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DELEGACIÓN DEL GOBIERNO PARA EL PLAN NACIONAL SOBRE DROGAS

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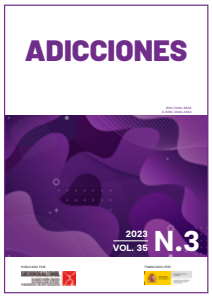

EDITORIAL

Drugs of abuse and epigenetics: Past, present and future

Drogas de abuso y epigenética: Pasado, presente y futuro

João P. Silva*,**; Félix Carvalho*, **.

* Associate Laboratory i4HB - Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal.
** UCIBIO, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313, Porto, Portugal.

Epigenetic changes

Epigenetic modifications are commonly defined as mitotically or meiotically heritable, and possibly reversible, changes in gene expression that do not entail any direct alteration in the DNA sequence (Dupont et al., 2009). Accumulating evidence suggests that drug use-related environmental (e.g., drug-taking behavior) and social (e.g., stress) factors may alter gene expression in the brain (and other organs) of drug abusers, causing developmental and behavioral changes in these individuals, and likely leading to the onset of substance use disorders (SUDs). Understanding the mechanisms underlying the interaction between these environmental and genetic factors thus assumes critical relevance to ascertaining the development, heredity, and possibly improving the treatment of SUDs.

There are three epigenetics mechanisms that have been mostly associated with substance use in animal models: DNA methylation, histone modifications, and generation of noncoding RNAs (Bastle and Neisewander, 2016). DNA methylation refers to the covalent modification of the fifth carbon in the cytosine base (5-mC), catalyzed by DNA methyltransferases (e.g., DNMT1, DNMT3a, DNMT3b), which mainly occurs in the CpG dinucleotides within the genome, and that is often associated with the repression of transcription (Kouzarides, 2007). Histone modifications relate to post-translational changes (e.g., acetylation, methylation, phosphorylation) in the amino acid residues of these proteins, which can cause transcriptional activation, silencing, and chromatin assembly. For example, histone acetyl transferases catalyze the addition of acetyl groups, usually on a lysine (K) residue, causing chromatin relaxation, which promotes a transcriptionally accessible state. Histone methylation may cause either gene activation or repression, depending on where it occurs. For example, promoter methylation may silence gene expression, whereas methylation occurring at another site of the DNA sequence may trigger the expression of a different gene (D'Addario et al., 2013).

Noncoding RNAs (e.g., miRNAs) comprise a family of small RNAs that post-transcriptionally regulate gene expression in a negative manner, controlling processes like chromosome dynamics, RNA editing or mRNA degradation (Korolev et al., 2018; Liu et al., 2018).

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■ **Send correspondence to:**
João P. Silva, Félix Carvalho. Associate Laboratory i4HB - Institute for Health and Bioeconomy, UCIBIO, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, 4050-313, Porto, Portugal. Emails: jpmsilva@ff.up.pt, felixdc@ff.up.pt

Abnormal epigenetic patterns and neuronal diseases

Epigenetic signaling has been reported to be a key regulator of several biological processes (e.g., neural stem cell fate) (Szutorisz and Hurd, 2018). As such, dysregulation of such mechanisms may lead to the onset of distinct disorders, with abnormal DNA methylation and histone acetylation patterns in the brain having already been associated with cognitive impairment or childhood brain overgrowth syndromes (Gomes et al., 2020).

For example, mutations in *dnmt3a* (leading to its down-regulation) are known to underlie Tatton-Brown-Rahman syndrome, and methylation of the *ezh2* gene is known to be involved in other overgrowth syndromes such as Sotos or Weaver syndromes. Sotos syndrome has also been correlated with mutations in the gene *nsd1,* coding for the Nuclear Receptor Binding SET Domain Protein 1, a protein displaying histone methyltransferase activity that is responsible for methylating lysine 36 at histone H3 (H3K36) and lysine 20 at histone H4 (H4K20). In addition to the loss of histone methyltransferase activity, the hypermethylation at the 5' regulatory region of this *nsd1* gene in human neuroblastoma and glioma cells has been shown to contribute to Sotos syndrome (Berdasco et al., 2009). A systematic review published by Dall'Aglio et al. (2018) has consistently found methylation at *prrt1*, *c11orf21/tspan32*, and *or2li3* genes (encoding for proline-rich transmembrane protein 1, chromosome 11 open reading frame 21, tetraspanin 32 and olfactory receptor family 2 subfamily L member, respectively) in autism spectrum disorders (Dall'Aglio et al., 2018). Methylation of the *vipr2* gene (which codes for vasoactive intestinal peptide receptor 2) has been detected in attention deficit and hyperactivity disorder (ADHD). Notably, since proteins encoded by *or2li3* (ASD) and *vipr2* (ADHD) are involved in G protein-coupled receptor-mediated neurotransmitter signaling, it seems that the epigenetic dysregulation of neurotransmission could underlie the onset of these disorders. Along with the methylation of *tspan32*, trimethylations and acetylation on lysine residue 27 of histone H3 (H3K27) have been found in Beckwith-Wiedemann syndrome, which is characterized by macrosomia and hemihyperplasia.

Mutations in the *mecp2* gene (encoding for methyl-CpG-binding protein, reported to regulate gene expression by binding to methylated DNA) have been correlated to Rett syndrome, a disorder associated with cognitive impairment in children (Good et al., 2021).

There is also accumulating evidence of epigenetic modifications in schizophrenia (SCZ) patients. For example, both hyper- and hypomethylation of different CpG sites have been correlated with reality distortion symptoms in SCZ patients (Liu et al., 2013). Moreover, increased levels of histone methyltransferases and increased acetylation in lysines 9 and 14 of histone H3 (H3K9K14ac) have been reported in patients with SCZ (Jin et al., 2008). Mutations in the *cbp* gene, encoding for the CREB-binding protein (CBP), have been reported as causing the loss of this protein's intrinsic histone acetyltransferase activity, resulting in a deficiency in cAMP response element-binding protein (CREB) recruitment that is typical of Rubinstein-Taybi syndrome (a neurodevelopmental disorder) and that has also been reported to occur in Alzheimer's disease (Caccamo et al., 2010). Interestingly, abnormal histone acetylation patterns have been recently confirmed to occur in patients with Alzheimer's, including the up-regulation of the acetylation of lysines 27 and 9 on histone H3 (H3K9ac and H3K27ac) or the losses of acetylation in lysine 16 on histone H4 (which normally increase with aging) (Nativio et al., 2020).

