a lower number of harms (aOR = 0.68, 95% CI [0.50, 0.91]). No statistically significant associations were observed between SGHS and age, employment status, income, or marital status ($p > 0.05$).

Figure 3 displays the aORs from Model 3, adjusted for overall gambling involvement and sociodemographic

Figure 2

Distribution of the number of gambling-related harms (SGHS) among participants for each type of gambling activity



variables, for each activity in relation to gambling severity and gambling-related harm. The full results of this model, together with those from Models 1 and 2, are presented in Table S1 of the supplementary material (https://osf.io/svzf4).

Discussion

The present study examined, in a sample of Spanish young adults, the relationship between recent participation in different traditional gambling activities (e.g., bingo, casino gambling, lotteries, sports betting) and gambling-like activities (video game–related betting and financial trading), with gambling severity and gambling-related harm.

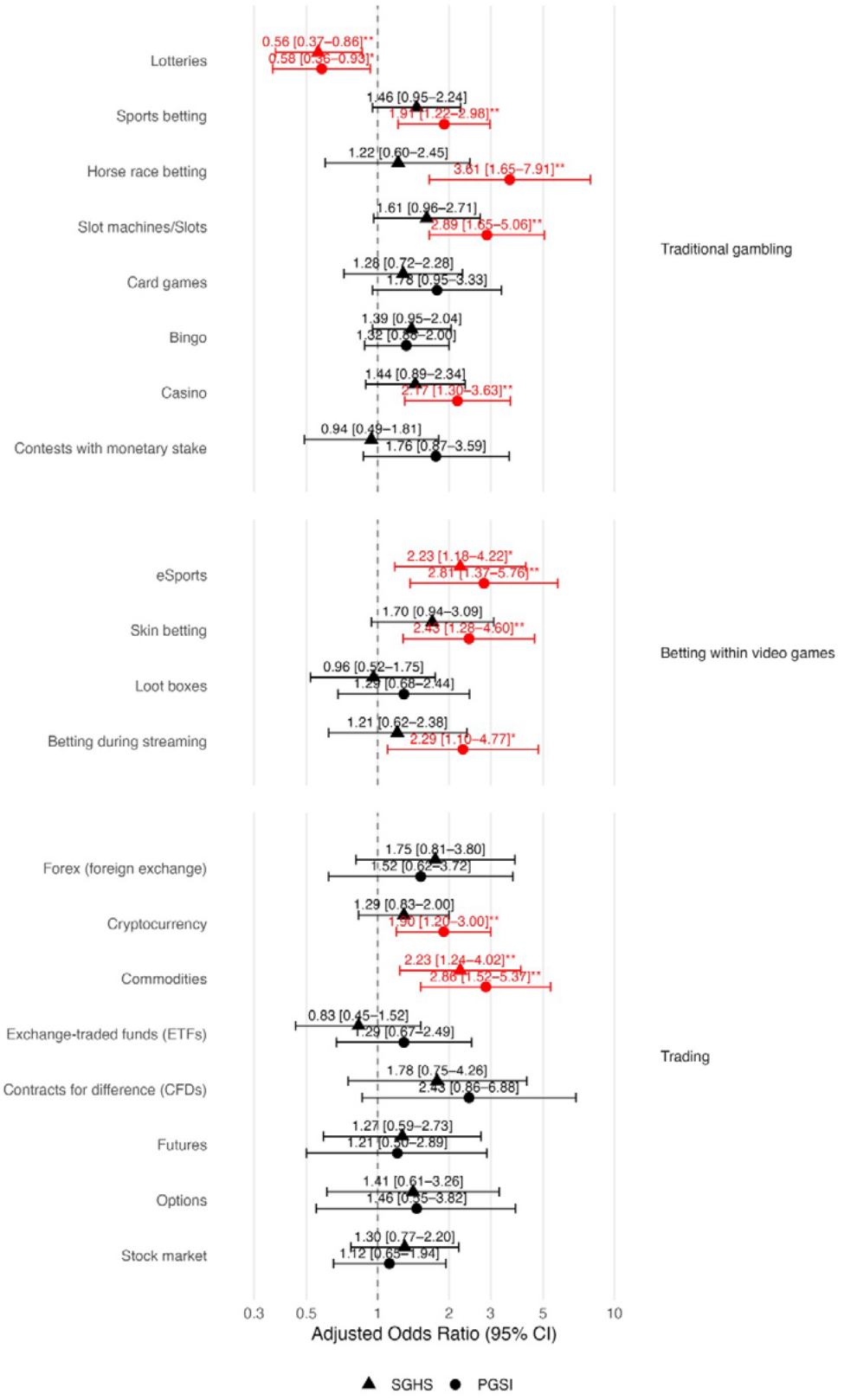
The most frequent traditional gambling modalities were consistent with those reported in national surveys, with the purchase of lotteries and coupons being the most widespread gambling modality in this sample (OEDA, 2024). However, the results also indicate a diversification of monetary expenditure towards products considered gamblified or gambling-analogous (Brock & Johnson, 2021; López-González & Griffiths, 2018; Macey & Hamari, 2024; Newall & Weiss-Cohen, 2022). Specifically, 33.2% of young people combined traditional gambling with spending on video game–related betting or financial asset trading, a pattern consistent with recent reports documenting an increase in these practices among the Spanish population (Coloma-Carmona, Carballo, Miró-Llinares, et al., 2024; Coloma-Carmona, Carballo, Sancho-Domingo, et al., 2024; Johnson et al., 2023; Spanish Observatory of Drugs and Addictions, 2024).

Regarding the distribution of the number of gambling-related harms, most young people (68.5%) did not report negative consequences derived from their involvement in gambling, a finding consistent with previous studies conducted in other populations (Browne et al., 2022; Tulloch et al., 2024). In terms of gambling severity, 11.2% reached scores consistent with problem gambling (PGSI ≥ 8), a prevalence higher than that observed in the general population but in line with that reported among young people (Nowak, 2018; OEDA, 2024).

In the descriptive analyses, it was observed that, alongside horse race betting, gambling-like activities, particularly high-risk financial asset trading (CFDs, futures, options) and betting within video game environments, concentrated a higher proportion of participants with scores indicative of problem gambling and of young people reporting six or more harms on the SGHS. At the opposite end, lotteries

Figure 3

Adjusted odds ratios from the fully adjusted model (Model 3) for gambling severity (PGSI) and gambling-related harm (SGHS) according to participation in each activity



Note. The model includes adjustments for maximum participation frequency, total number of activities, and sociodemographic variables (age, sex, marital status, educational level, income, and employment or education/training status), which are not shown in the figure.

grouped the highest percentage of participants without associated harms and the lowest rates of problem gambling.

Ordinal regression models, which simultaneously included all gambling and gambling-like activities, confirmed this general pattern. The explanatory capacity of both models was high ($R^2 = 0.418$ for gambling severity and $R^2 = 0.296$ for gambling-related harm) and greater than that observed in previous studies that have assessed gambling participation using broader time frames, such as the past year (Greer et al., 2023; Krotter et al., 2024). This finding suggests that the use of recent participation measures (past 60 days) may contribute to a better explanation of gambling severity and related harms.

Ordered by strength of association, the activities related to gambling severity were horse race betting, slot machine gambling/electronic gaming machines, commodity trading, eSports betting, skin betting, betting on live-streamed matches, casino gambling, sports betting, and cryptocurrency trading. In contrast, participation in lotteries was consistently associated with lower severity, in line with evidence indicating a lower relative risk for this activity compared with other gambling products (Booth et al., 2020; Tran et al., 2024; Wardle & Tipping, 2023, 2026).

Involvement in gambling-like activities was associated with a two- to threefold higher likelihood of being classified in higher severity categories (aOR = 1.90–2.86), magnitudes comparable to those observed for traditional gambling products considered high risk, such as slot machines, casino games, and sports betting, whose elevated potential to generate gambling-related problems has been widely documented (Allami et al., 2021; Currie et al., 2021; Luquiens et al., 2022; Tran et al., 2024; Wardle & Tipping, 2026).

Within gamblified products, betting in video game environments stood out among those most strongly associated with gambling severity, with the exception of loot box purchases, which did not show significant associations with either severity or gambling-related harm. This finding is consistent with international evidence identifying a stronger role for eSports betting and skin betting than for loot boxes in predicting gambling problems (Greer et al., 2023; Hing et al., 2021; Kim et al., 2023; Wardle & Tipping, 2023), despite the latter having received greater research attention.

However, the model results also indicate that the analytical focus should not be limited to the video game ecosystem. In this regard, although cryptocurrency trading has been the primary focus of the literature examining the intersection between speculative investment and problem gambling (Davies & Ferris, 2022; Johnson et al., 2023; Kim, 2024; Loscalzo et al., 2025), the data from the present study indicate that commodity trading (e.g., gold, agricultural products) was the gambling-like activity most strongly associated with gambling severity, showing a stronger relationship than cryptocurrency trading (aOR = 2.83 vs. 1.90). Moreover, participation in commodity trading, together with eSports betting, was the only activity associated with a higher number of gambling-related harms, doubling the likelihood of experiencing negative consequences. These findings are consistent with recent studies suggesting that the relationship between cryptocurrency trading and problem gambling is not necessarily consistent, and that participation in markets characterised by greater volatility and risk, such as commodities or Forex, may be more closely linked to gambling severity (Coloma-Carmona, Carballo, Miró-Llinares, & C. Aguerri, 2025).

To test the hypothesis proposed by LaPlante et al. (2013, 2014), the models included adjustments for maximum participation frequency (depth) and the number of gambling activities undertaken (breadth). The number of gambling activities was not a significant predictor of either gambling severity or gambling-related harm, whereas participation frequency was. Moreover, the associations initially observed did not attenuate after introducing these adjustments. This pattern has also been reported in other studies, where mere participation in activities such as casino gambling or those conducted predominantly in online environments remains associated with gambling severity even after controlling for overall involvement (Allami et al., 2021; Binde et al., 2017; Gainsbury et al., 2019; Gooding & Williams, 2024; Mazar et al., 2020; Nelson et al., 2018; Wardle & Tipping, 2026).