Drug abuse and epigenetics

Substances of abuse may induce epigenetic modifications, namely DNA methylation and histone modifications, which have already been associated with changes in the reward system, psychomotor activity, craving, and relapse. Indeed, the interaction of these substances with proteins involved in different signaling pathways (e.g., neurotransmitters, transporters), may propagate intracellular signaling into the nucleus, affecting gene expression and subsequently gene transcription (Nielsen et al., 2012). Moreover, the brain region at which such changes occur may determine most of the SUD-related outcomes. For example, DNA methylation and histone modifications occurring in the nucleus accumbens (NAc), a brain region associated with the reward system, may contribute to the regulation of addictive behavior (Flagel et al., 2016). Also, increased gene expression resulting from exposure to substances of abuse is often associated with increased histone acetylation levels, as acetylation usually turns the chromatin into a more relaxed, more transcriptionally active state. Nevertheless, some psychoactive substances have been associated with increased activity of histone deacetylases (HDACs), resulting in decreased histone acetylation, and subsequent transcriptional gene repression. For example, alcohol has been shown to increase HDAC11 and nicotine has been reported to increase the transcription of HDAC1 (Bala et al., 2017; Brooks and Henderson, 2021).

Exposure to substances of abuse (e.g., cocaine, opioids) may also cause a decrease in histone methyltransferase G9a expression (an enzyme responsible for the dimethylation of lysine 9 in histone H3, H3K9me2, in the NAc, which is often associated with transcriptional repression). Notably, decreased G9a has been correlated with a depressive-like behavior in mice (including decreased social interaction and increased anhedonia), and has been detected in the postmortem NAc tissue of clinically depressed individuals (Covington et al., 2011). Interestingly, drug-induced

decreased G9a expression is often associated with ΔFosB expression in that same region, suggesting a link between these two proteins (Maze et al., 2014).

Drug-induced modulation of noncoding RNAs has also been reported to underlie SUDs. For example, upregulation of the miRNA miR-212 in the dorsal striatum of rats, a brain region involved in drug tolerance, has been shown to mimic the compulsive drug-taking behavior observed in drug addicts (Sadakierska-Chudy et al., 2017). Increased miR-206 in the medial prefrontal cortex (e.g., as induced by alcohol) enhances the drug-seeking behavior, most likely by suppressing brain-derived neurotrophic factor (BDNF) expression.

Importantly, it is worth noting that epigenetic marks can be passed on to future generations, provided such modifications occur in the germ cells. For example, it has been observed that male adult rats with a compulsive cocaine self-administration behavior passed an addiction-resistance phenotype onto their male (but not female) descendants, which was most likely mediated by increased H3 acetylation of the BDNF promoter (also known as being associated with resistance to drug effects) (Vassoler et al., 2013). Moreover, male offspring of F0 female adolescent rats repeatedly administered morphine were shown to be more sensitive to the effects of morphine (Byrnes et al., 2011). Similarly, exposure of F0 males to ethanol decreased ethanol intake and increased the sensitivity of their F1 offspring to the inhibitory effects of ethanol on anxiety-like behavior (Bastle and Neisewander, 2016). Some of the drugs most commonly associated with promoting epigenetic changes and respective induced epigenetic changes are summarized below.

Alcohol

Alcohol breakdown in the liver increases blood acetate levels, which in turn may contribute to increased histone acetylation levels in the brain (Mews et al., 2019). In fact, acute and chronic alcohol intake has been shown to promote epigenetic modifications. For example, chronic ethanol exposure has been shown to cause the demethylation of CpG islands in the NR2B subunit of the N-methyl-D-aspartate (NMDA) receptor, as well as increased H3K9 acetylation in *nr2b*'s gene promoter in primary cortical neurons of mice administered alcohol (Marutha Ravindran et al., 2005). Acute ethanol administration decreased HDAC activity, and subsequently increased H3 and H4 acetylation in rats' amygdala (Gapp et al., 2014), whereas withdrawal from chronic ethanol treatment produced the opposite effects (i.e., increased HDAC activity, decreased H3/H4 acetylation) in the same brain region, and was associated with anxiety-like behavior in the animals.

Interestingly, data from different epigenome-wide analysis studies have identified several genes (e.g., *hnrnpa1*, *lrrc20*, *plekhg4b*, *lmf1*) methylated following alcohol exposure that were associated with immune regulation, suggesting the importance of immune modulation in alcohol use disorders (Mews et al., 2019). Specifically, hypermethylation of the *herp* (coding for homocysteine), *snca* (coding for a-synuclein) and *avp* (coding for vasopressin) genes has been observed in alcoholics (Bastle and Neisewander, 2016).

Moreover, it has been reported that alcohol increases the sensivity of Kupffer cells of alcohol-treated mice to pro-inflammatory agents (e.g., lipopolysaccharide) by inducing the inflammatory miR-155 and regulating HDAC11 levels (Bala et al., 2017). Also, alcohol-mediated increase of miR-206 levels in the medial prefrontal cortex of alcohol-dependent rats was shown to contribute to the onset of alcohol dependence in the treated animals (Tapocik et al., 2014).

Cannabinoids

Epigenetic modifications have also been observed following cannabinoid exposure. For example, higher methylation status in the promoter of the *cnr1* gene, coding for cannabinoid type-1 receptor (CB1R), has been observed in THC-dependent subjects, compared to control groups, an alteration that was negatively correlated with CB1R mRNA expression and that suggests the involvement of *cnr1* methylation in regulating THC dependence (Rotter et al., 2013). Tomasiewicz et al. (2012) observed a THC-mediated alteration in the transcriptional and epigenetic state of the dopaminergic D_2 receptor (*drd2*) and the opioid neuropeptide proenkephalin (*penk*) genes as a result of reduced histone H3K9 methylation, namely the trimethylation of lysine 4 on histone H3 (H3K4me3) and dimethylation of lysine 9 on histone H3 (H3K9me2) in the nucleus accumbens of THC-exposed male rats, suggesting that cannabis use could increase its user's vulnerability to the effects of opiates. Moreover, Prini et al. observed that chronic administration of THC to adolescent female rats resulted in transcriptional repression immediately after exposure, mediated by increased trimethylation of H3K9 (H3K9me3), followed by transcriptional activation at later timepoints (i.e., 48h) via increased acetylation of H3K9 (H3K9ac) (Prini et al., 2018). Notably, increased H3K9me3 levels were shown to downregulate the expression of several genes, including *Homer1*, *Mgll*, and *Dlg4*.