In the present study, activities such as slot machine use, casino gambling, and betting within video games not only retained their association but showed stronger effects after adjustment, suggesting that controlling for maximum annual participation frequency in these activities may help isolate the specific contribution that recent participation in these modalities has on gambling severity.

The final adjustment for sociodemographic variables (specifically age, sex, marital status, educational level, monthly income, and employment or training status) did not substantially modify the associations observed with gambling severity. However, in this model, employment and university education appeared to act as protective factors, in line with previous findings (Moreira et al., 2023) and with the importance attributed to social determinants in shaping vulnerability to mental health problems (Al-Halabí & Fonseca-Pedrero, 2024). By contrast, in the gambling-related harm model, sociodemographic adjustment reduced the magnitude of the associations with sports betting, slot machine gambling, and skin betting, which were no longer significant. In this case, having a university education was associated with a lower number of harms, whereas being male was associated with a higher number of reported harms (Browne et al., 2019; Raisamo et al., 2013; Raybould et al., 2021).

Across the models, differences in the explanatory capacity of the various activities to predict gambling severity and

gambling-related harm were observed, with explanatory power being lower for harm. This pattern, also described in the literature (Gainsbury et al., 2019; Greer et al., 2023), reinforces evidence that both measures capture related but non-equivalent dimensions (Browne et al., 2022). Whereas the PGSI assesses behaviours associated with excessive gambling or loss of control, the SGHS captures negative consequences that have actually been experienced (Browne et al., 2018, 2022; Delfabbro et al., 2020).

Accordingly, the fact that certain activities did not remain statistically significant after sociodemographic adjustment suggests that the experience of harm may be particularly sensitive to sociodemographic or contextual factors. This may also help explain why negative effects of gambling can emerge even at subclinical levels of severity (Browne et al., 2017, 2018, 2022; Browne & Rockloff, 2017; Canale et al., 2016; Hwang et al., 2024; Wardle et al., 2024), highlighting the importance of not focusing the analysis of harm on static risk categories that may be insufficient to capture processes that, in addition to being dynamic, are highly dependent on the context in which they occur (Al-Halabí & Fonseca-Pedrero, 2024; Fonseca-Pedrero & Al-Halabí, 2024).

The findings of the present study should be interpreted in light of several limitations. The use of an online panel as a recruitment strategy limits the generalisability of the results, as individuals who are members of such panels may have greater engagement with digital environments or higher rates of problem gambling (Hays et al., 2015; Hing, Dittman, et al., 2022; Williams & Volberg, 2012). Nevertheless, the rates of problem gambling observed in this study are consistent with those reported in national surveys for this age group (OEDA, 2024). Moreover, several studies have shown that online panels consistently reproduce associations between gambling-related variables, supporting the validity of this methodology for the purposes of the present study (Delfabbro, King, Williams, et al., 2021; Lee et al., 2023; Russell et al., 2022; Wardle & Tipping, 2023).

Another limitation of the study is its cross-sectional design, which prevents establishing causal relationships between participation in the activities assessed and gambling severity or related harm. Likewise, although the study focused on analysing the relationship between recent participation and indicators of severity and harm, activities were assessed without differentiating the specific access channel (online or land-based). Future studies could incorporate this distinction, allowing a more precise examination of the potential role of the gambling context in the emergence of problems or negative consequences. Finally, although the SGHS is a widely used instrument for measuring harm and has strong psychometric support (Browne et al., 2021), its brief 10-item format may not comprehensively cover all harm domains described in the literature (Langham et al., 2016). Future studies could use broader measures of gambling-related harm, such as the extended GHS-20 version (Browne, Rawat, et al., 2025), to assess different domains of impact in greater detail and provide a more comprehensive estimate of harm.

Despite these limitations, the present study contributes to addressing an important gap in the literature by jointly analysing the impact of participation in video game–related betting and financial trading alongside traditional forms of gambling on gambling severity and gambling-related harm among young adults. This approach advances understanding of the role of these emerging forms of digital expenditure in a context where video games and cryptocurrencies already constitute the first and third forms of monetary spending among young people in Spain (OEDA, 2024). In addition, the use of a recent time frame to measure participation, together with adjustment for overall involvement and sociodemographic factors to replicate the analytical approach of previous studies (LaPlante et al., 2014; Wardle & Tipping, 2023, 2026), enabled the identification of differential patterns between traditional and gambling-like activities, with the latter showing associations comparable to those observed for higher-risk traditional gambling products.

From a public health perspective, the evidence that activities not legally recognised as gambling can be associated with gambling severity and related harm underscores the need to incorporate them into assessment and prevention strategies.

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Conflict of interest

All authors declare no conflicts of interest related to the research, authorship, and publication of this article.