Synthetic cannabinoids (SCs) have also been reported to promote epigenetic modifications. For example, both specific CB1R and CB2R cannabinoid receptor agonists (HU-210 and JWH-133, respectively) have been shown to regulate the differentiation of glioma cells by increasing trimethylated H3K9 (H3K9me3) levels in a cannabinoid receptor activation-dependent manner (Aguado et al., 2007). Moreover, adolescent rats exposed to the SC WIN55212.2 showed increased DNA hypermethylation in the *rgs7* gene (coding for a protein involved in the acceleration of GTP hydrolysis on G protein) (Tomas-Roig

et al., 2017). Additionally, JWH-133-exposed male mice have shown decreased expression of all *tet* genes (coding for the TET enzymes) in sperm cells. Since TET enzymes promote DNA demethylation, this SC-induced effect was associated with increased DNA methylation, specifically in *dio3*, *dlk1*, *hymai,* or *igf2*, which are mostly associated with cell growth and differentiation (Innocenzi et al., 2019).

Cocaine

Cocaine use has been shown to promote histone modifications in male mice, including the trimethylation of lysine residues 9 and 27 in the silent chromatin of histone H3 (H3K9me3 and H3K27me3), and decreased active marks H3K27ac (enhancer) and H3K4me3 (promoter) of isolated germ cells. Cocaine was further noted to increase the activities of acetyltransferase KAT8/MOF, deacetylase SIRT1, and methyltransferase KMT2C/G9A. Moreover, cocaine has been shown to decrease the activity of HDAC1, 2, and 3 in mice NAc, further causing changes in synaptic plasticity (González et al., 2020). Interestingly, these cocaine-induced epigenetic changes were found to be mediated by the dopamine receptor 1 (DRD1) (Campbell et al., 2021; González et al., 2020).

Acute cocaine administration to mice has been reported to promote H4 acetylation, leading to increased *c-fos* expression (involved in the initial response to psychostimulants) in the mouse striatum. However, following repeated cocaine exposure, H4 acetylation at the *fosB* promoter increased the expression of Δ*fosB* and *fosB*, increasing the animals' sensitivity to cocaine. Moreover, Δ*fosB* accumulation recruits HDAC1 to the *c-fos* promoter, thus decreasing *c-fos* expression and activity. This is also accompanied by an H3 acetylation-mediated upregulation of *bdnf* and *cdk5*. Notably, the long-term accumulation of these effects has been shown to correlate with the increased reward response and locomotor activity that typically occurs after cocaine use (Bastle and Neisewander, 2016).

Acute cocaine exposure has also been shown to promote *dnmt3a* and *dnmt3b* expression in the NAc of mice, which was associated with the hypermethylation of the *pp1* promoter, and subsequent decreased *pp1* gene expression. The resulting decrease in protein Ser/Thr phosphatase activity may then contribute to the increased phosphorylation of MeCP2 protein (at serine 421), preventing its activity as a transcriptional repressor. In rats, MeCP2 phosphorylation in the striatum and NAc has been shown to regulate the response to cocaine (Ausió, 2016).

Opioids

The ability of opioids to promote epigenetic modifications has also been reported. In contrast to cocaine, chronic opioid administration has been shown to decrease H3 acetylation at the *bdnf* promoter in the ventral tegmental area, leading to decreased *bdnf* expression, thus impairing the maintenance of the synaptic structure (Koo et al., 2015).

Epigenetic changes at the *Oprm1* gene (coding for the μ-opioid receptor) seem to play a central role in the response to opioids. For example, increased methylation at the *oprm1* promoter and histone deacetylation have been shown to cause decreased *oprm1* mRNA expression, leading to decreased sensitivity of μ-opioid receptors and subsequent enhanced tolerance to opioids (Jindal et al., 2021). MeCP2 expression is crucial to the silencing of μ-opioid receptors in the dorsal root ganglion, as this epigenetic repressor recruits HDAC1 and binds to the methylation regions of the *oprm1* promoter (Sun et al., 2021).

A recent study examining the genome-wide changes in human midbrain specimens collected from autopsies of opioid abusers showed that these substances promote several transcriptional changes in the midbrain that could be associated within inter-related gene hubs. Genes in two of these hubs, associated with synaptic transmission and other neuronal functions, displayed down-regulated expression in opioid users, whereas genes in a third large drug-responsive gene hub associated with immune modulation and transcription regulation (e.g., *fos, fosl1, fosl2, jun, junb, atf3*) were found to be mostly upregulated. Noteworthy, this same study found strong evidence of downstream gene regulation by long noncoding RNA (lncRNAs). For example, the lncRNA *MIR210HG* was associated with increased levels of *gadd45b* (involved in neuronal gene expression via DNA methylation) and *nfkb1a* (related to the regulation of NF-kB-mediated transcription), which have been implicated in drug abuse (Saad et al., 2019).

Future perspectives

Epigenetics is a fast-evolving field, which in recent years has provided interesting insights towards understanding the mechanisms underlying the (neuro)toxicity of substances of abuse and their correlation with SUDs. Considering the reversibility of most epigenetic changes, it is reasonable to expect that the development and/or repurposing of pharmaceuticals able, for example, to inhibit DNA methylation (e.g., azacytidine) or histone deacetylase activity (e.g., valproic acid) could represent interesting therapeutics to SUDs. Alternatively, DNA methylation can be pharmacologically altered by the administration of methionine, an amino acid present in the diet, whose metabolism yields methyl groups that may act as donors for DNA methylation. Indeed, rats receiving methyl supplementation via daily, systemic administration of methionine showed reduced rewarding and motivating effects in response to cocaine (Wright et al., 2015). Administration of HDAC inhibitors trichostatin A and phenylbutyrate to rats subjected to the cocaine self-administration paradigm, dose-dependently reduced

the rats' motivation for the drug, hence their cocaine self-administration (Romieu et al., 2008). Also, the class I-specific inhibitor MS-275 was shown to reduce the alcohol-drinking motivation of rats trained to self-administer high alcohol levels (Jeanblanc et al., 2015).

Notably, as most epigenetic marks are specific to certain brain regions, SUD-related therapeutics would also have to be targeted to those same regions (e.g., NAc, prefrontal cortex). For example, nanotubes containing such agents have already been tested for their ability to attach to a neuron-specific receptor ligand (e.g., a cocaine-like molecule) and further bind to the same receptor of the ligand (e.g., a dopamine transporter in the case of cocaine), releasing the therapeutic agent in the target neuron. Also, non-replicative viral vectors comprising, for example, a DNA sequence from a gene of interest or a short-interfering RNA (siRNA), could also be used (e.g., using the CRISPR-Cas9 system), to target such gene or siRNA to specific locations (e.g., specific neuron population) to either increase gene expression or prevent gene transcription, respectively.

Moreover, the detection of epigenetic modifications in children could pave the way to identifying potential risks for developing addictions or any developmental disorders, as well as novel therapeutic targets. Interestingly, this strategy has already provided interesting insights regarding the predisposition of children to develop leukemia (Ramos et al., 2018), and has allowed associating specific DNA methylation changes in the blood of newborns with gestational age-related health effects (Merid et al., 2020).

As evidence accumulates on the key role played by non-coding RNAs in the regulation of several distinct intracellular signaling processes, it becomes important to analyze existing databases to ascertain candidate noncoding RNAs that may be involved in SUD-related mechanisms. For example, analysis of enriched targets in the Knowledge-base of addiction-related genes database using bioinformatic tools has led to the identification of miR-495 as a candidate miRNA associated with the regulation of expression of several addiction-related genes (Bastle et al., 2018).

Conclusions

The relevance of epigenetic changes, including DNA methylation or histone modifications, to the modulation of several biological processes has been unveiled in recent years, with specific epigenetic modifications or mutations in key elements of the epigenetic machinery having been correlated with a distinct set of disorders (mostly related to cognitive impairment or childhood brain overgrowth).

In particular, there is increasing evidence demonstrating the association of drugs of abuse with epigenetic changes, namely with the methylation of specific genes (e.g., *fosB*, *drd1, oprm1*), histone modifications (e.g., H3K9me2), and changes in the activity of enzymes responsible for epigenetic modifications (e.g., DNMTs, HDACs). All these changes may modulate the drug users' response to these same substances, by affecting the expression of genes mostly related to reward, tolerance, or neuronal plasticity, which have been suggested to underlie the onset of SUDs.

At the same time, considering the reversibility of most of epigenetic changes, their identification and assessment of their contribution to the onset to distinct disorders, open interesting perspectives towards finding novel therapeutic strategies for such disorders. In this sense, understanding the role of drug-induced epigenetic modifications assumes a critical role to assess the potential risks of developing a given disorder, as well as to improve therapeutical strategies.

Conflict of interests

The authors declare that they have no conflict of interests.

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References

Aguado, T., Carracedo, A., Julien, B., Velasco, G., Milman, G., Mechoulam, R., Alvarez, L., Guzmán, M. & Galve-Roperh, I. (2007). Cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis. *Journal of Biological Chemistry*, *282*, 6854-6862. doi:10.1074/jbc.M608900200.

Ausió, J. (2016). MeCP2 and the enigmatic organization of brain chromatin. Implications for depression and cocaine addiction. *Clinical Epigenetics*, *8*, 58. doi:10.1186/s13148-016-0214-5.

Bala, S., Csak, T., Kodys, K., Catalano, D., Ambade, A., Furi, I., Lowe, P., Cho, Y., Iracheta-Vellve, A. & Szabo, G. (2017). Alcohol-induced miR-155 and HDAC11 inhibit negative regulators of the TLR4 pathway and lead to increased LPS responsiveness of Kupffer cells in alcoholic liver disease. *Journal of Leukocyte Biology*, *102*, 487-498. doi:10.1189/jlb.3A0716-310R.

Bastle, R. M. & Neisewander, J. L. (2016). Epigenetics and drug abuse. In: Meil, W. M. & Ruby, C. L. (Eds.)

Recent advances in drug addiction research and clinical applications. IntechOpen. doi:10.5772/63952.

Bastle, R. M., Oliver, R. J., Gardiner, A. S., Pentkowski, N. S., Bolognani, F., Allan, A. M., Chaudhury, T., St Peter, M., Galles, N., Smith, C., Neisewander, J. L. & Perrone-Bizzozero, N. I. (2018). In silico identification and in vivo validation of miR-495 as a novel regulator of motivation for cocaine that targets multiple addiction-related networks in the nucleus accumbens. *Molecular Psychiatry*, *23*, 434-443. doi:10.1038/mp.2016.238.

Berdasco, M., Ropero, S., Setien, F., Fraga, M. F., Lapunzina, P., Losson, R., Alaminos, M., Cheung, N. K., Rahman, N. & Esteller, M. (2009). Epigenetic inactivation of the Sotos overgrowth syndrome gene histone methyltransferase NSD1 in human neuroblastoma and glioma. *Proceedings of the National Academy of Sciences*, *106*, 21830-21835. doi:10.1073/pnas.0906831106.

Brooks, A. C. & Henderson, B. J. (2021). Systematic review of nicotine exposure's effects on neural stem and progenitor cells. *Brain Sciences*, *11*. doi:10.3390/brainsci11020172.

Byrnes, J. J., Babb, J. A., Scanlan, V. F. & Byrnes, E. M. (2011). Adolescent opioid exposure in female rats: Transgenerational effects on morphine analgesia and anxiety-like behavior in adult offspring. *Behavioural Brain Research*, *218*, 200-205. doi:10.1016/j.bbr.2010.11.059.

Caccamo, A., Maldonado, M. A., Bokov, A. F., Majumder, S. & Oddo, S. (2010). CBP gene transfer increases BDNF levels and ameliorates learning and memory deficits in a mouse model of Alzheimer's disease. *Proceedings of the National Academy of Sciences*, *107*, 22687-22692. doi:10.1073/pnas.1012851108.

Campbell, R. R., Kramár, E. A., Pham, L., Beardwood, J. H., Augustynski, A. S., López, A. J., Chitnis, O. S., Delima, G., Banihani, J., Matheos, D. P. & Wood, M. A. (2021). HDAC3 activity within the nucleus accumbens regulates cocaine-induced plasticity and behavior in a cell-type-specific manner. *The Journal of Neuroscience*, *41*, 2814-2827. doi:10.1523/jneurosci.2829-20.2021.

Covington, H. E., Maze, I., Sun, H., Bomze, H. M., DeMaio, K. D., Wu, E. Y., Dietz, D. M., Lobo, M. K.,Ghose, S., Mouzon, E., Neve, R. L., Tamminga, C. A. & Nestler, E. J. (2011). A role for repressive histone methylation in cocaine-induced vulnerability to stress. *Neuron*, *71*, 656-670. doi:10.1016/j.neuron.2011.06.007.

D'Addario, C., Di Francesco, A., Pucci, M., Finazzi Agrò, A. & Maccarrone, M. (2013). Epigenetic mechanisms and endocannabinoid signalling. *The FEBS Journal*, *280*, 1905-1917. doi 10.1111/febs.12125.