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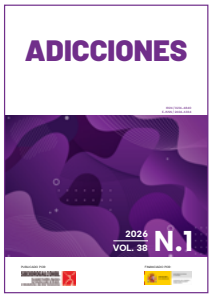
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LETTER TO THE EDITOR

False positives in amphetamine drug screening due to dimethyltryptamine

Falso positivo en el cribado de anfetaminas secundario a dimetiltriptamina

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Classic psychedelic compounds such as psilocybin, D-lysergic acid (LSD), N,N-dimethyltryptamine (DMT) and mescaline, among others, are frequently used worldwide today (Wilkes et al., 2024), and the use of ayahuasca has also expanded everywhere. Despite evidence supporting its therapeutic potential, more scientific proof is needed to fully assess therapeutic benefits (Ruffell et al., 2023). Also, ayahuasca can be used by alleged shamans to commit acts of sexual violence (Strano Rossi et al., 2019).

We present the case of a 45-year-old female patient admitted to the emergency department after suffering physical assault during a spiritual ceremony in a rural setting, from which she managed to escape. The patient admitted consuming ayahuasca, but did not report sexual assault or head trauma. Physical examination: blood pressure: 106/75 mmHg, heart rate: 104 bpm, temperature: 36ºC, SpO2: 100%. Good general condition, afebrile and hemodynamically stable. Nervous. Glasgow Coma Scale score of 15, no focal neurological deficits, no meningismus. Multiple abrasions on the upper and lower extremities. X-rays of both knees and knee bones showed no signs of fractures.

The urine toxicology screen was positive for cannabis (SureStep™ Urine Drug Test Cassette), and the toxicology protocol for chemical submission was requested from the referral hospital laboratory. The patient was discharged with a treatment of amoxicillin-clavulanic acid and ibuprofen.

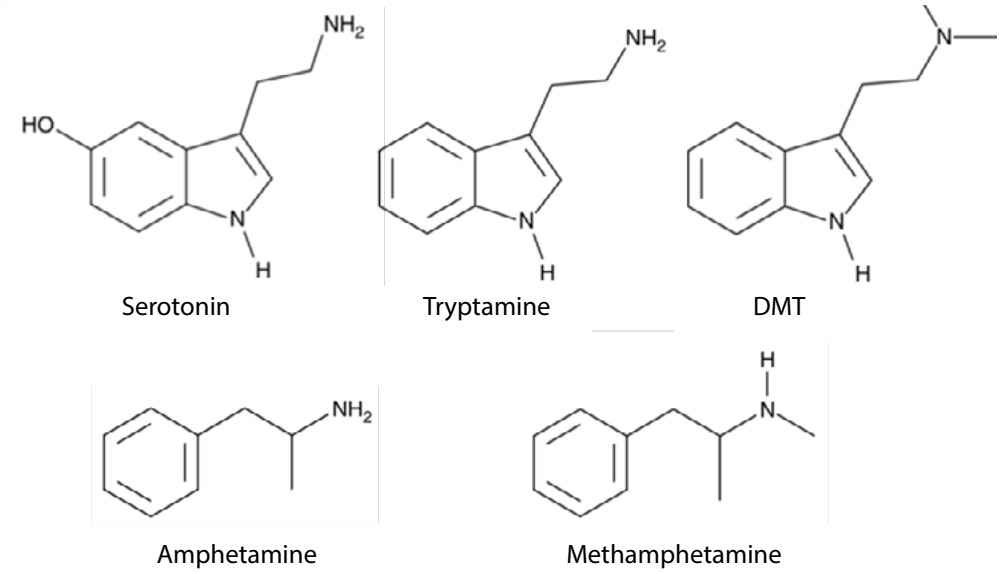
The referral hospital's urine toxicology screen was positive for amphetamines (>2000 ng/mL) and cannabis, and negative for ethyl glucuronide, cocaine, ecstasy, opiates, LSD, ketamine, methadone, and benzodiazepines (DRI® Assay, Microgenics Corporation). Blood alcohol concentration was undetectable. The presence of amphetamine, methamphetamine, or any substance known to produce false positives in the amphetamine immunoassay could not be confirmed by GC-MS. Scopolamine and GHB were also not detected. Using LC-MS/MS with a method capable of detecting 108 substances (MassTox® Drugs of

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Figure 1

Chemical structures: Serotonin, Tryptamine, N,N-Dimethyltryptamine (DMT), Amphetamine and Methamphetamine



Abuse, Chromsystems), only cannabis was detected (THC-COOH 45 ng/mL). Given the patient's reported history of voluntary intake, DMT and metabolites of β-carboline alkaloids were specifically sought in the non-targeted GC-MS analysis. DMT and hamol, the main metabolite of harmine, were identified using the National Institute of Standards and Technology Mass Spectral Library (NIST23).

Ayahuasca is a traditional Amazonian brew prepared by mixing two plants: *Banisteriopsis caapi vine* (containing β-carbolines) and *Psychotria viridis* (containing DMT). DMT is a tryptamine, a hallucinogenic compound structurally analogous to serotonin (Figure 1). It does not produce oral psychotropic effects on its own due to hepatic metabolism. However, the β-carbolines present in ayahuasca inhibit monoamine oxidases, allowing DMT to reach the central nervous system (Hamill et al., 2019). Ayahuasca causes cognitive, sensory, and emotional changes, including possible hallucinations and erratic behaviour, and patients may develop long-term cognitive impairment (dos Santos et al., 2017). The onset of these effects occurs 30-60 minutes after ingestion and lasts up to 4 hours. Common adverse effects include nausea and vomiting, tachycardia, agitation, hypertension, mydriasis, seizures, and neuroendocrine disturbances.