Dall'Aglio, L., Muka, T., Cecil, C. A. M., Bramer, W. M., Verbiest, M. M. P. J., Nano, J., Hidalgo, A. C., Franco, O. H. & Tiemeier, H. (2018). The role of epigenetic modifications in neurodevelopmental disorders: A systematic review. *Neuroscience & Biobehavioral Reviews*, *94*, 17-30. doi:10.1016/j.neubiorev.2018.07.011.

Dupont, C., Armant, D. R. & Brenner, C. A. (2009). Epigenetics: Definition, mechanisms and clinical perspective. *Seminars in Reproductive Medicine*, *27*, 351-357. doi:10.1055/s-0029-1237423.

Flagel, S. B., Chaudhury, S., Waselus, M., Kelly, R., Sewani, S., Clinton, S. M., Thompson, R. C., Watson, S. J. & Akil, H. (2016). Genetic background and epigenetic modifications in the core of the nucleus accumbens predict addiction-like behavior in a rat model. *Proceedings of the National Academy of Sciences*, *113*, E2861-E2870. doi:doi:10.1073/pnas.1520491113.

Gapp, K., von Ziegler, L., Tweedie-Cullen, R. Y. & Mansuy, I. M. (2014). Early life epigenetic programming and transmission of stress-induced traits in mammals. *Bioessays*, *36*, 491-502. doi:10.1002/bies.201300116.

Gomes, T. M., Dias da Silva, D., Carmo, H., Carvalho, F. & Silva, J. P. (2020). Epigenetics and the endocannabinoid system signaling: An intricate interplay modulating neurodevelopment. *Pharmacological Research*, 105237. doi:10.1016/j.phrs.2020.105237.

González, B., Gancedo, S. N., Garazatua, S. A. J., Roldán, E., Vitullo, A. D. & González, C. R. (2020). Dopamine receptor D1 contributes to cocaine epigenetic reprogramming of histone modifications in male germ cells. *Frontiers in Cell and Developmental Biology*, *8*, doi:10.3389/fcell.2020.00216.

Good, K. V., Vincent, J. B. & Ausió, J. (2021). MeCP2: The genetic driver of Rett Syndrome eEpigenetics. *Frontiers in Genetics*, *12*, doi:10.3389/fgene.2021.620859.

Innocenzi, E., De Domenico, E., Ciccarone, F., Zampieri, M., Rossi, G., Cicconi, R., Bernardini, R., Mattei, M. & Grimaldi, P. (2019). Paternal activation of CB(2) cannabinoid receptor impairs placental and embryonic growth via an epigenetic mechanism. *Scientific Reports*, *9*, 17034-17034. doi:10.1038/s41598-019-53579-3.

Jeanblanc, J., Lemoine, S., Jeanblanc, V., Alaux-Cantin, S. & Naassila, M. (2015). The class I-specific HDAC inhibitor MS-275 decreases motivation to consume alcohol and relapse in heavy drinking rats. *International Journal of Neuropsychopharmacology*, *18*, doi:10.1093/ijnp/pyv029.

Jin, B., Tao, Q., Peng, J., Soo, H. M., Wu, W., Ying, J., Fields, C. R., Delmas, A. L., Liu, X., Qiu, J. & Robertson, K. D. (2008). DNA methyltransferase 3B (DNMT3B) mutations in ICF syndrome lead to altered epigenetic modifications and aberrant expression of genes regulating development, neurogenesis and immune function. *Human Molecular Genetics*, *17*, 690-709. doi:10.1093/hmg/ddm341.

Jindal, S., Kumar, N., Shah, A. A., Shah, A., Gourishetti, K. & Chamallamudi, M. R. (2021). Histone deacetylase inhibitors prevented the development of morphine

tolerance by decreasing IL6 production and upregulating mu-opioid receptors. *CNS Neurological Disorders and Drug Targets*, *20*, 190-198. doi:10.2174/1871527319999201113102852.

Koo, J. W., Mazei-Robison, M. S., LaPlant, Q., Egervari, G., Braunscheidel, K. M., Adank, D. N., Ferguson, D., Feng, J., Sun, H., Scobie, K. N., Damez-Werno, D. M., Ribeiro, E., Peña, C. J., Walker, D., Bagot, R. C., Cahill, M. E., Anderson, S. A. R., Labonté, B., Hodes, G. E.,... Nestler, E. J. (2015). Epigenetic basis of opiate suppression of *Bdnf* gene expression in the ventral tegmental area. *Nature Neuroscience*, *18*, 415-422. doi:10.1038/nn.3932.

Korolev, N., Lyubartsev, A. P. & Nordenskiöld, L. (2018). A systematic analysis of nucleosome core particle and nucleosome-nucleosome stacking structure. *Scientific Reports*, *8*, 1543. doi:10.1038/s41598-018-19875-0.

Kouzarides, T. (2007). Chromatin nodifications and their function. *Cell*, *128*, 693-705. doi:10.1016/j.cell.2007.02.005.

Liu, G., Xing, Y., Zhao, H., Cai, L. & Wang, J. (2018). The implication of DNA bending energy for nucleosome positioning and sliding. *Scientific Reports*, *8*, 8853. doi:10.1038/s41598-018-27247-x.

Liu, J., Chen, J., Ehrlich, S., Walton, E., White, T., Perrone-Bizzozero, N., Bustillo, J., Turner, J. A. & Calhoun, V. D. (2013). Methylation patterns in whole blood correlate with symptoms in schizophrenia patients. *Schizophrenia Bulletin*, *40*, 769-776. doi:10.1093/schbul/sbt080.

Marutha Ravindran, C. R. & Ticku, M. K. (2005). Role of CpG islands in the up-regulation of NMDA receptor NR2B gene expression following chronic ethanol treatment of cultured cortical neurons of mice. *Neurochemistry international, 46*, 313–327. doi: 10.1016/j.neuint.2004.10.004.

Maze, I., Chaudhury, D., Dietz, D. M., Von Schimmelmann, M., Kennedy, P. J., Lobo, M. K., Sillivan, S. E., Miller, M. L., Bagot, R. C., Sun, H., Turecki, G., Neve, R. L., Hurd, Y. L., Shen, L., Han, M.-H., Schaefer, A. & Nestler, E. J. (2014). G9a influences neuronal subtype specification in striatum. *Nature Neuroscience*, *17*, 533-539. doi:10.1038/nn.3670.

Merid, S. K., Novoloaca, A., Sharp, G. C., Küpers, L. K., Kho, A. T., Roy, R., Gao, L., Annesi-Maesano, I., Jain, P., Plusquin, M., Kogevinas, M., Allard, C., Vehmeijer, F. O., Kazmi, N., Salas, L. A., Rezwan, F. I., Zhang, H., Sebert, S., Czamara, D., Rifas-Shiman, S. L.,... Melén, E. (2020). Epigenome-wide meta-analysis of blood DNA methylation in newborns and children identifies numerous loci related to gestational age. *Genome Medicine*, *12*, 25-25. doi:10.1186/s13073-020-0716-9.

Mews, P., Egervari, G., Nativio, R., Sidoli, S., Donahue, G., Lombroso, S. I., Alexander, D. C., Riesche, S. L., Heller, E. A., Nestler, E. J., Garcia, B. A. & Berger, S. L. (2019). Alcohol metabolism contributes to brain histone acetylation. *Nature*, *574*, 717-721. doi:10.1038/s41586-019-1700-7.

Nativio, R., Lan, Y., Donahue, G., Sidoli, S., Berson, A., Srinivasan, A. R., Shcherbakova, O., Amlie-Wolf, A., Nie, J., Cui, X., He, C., Wang, L. S., Garcia, B. A., Trojanowski, J. Q., Bonini, N. M. & Berger, S. L. (2020). An integrated multi-omics approach identifies epigenetic alterations associated with Alzheimer's disease. *Nature Genetics*, *52*, 1024-1035. doi:10.1038/s41588-020-0696-0.

Nielsen, D. A., Utrankar, A., Reyes, J. A., Simons, D. D. & Kosten, T. R. (2012). Epigenetics of drug abuse: Predisposition or response. *Pharmacogenomics*, *13*, 1149-1160. doi:10.2217/pgs.12.94.

Prini, P., Rusconi, F., Zamberletti, E., Gabaglio, M., Penna, F., Fasano, M., Battaglioli, E., Parolaro, D. & Rubino, T. (2018). Adolescent THC exposure in female rats leads to cognitive deficits through a mechanism involving chromatin modifications in the prefrontal cortex. *Journal of Psychiatry and Neurosciences*, *43*, 87-101. doi:10.1503/jpn.170082.

Ramos, K. N., Ramos, I. N., Zeng, Y. & Ramos, K. S. (2018). Genetics and epigenetics of pediatric leukemia in the era of precision medicine. *F1000 Research*, *7*, F1000 Faculty Rev-1104. doi:10.12688/f1000research.14634.1.

Romieu, P., Host, L., Gobaille, S., Sandner, G., Aunis, D. & Zwiller, J. (2008). Histone deacetylase inhibitors decrease cocaine but not sucrose self-administration in rats. *The Journal of Neuroscience*, *28*, 9342-9348. doi:10.1523/JNEUROSCI.0379-08.2008.

Rotter, A., Bayerlein, K., Hansbauer, M., Weiland, J., Sperling, W., Kornhuber, J. & Biermann, T. (2013). CB1 and CB2 receptor expression and promoter methylation in patients with cannabis dependence. *European Addiction Research*, *19*, 13-20. doi:10.1159/000338642.

Saad, M. H., Rumschlag, M., Guerra, M. H., Savonen, C. L., Jaster, A. M., Olson, P. D., Alazizi, A., Luca, F., Pique-Regi, R., Schmidt, C. J. & Bannon, M. J. (2019). Differentially expressed gene networks, biomarkers, long noncoding RNAs, and shared responses with cocaine identified in the midbrains of human opioid abusers. *Scientific Reports*, *9*, 1534. doi:10.1038/s41598-018-38209-8.

Sadakierska-Chudy, A., Frankowska, M., Miszkiel, J., Wydra, K., Jastrzębska, J. & Filip, M. (2017). Prolonged induction of miR-212/132 and REST expression in rat striatum following cocaine self-administration. *Molecular Neurobiology*, *54*, 2241-2254. doi:10.1007/s12035-016-9817-2.

Sun, N., Yu, L., Gao, Y., Ma, L., Ren, J., Liu, Y., Gao, D. S., Xie, C., Wu, Y., Wang, L., Hong, J. & Yan, M. (2021). MeCP2 epigenetic silencing of Oprm1 gene in primary sensory neurons under neuropathic pain conditions. *Frontiers in Neuroscience*, *15*, doi:10.3389/fnins.2021.743207.

Szutorisz, H. & Hurd, Y. L. (2018). High times for cannabis: Epigenetic imprint and its legacy on brain and behavior. *Neuroscience & Biobehavioral Reviews*, *85*, 93-101. doi:10.1016/j.neubiorev.2017.05.011.

Tapocik, J. D., Barbier, E., Flanigan, M., Solomon, M., Pincus, A., Pilling, A., Sun, H., Schank, J. R., King, C. & Heilig, M. (2014). MicroRNA-206 in rat medial prefrontal cortex regulates BDNF expression and alcohol drinking. *Journal of Neuroscience*, *34*, 4581-4588. doi:10.1523/Jneurosci.0445-14.2014.

Tomas-Roig, J., Benito, E., Agis-Balboa, R., Piscitelli, F., Hoyer-Fender, S., Di Marzo, V. & Havemann-Reinecke, U. (2017). Chronic exposure to cannabinoids during adolescence causes long-lasting behavioral deficits in adult mice. *Addiction Biology*, *22*, 1778-1789. doi:10.1111/adb.12446.

Tomasiewicz, H. C., Jacobs, M. M., Wilkinson, M. B., Wilson, S. P., Nestler, E. J. & Hurd, Y. L. (2012). Proenkephalin mediates the enduring effects of adolescent cannabis exposure associated with adult opiate vulnerability. *Biological Psychiatry*, *72*, 803-810. doi:10.1016/j.biopsych.2012.04.026.

Vassoler, F. M., White, S. L., Schmidt, H. D., Sadri-Vakili, G. & Pierce, R. C. (2013). Epigenetic inheritance of a cocaine-resistance phenotype. *Nature Neuroscience*, *16*, 42-47. doi:10.1038/nn.3280.

Wright, K. N., Hollis, F., Duclot, F., Dossat, A. M., Strong, C. E., Francis, T. C., Mercer, R., Feng, J., Dietz, D. M., Lobo, M. K., Nestler, E. J. & Kabbaj, M. (2015). Methyl supplementation attenuates cocaine-seeking behaviors and cocaine-induced c-Fos activation in a DNA methylation-dependent manner. *The Journal of Neuroscience*, *35*, 8948-8958. doi:10.1523/JNEUROSCI.5227-14.2015.

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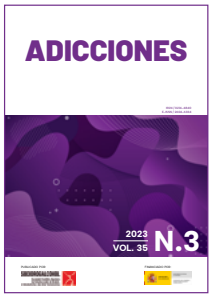

ORIGINAL

Substance-using adolescents admitted to inpatient treatment: Characteristics and factors associated with length of time in treatment

Adolescentes usuarios de sustancias ingresados en tratamiento: Características y factores asociados a la duración del tratamiento

Alexandre Quelho Comandule*,**; Maria de Fatima Rato Padin**,***; Martha Canfield****; Ronaldo Laranjeira**,***.