From a therapeutic perspective, family, social, and psychiatric history should be considered, toxicological screening should be ordered, symptomatic supportive care should be provided, and patients should be closely monitored. Benzodiazepines are indicated to control anxiety or agitation, and neuroleptics may also be necessary. Withdrawal syndromes are rare.

The lack of a specific immunoassay for DMT detection, and its very short half-life t1/2, makes DMT a difficult toxicological target in urine. Fatal cases with analytical confirmation of DMT are very rarely published. Sklerov et al. (2005) presented the case of a 25-year-old man found dead the morning after consuming herbal extracts containing hallucinogenic β-carbolines and tryptamines (Sklerov et al., 2005). In our setting, it has been detected and documented in two male patients in ED, also under application of a chemical submission protocol (Fernández Alonso et al., 2024). While LSD screening methods do not show cross-reactivity with DMT, false-positives have been documented in amphetamine screenings due to the structural similarity of DMT to amphetamine (Regester et al., 2015) (Figure 1). There are specific analytical methods allowing these alkaloids (DMT and β-carbolines) to be identified in conventional and alternative biological samples (Brito-da-Costa et al., 2020; Tavares et al., 2020).

In summary, DMT screening is recommended in drug-facilitated sexual assault protocols when victims are suspected of participating in spiritual rituals or when patients report experiencing brief but intense visual and auditory hallucinations. The potential for false positives in amphetamine screening caused by DMT should raise suspicion of its presence, although not all screening methods are affected in the same way.

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Conflict of interests

The authors declare no conflict of interest.

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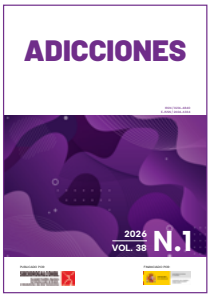
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CORRIGENDUM

ALCO-VR Project: A randomized clinical trial evaluating virtual reality cue-exposure Therapy for Treatment-Resistant Alcohol Use Disorder patients

Proyecto ALCO-VR: Un ensayo clínico aleatorizado para la evaluación de la eficacia de la Terapia de Exposición a Señales con Realidad Virtual en pacientes resistentes al tratamiento diagnosticados con trastorno por uso de alcohol

Alexandra Ghiță*; Olga Hernández-Serrano**; Jolanda Fernández-Ruiz***; Mariano Gacto-Sánchez****; Miquel Monras *****; Antoni Gual*****; Bruno Porras -García******; Marta Ferrer-García***; José Gutiérrez-Maldonado***.

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Text that appears in the published article (vol. 38-3, page 212):

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Correction:

Funding and Acknowledgements

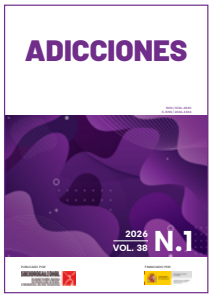
Research funded by the Spanish Ministry of Health, Delegation of the Government for the National Plan on Drugs (FEDER/EU/Project 2016I078: ALCO-VR: Virtual reality-based protocol for the treatment of patients diagnosed with severe alcohol use disorder). The study was also supported by AGAUR, Research Agency from Catalunya, 2017SGR1693, and by the grant JDC2022-048939-I; funded by the MCIN/Agencia Española de Investigación and by the European Union NextGenerationEU/PRTR.

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OBITUARY

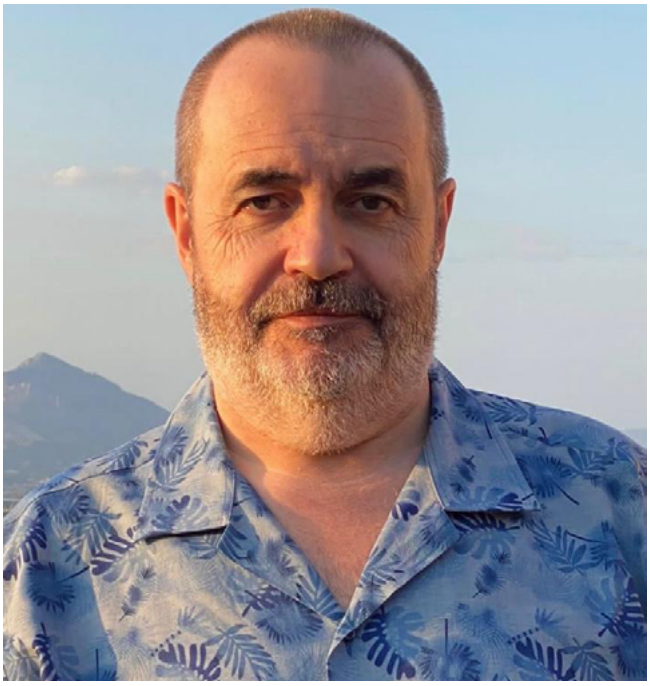
Jorge Manzanares: posthumous tribute to a great researcher, teacher, and friend