* Santa Casa de Misericordia de Sorocaba, Sorocaba, São Paulo. Brazil. ** National Institute of Public Policy for Alcohol and Other Drugs, São Paulo. Brazil. *** Department of Psychiatry. Federal University São Paulo, São Paulo. Brazil. **** Health Psychology Section, Psychology Department, Institute of Psychiatry, Psychology and Neuroscience. King's College London, London. UK.

Abstract

Studies of adolescents receiving inpatient substance use treatment remain limited. We explored the characteristics of adolescents who received substance use treatment as inpatients in a psychiatric hospital in Brazil and factors associated with length of time in this treatment. Methods: A retrospective observational study was performed. Electronic treatment records of 172 young people (aged 17 and below) receiving substance use treatment at Hospital Lacan in Brazil were analysed. Results: The mean age of participants was 15.18 years (SD = 1.39). The sample was characterised as predominately male (68.60%), who entered treatment involuntarily (80.81%), were out of school (89.82%), were involved with the criminal justice system (59.88%) and came from a family with substance use problems (74.67%). Re-admission to inpatient treatment for substance use problems was common. On average, adolescents received inpatient treatment for 3 months. Length of time in treatment was associated with: involuntary admission to treatment, re-admission to inpatient treatment, requests of discharge from treatment by a relative/caretaker, education level, leaving school due to aggressive behaviours and cocaine use. Conclusion: Findings highlight the complex profiles of adolescents receiving substance use treatment in Brazil. Cross-system collaboration between mental health, educational and justice services are needed to treat adolescents' substance use.

Keywords: adolescents, inpatient treatment, substance use

Resumen

Los estudios sobre adolescentes ingresados para tratamiento de uso de sustancias son limitados. Analizamos las características de adolescentes ingresados para tratamiento en un hospital psiquiátrico en Brasil y los factores asociados con la duración de su tratamiento. Métodos: estudio observacional retrospectivo. Analizamos los registros electrónicos de tratamiento de 172 jóvenes (hasta los 17 años de edad) ingresados para tratamiento por uso de sustancias en el Hospital Lacan en Brasil. Resultados: La edad media de los participantes era 15,18 años (SD = 1,39). La muestra era mayoritariamente masculina (68,60%), cuyo ingreso fue involuntario (80,81%), sin escolarizar (89,82%), involucrada en el sistema de justicia penal (59,88%) y proveniente de una familia con problemas relacionados con el uso de sustancias (74,67%). La readmisión como paciente a tratamiento por problemas de uso de sustancias era frecuente. Como media, los adolescentes estuvieron ingresados para tratamiento durante 3 meses. La duración del tratamiento estaba asociada con: admisión involuntaria al tratamiento, reingreso hospitalario para tratamiento, solicitudes de alta del tratamiento por parte de familiares/cuidadores, nivel de estudios, abandono escolar debido a conducta agresiva, y uso de cocaína. Conclusión: Los hallazgos destacan los perfiles complejos de los adolescentes ingresados para tratamiento por el uso de sustancias en Brasil. Es necesaria una colaboración entre los sistemas de salud mental, educación y servicios de justicia para tratar el uso de sustancias entre adolescentes.

Palabras clave: adolescentes, tratamiento hospitalario, uso de sustancias

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■ **Send correspondence to:**
Alexandre Quelho Comandule. Departamento de Psiquiatría. Santa Casa de Misericordia de Sorocaba. Av. São Paulo, 750 - Jardim Árvore Grande. Sorocaba, 18013-000 Brasil. Email: aquelho@gmail.com

Despite emerging evidence of downward shift in substance use among young people in some countries (Broadfiled, 2017; Dennis & Scott, 2007; Miech, Johnston, O'Malley, Bachman & Schulenberg, 2016; Plettinckx et al., 2014) treatment admissions for adolescents with alcohol and other substance use disorders continue to increase (Roxburgh & Burns, 2013). In Brazil, it is estimated a high prevalence of substance use among adolescents: 42.4% of alcohol, 9.6% of tobacco and 25.5% of illicit substances (Carlini et al., 2010; Malta et al., 2011). Cannabis and inhalants/solvents are the most used illicit substance among Brazilian adolescents (Carlini et al., 2010; Madruga et al., 2012). According to the latest national survey on crack-cocaine use in Brazil, young people under the age of 18 years old accounts for approximately 14% of regular crack-cocaine users (Bastos & Bertoni, 2014). Presently, there is no available data related to the prevalence of adolescents receiving substance use treatment in Brazil (Vasters & Pillon, 2011). Evidence from the international literature suggests that adolescents may be relatively less likely to seek treatment than adults (Cornelius et al., 2003; Sussman, Skara & Ames, 2009; Winters, Tanner-Smith, Bresani & Meyers, 2014). Figures from the US shows that only 10% of adolescents with substance use problems are admitted to treatment (Substance Abuse and Mental Health Services Administration, 2013).

In line with other countries, attempts have been made in Brazil to provide treatment services that recognize the stage of psychological and physical development (Castellanos-Ryan, O'Leary-Barret & Conrod, 2013; Winters et al., 2014) and specific problems in family functioning that might be associated to the adolescent's substance use (Bertrand et al., 2013; Coatsworth, Santisteban, McBride & Szapocznik, 2001). However, it remains common to adolescents to be integrated into programmes that are merely modifications of adults' programmes. There is a clear consensus in the Brazilian and international literature that adolescent-only services represent a minimum threshold of substance use treatment quality (Lopes, Nobrega, Del Prette & Scivoletto 2013; NIDA, 2014), and that differences in treatment adherence and outcomes are largely explained by individual client characteristics (Knudsen, 2009). Currently, there is a great demand in Brazil for substance use treatments that are tailored to the needs of substance using adolescents. Information about the characteristics of those Brazilian adolescents receiving inpatient treatment for substance use, and possible associations with services outcomes, is lacking.