Jorge Manzanares: homenaje póstumo a un gran investigador, docente y amigo

Navarrete, F.*; García-Gutiérrez, M.S.*; Rubio, G.*; Maldonado, R.*; Ambrosio, E.*; Burillo-Putze, G.*; Colado, M.I.*; Costas, J.*; Cuesta-Zorita, M.J.*; Farré, M.; García de Jalón, E.*; García-Fuster, M.J.*; Gerrikagoitia, I.*; Grandes, P.*; Herradón, G.*; Marcos-Martín, M.*; Miñarro, J.*; Muga, R.*; Orio, L.*; Quintana, J.B.*; Rodríguez-Arias, M.*; Roncero, C.*; Ruiz-Idiago, J.M.*; Spuch, C.*; Valverde, O.*; Viveros, M.P.*; Rodríguez de Fonseca, F.*; Torrens, M.*

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Today we bid farewell to Jorge Manzanares, a great researcher and academic, mentor, loyal friend and, above all, an extraordinary human being who has left an indelible mark on those of us who had the privilege of knowing him. His scientific legacy is immense, but even greater is the memory of his integrity, his constant struggle and his way of being in the world, without concessions. As members of his research team, colleagues from the field of Addictions, disciples and friends, we pay tribute to him, remembering his irreplaceable figure. We all remember his enthusiastic and vital spirit, displayed both in the laboratory and in the small things of everyday life, to which he devoted himself passionately until the very last day.



Jorge Manzanares Robles graduated in Pharmacy from the Complutense University of Madrid in 1985 and obtained his PhD in Pharmacology in 1987, carrying out his predoctoral stage in hospitals such as Ramón y Cajal and La Paz. Between 1988 and 1993 he was a researcher at Michigan State University (East Lansing, USA). Upon

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his return to Spain, he worked in different centres such as Complutense University, CSIC or 12 de Octubre Hospital, linked to research in pharmacology, neurobiology and psychiatry. In 2004 he obtained the position of Associate Professor at Miguel Hernández University (UMH), joining as Principal Investigator of the Laboratory of Translational Neuropsychopharmacology of Neurological and Psychiatric Diseases at the Institute of Neurosciences, a joint UMH-CSIC centre (San Juan de Alicante, Spain). Since 2011 he had been Full Professor of Pharmacology and Dean of the Faculty of Pharmacy at UMH. His professional life was not only centred on his university, but also on multiple national and international centres. Between 2007 and 2011 he promoted and directed the Unit of Translational Neuropsychopharmacology at the University Hospital Complex of Albacete. Subsequently, he carried out leadership and advisory functions in different academic and international spheres, including the scientific direction of a chair on Parkinson's disease, his participation in the Ibero-American Conference of Faculties of Pharmacy (COIFFA), where he was member, vice-president and, recently, President, and his links as Adjunct Professor at New York University (USA) and as Honorary Professor at Norbert Wiener University in Lima (Peru). In addition, he was part of the Executive Committee of the Spanish Society of Dual Disorders and acted as academic advisor for the harmonisation of studies in Bolivian public universities.

But all this academic activity becomes small if we consider his true vocation as a researcher in the field of translational neuropsychopharmacology and, especially, in addictive disorders. Founder of the Translational Neuropsychopharmacology research group at Miguel Hernández University, together with Francisco Navarrete and María Salud García-Gutiérrez, he carried out tireless work in translational research in the neuropharmacology of addiction and neuropsychiatry, as well as in the training of top-level scientists who today proudly take on the challenge of continuing his work and his leadership. From the beginning, Jorge was interested in the role of the opioid system and, shortly afterwards, of the cannabinoid system, in the control of motivated behaviour, emotions and pain. He was a pioneer in the study of the interactions between endogenous opioids and cannabinoids in pain, in neuroendocrine control, and in the pathogenesis of complex psychiatric diseases such as addictions to alcohol, opiates, cannabis and psychostimulants, including their main comorbidities, namely anxiety, depression and psychosis. Author of more than 250 works of great scientific impact, we may highlight his studies on the role of the CB2 cannabinoid receptor in neuropathic pain and in addictions, in collaboration with Rafael Maldonado; the impact of environmental factors (such as abuse) on alcohol use disorder and the development of cannabidiol-based therapies for it, in collaboration with Gabriel Rubio; the role of opioid peptides in cocaine addiction, in collaboration with Emilio Ambrosio; the influence of a high-fat diet on the response to psychostimulants with Marta Rodríguez-Arias and José Miñarro; the impact of alcohol or cannabis use during pregnancy and lactation on offspring and their mothers; or the most recent and innovative research on the therapeutic potential of modulation of the GLP-1 peptide receptor in addictions.

He shared all this immense work, through numerous collaborations, with scientists from all over the world and, especially, with the Spanish community of addiction researchers. He was always at the forefront in the defence and promotion of addiction research. His commitment was first expressed through the Network of Addictive Disorders (RTA), and currently in the Addiction Primary Care Research Network (RIAPAd), both funded by the Carlos III Institute of Health (ISCIII). Thanks to these networks, Jorge devoted the last 20 years to weaving a dense network of collaborations that enabled him to develop complex and innovative translational projects that earned him the respect and admiration of everyone, and their friendship. Because Jorge was a loyal and sincere person with his friends, undaunted, combative against what he believed were injustices and, at the same time, extremely amusing. He did not leave you indifferent. As a mentor, he supervised fourteen doctoral theses, with all his doctoral students developing professional careers in the academic, scientific or healthcare fields with notable success, and constituting the structural basis of his research group, which will now continue his work.

The recognitions he received are the result of this intense academic and research life. In 2018 he was elected Corresponding Academician of the Santa María de Murcia Academy of Pharmacy, Corresponding Academician of the Ibero-American Academy of Pharmacy, and Senior Professor and Consulting Researcher of the Faculty of Medicine of the University of Cartagena de Indias in Colombia. In 2019 he was appointed Full Academician (medal 49) of the Royal National Academy of Pharmacy (RANF) of the Institute of Spain, Foreign Corresponding Academician of the National Academy of Pharmaceutical Sciences of Mexico, and Corresponding Academician of the Mexican Academy of Psychiatry and Mental Health. In 2021 he was appointed Distinguished Professor by the Faculty of Chemical Sciences of the National University of Córdoba in Argentina. In 2022, he was named Distinguished Visitor by the Deliberative Council of the City of Rosario and received the "Honoris Causa" Doctorate from the National University of Rosario (Argentina). In 2023 he was appointed Corresponding Academician of the National Academy of Medicine of Mexico and member of the Executive Committee of the European Association of Faculties of Pharmacy (EAFP). In

2025 he was appointed Full Academician by the Academy of Pharmacy of the Valencian Community (AFCV) and, very recently, in 2026, he was appointed Corresponding Academician of the Academy of Pharmaceutical Sciences of Portugal (ACFP). In addition, he obtained numerous Research Performance Awards for Full Professors of UMH uninterruptedly between 2014 and 2019, as well as the 2016 Award of the Ibero-American Academy of Pharmacy.

Science is a community of knowledge and curiosity. It is much more than methods, hypotheses, prizes and recognitions. Science is made up of extraordinary men and women who devote their effort and enthusiastic will to the search for the elusive understanding of our own essence as human beings. When one encounters a true scientist and a person with as much humanity as Jorge Manzanares, curiosity, innovation and the need to know more flourish spontaneously. All those of us who had the privilege of his friendship and of his excellence have the duty to keep his spirit alive. He leaves behind his wife, Paz, and two daughters, Marta and Laura, whom we accompany in the pain of their loss. His memory and his legacy will endure both in his family and in the community of researchers who struggle daily against addiction. May he rest in peace.

GUIDELINES FOR AUTHORS

Adicciones is edited by Socidrogalcohol, Spanish Scientific Society for Studies on Alcohol, Alcoholism and Other Drug Dependencies.

Adicciones publishes original articles in the field of addictions, including publications on treatment, prevention, basic and descriptive studies from different disciplines (medicine, psychology, basic research, social research, etc.). All articles are selected after undergoing an anonymous review process carried out by experts in each topic.

Adicciones publishes 4 issues per year in March, June, September and December. The journal includes five types of publications: editorials, original articles, review articles and letters to the editor.

In order to facilitate reading and avoid possible grammatical errors, references in these guidelines to author and authors, reviewer, reviewers, editor, editors, must be understood as referring respectively to author (male or female), authors (male or female), reviewer (male or female), reviewers (male or female), editor (male or female), editors (male or female).

1. GENERAL CONSIDERATIONS

The journal Adicciones adheres to the Farmington agreement, which authors may consult when preparing their manuscripts and which includes the recommendations and ethical principles of ISAJE (International Society of Addiction Journal Editors): **https://www.isaje.net/farmington-consensus.html**

The publication guidelines of the American Psychological Association, 7th edition (2020), may also be consulted.

In addition, the journal Adicciones adheres to the Declaration on Research Assessment (DORA), which recognizes the need to improve the methods for evaluating the results of academic research.

Languages

The journal accepts articles in Spanish and English for review. The final version of the articles will be published in both languages.

Policy on originality, authorship, and contributions

Articles must be original and must not have been previously published. Authors must ensure that no significant part of the submitted material has been previously published. In case of doubt, previously presented or published material in other journals must be provided before the article can be considered for review.

Only those who have made substantial contributions should be considered authors:

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2. to the drafting of the article or its critical revision; and
3. who have given approval of the final version to be published.

All authors shall accept authorship and must declare that they have actively participated in the preparation of the manuscript, and that both the draft and the final version have been read and approved by each of them.

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Additionally, it should be stated, where applicable, whether generative intelligence has been used in the preparation and/or review of the manuscript and what tasks have been performed with the support of such intelligence.

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The journal will not accept manuscripts in which fabrication and/or falsification of data is suspected. All results presented must be verifiable and derived from rigorous scientific methodologies, and authors may be asked to demonstrate this. If detected, the manuscript will be rejected or retracted if it has already been published.

All manuscripts will be submitted to plagiarism detection systems, as plagiarism is strictly prohibited, before being sent for peer review. If a significant percentage of non-original content is identified, the editorial proposal will be rejected.

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The journal policy requires that all articles and editorials explicitly state the existence or absence of conflicts of interest in the corresponding section.

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All submitted works must indicate compliance with the ethical principles necessary to conduct the research, including reference to the ethics committee or research office that evaluated and endorsed the adequacy of the research within the corresponding ethical and legal framework, and must include informed consent tools when necessary.

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Editors, guest editors, members of the editorial board and reviewers must declare possible conflicts of interest and abstain from participating in peer review if any exist. This includes, for example, having published with the authors in the last 3 years or belonging to the same institution.

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The journal reserves the right to accept such changes or to withdraw any publication that may contain erroneous information or result from research misconduct.

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Complaints must clearly include the reason, contact details, and relevant supporting evidence. Complaints not supported by evidence, based on opinion, or with defamatory intent will be rejected.

Complaints regarding content published in the journal must first be addressed to the authors, and if it is not possible to contact them, one may write directly to the journal Adicciones.

Well-documented complaints supported by evidence will be reviewed by the Editorial Committee following the rules of the Committee on Publication Ethics (COPE). If necessary, external experts or relevant entities, including legal advice, will be consulted.

Open Access Policy

Adicciones is an Open Access journal committed to open science; therefore, it encourages authors to publish preprints and postprints of their manuscripts.

When these manuscripts are published and have a final version, authors must indicate that the final version is available on the Adicciones journal website, adding the corresponding link to their article as well as the DOI.

2. PREPARATION OF MANUSCRIPTS

Authors must follow exclusively the Publication Manual of the American Psychological Association, 7th edition (2020) (**www.apastyle.org**).

The journal Adicciones respects and promotes diversity. Authors must use inclusive language free of bias and stereotypes.

Following the DORA declaration, there is no exact word limit nor limit on bibliographic references for submitted works. Nevertheless, all included information must be strictly necessary, and brevity and conciseness are recommended.

Articles must be of great interest to the scientific community in the field of addictions, representing a significant impact in their area of research and offering clearly novel conclusions and implications.

Works referring to very specific realities or highly particular situations, or that are basically descriptive, will be avoided — unless they are highly novel.

In preparing manuscripts, authors are recommended to follow the reporting guidelines for each type of addiction research from ISAJE: **https://www.isaje.net/reporting-guidelines.html** and the guidelines for research types included in the Equator Network: **https://www.equator-network.org/**

Types of Articles

Editorials

As a general rule, editorials are brief manuscripts commissioned by the Editorial Committee from authors or research groups of recognized prestige. Their usual and indicative length is approximately 3,000 words and they are published at the beginning of each issue of the journal.

The main objective of these contributions is to guide, comment on, or reflect upon topics of interest and current relevance for the scientific and professional community. They usually include, concisely, analyses and positions on emerging trends or relevant debates in the field of addictions.

Original Articles

These will preferably be clinical or experimental research works in the field of addictions. Empirical articles with large samples and solid methodologies appropriate to the objectives pursued will be especially valued.

Review Articles

They will present the update of a topic in a rigorous and exhaustive manner. In general terms, only systematic reviews and meta-analyses will be accepted. These reviews must follow systematized methods (e.g., PRISMA criteria) and be registered in review protocol databases (e.g., PROSPERO).

Letters to the Editor

They consist of a brief presentation on a particularly novel and original area of research, or a reply or clarification to an article published in the journal. In the latter case, the letter must be received within 10–12 weeks following the publication of the article in the journal issue.

They will have a maximum length of approximately 800 words, 10 references, and one table or figure.

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All articles must be submitted through **www.adicciones.es**. On the platform, all instructions for preparing and uploading the manuscript can be found.

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All authors and co-authors must be registered on the journal platform and their contact details (e.g., email and telephone) must be indicated in the first step of submission to initiate the process.

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Every manuscript submitted for consideration for publication in the journal Adicciones must be accompanied by a letter signed by all authors or by the corresponding author with authorization from the other authors.

This document must literally state the following:

Review document signed by all authors

All signatories of the manuscript accept authorship and declare that we have actively participated in the preparation of the manuscript, and that both the draft and the final version have been read and approved by each of us.

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It is advisable to clearly divide the work into sections, following, whenever possible according to the characteristics of the study, the following general scheme: Introduction (however, the word introduction will not be included, as it is assumed), Method, Results, Discussion, Acknowledgements, Conflict of Interest, Contribution and Authorship, and References.

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The method used must be clearly described (sample selection, how data were collected, data collection or assessment instruments, procedure, etc.). Assessment instruments, treatments, drugs used, apparatus, evaluation systems, statistical tests, etc., must be identified. The type of study (descriptive, epidemiological, experimental, clinical trial, etc.) must be specified.

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Acknowledgements

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References

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