The purpose of our study is to begin to address these issues by describing the characteristics of adolescents who received substance use treatment as an inpatient in a psychiatric hospital in Brazil. Since prior research has revealed that duration in inpatient programs is associated with treatment outcomes, including relapse once they return to their natural environment (Battjes, Gordon, O'Grady, Kinlock & Carswell, 2003; Chung & Maisto, 2006), a second objective of this study was to identify factors associated with the length of time receiving inpatient treatment. Evidence suggests that the length of treatment varies according to the severity of the adolescent's substance use problem (Battjes, Gordon, O'Grady & Kinlock, 2004; Winters et al., 2018). Severe substance use dependence among young people has been associated with a variety of complex forces, including family functioning, deviant peers and school problems (Serrano et al., 2018; Svensson, 2000; Sussman et al., 2009). Research into factors associated with length of time in inpatient treatment in hospitals among adolescents is limited. We hope that this study will provide a starting point for implementing comprehensive, targeted, and tailored programs for adolescents with substance use problems in Brazil, while at the same time shedding light to the international literature on which factors are associated with the duration of inpatient substance use treatment among adolescents.

Methods

A retrospective observational study was performed. Data came from service records of 172 young people (aged 17 and below) referred to Lacan's Psychiatric Hospital in the city of Sao Paulo, between 2014 to 2016. This treatment facility is run by a partnership between the Brazilian Public Health System (SUS) and philanthropic funding, which provides free of charge inpatient care (i.e., psychiatric, psychological and occupational care) for young and adult populations with psychiatric disorders, including substance use dependence. Data of all young patients that were referred to Lacan due to substance use problems with/without other psychiatric problems were analysed in this study. Patients might have entered the treatment voluntary or involuntary (referrals and pressures from families or the criminal justice system). The substance use service at Lacan is designed to promote substance abstinence, diagnostic elucidation, and establishment or optimization of medication. As part of the medical intervention, patients at Lacan receive counseling and family group sessions. Patients are not allowed to leave the service; not even to attend educational classes. After hospitalization, patients are referred to the available mental health network in the cities where they come from. Ethical approval to conduct this study was granted by the Federal University of Sao Paulo. Anonymised data was released to the research team by the hospital data management, protecting the privacy and confidentiality of patients.

Assessments

All data were collected as part of routine assessment and treatment of adolescents at Lacan's hospital.

Socio-demographic characteristics

Information on participant's age, gender, and educational level at the time they entered treatment was collected at first contact with the service. If not attending school at the time of admission, reason for absence was asked. Information about whom the patient resided with (i.e., mothers only, grandparents, out of family home) was also collected.

Treatment characteristics

Treatment variables included how many days in treatment, and whether discharge from current treatment was given by the service or a request from a relative/carer, both of which are routinely recorded by the service. Information about how the patient entered treatment (i.e., voluntary and involuntary – due to referrals and pressures from schools, families, or the criminal justice system), number of times admitted to inpatient treatment and length of time since previous treatment was assessed at the first clinical assessment.

Clinical characteristics

Primary ICD-10 diagnosis is routinely recorded in a structured field. Data was extracted for all those patients with substance use problem as primary or secondary diagnosis. Information about pattern of substance use was extracted from the first clinical assessment - or in some cases during first or second consultation with the clinical psychologist - using a structured instrument designed by the service. This includes questions about types of substances used and frequency of use (i.e., sporadic, almost every day, daily, once a day, twice a day). Participants were coded as using a specific substance daily if they reported using at any frequency every day. Participants were also asked to report age of onset for licit and illicit substances and whether he/she was aware of substance use problems among other family members. Participants were coded as having a history of a mental health disorder before treatment admission where this was indicated in the first clinical assessment. Reports of mental heath disorder at treatment admission was coded for participants who indicated a mental health disorder not necessarily associated with substance use in the ICD-10.

Criminal characteristics

Criminal justice variables included history of involvement with the criminal justice, drug trafficking and theft to sustain substance use practices. All this information was assessed at first contact with the service using a structured instrument designed by the service.

Data Analysis

Descriptive statistics were calculated using frequencies and percentages for categorical data, means and standard deviations for continuous data. An ordinal variable for *length of time in treatment* ranging from 1 to 5 was created according to the following days in treatment: up to 30 days; 31 to 60 days; 61 to 90 days; 91 to 120 days; 121 to 255 days. The median and interquartile range was calculated. Factors associated with length of time in treatment were considered using ordinal logistic models. Odds ratios (OR) and 95% confidence intervals (CI) of unadjusted and adjusted (controlling for participant's age and gender) models are reported.

Results

The mean age of participants was 15.18 years (SD=1.39). The majority of participants was male (68.60%), entered treatment involuntarily (80.81%) and were out of school at the time of admission (89.82%). Of those who were not at school, 62.18% reported substance use as the reason for being out. Almost all patients were referred to continued care post inpatient treatment: 54.01% to addiction services; 25.00% to children & adolescents services; and 19.02% to mental health services. Reports of history of involvement with criminal justice were high (59.88%). Re-admission to inpatient treatment was common (38.36%) and it took an average of 3 years for re-entering. The following characteristics were also commonly reported: mental health disorder at the time of admission (25.00%; the most common mental health disorders reported includes attention deficit hyperactivity disorder and mood disorders), involvement in drug trafficking (37.87%) and theft (22.10%) and reports of living with their mother (41.52%). Three quarter of the sample reported to have a family relative with substance use problems (74.67%) and that this relative was a close family member (75.89%).

Nearly all participants reported to use cannabis (97.09%) and to use it daily (89.51%). The use of alcohol and tobacco were also highly reported (88.37% and 78.49%, respectively). Over a quarter of those who reported to drink alcohol, consume it everyday (28.94%). A large proportion of the sample reported to use cocaine (80.81%) and to use it daily (71.94%). Over a quarter of the sample reported to use crack-cocaine (29.07%) and, of those who reported to use this substance, 72% used it daily. The average age of substance use onset was 12.03 (SD=1.72) years old.

Variables associated with length of time receiving inpatient substance use treatment

The number of days in treatment ranged from 2 to 255, with a median of 61 to 90 days (IQR=31 to 60 days). Univariate analysis (Table 1) revealed that the likelihood of lower length of time in treatment was associated with requests of discharge from treatment by a relative/carer, higher educational level and living with the mothers. Yet, greater length of time in treatment was associated with being female, entering treatment involuntarily, re-

Table 1
Univariate factors associated with the length of time receiving inpatient treatment (N=172)

Variables	N (%)	Unadjusted OR (95%CI)	Adjusted OR (95%CI)[a]
Gender (male= 0)	118 (68.60)	**1.82 (1.08, 3.06)***	
Age (Mean SD)	15.18 (1.39)	(.78, 1.34)	
Treatment variables			
Involuntarily admission[1]			
Re-admission to inpatient substance use treatment			
Number of previous inpatient treatment received	139 (80.81)	**2.41 (1.21, 4.80)***	**3.06 (1.41, 6.67)***
(Mean SD)	66 (38.36)	**1.87 (1.07, 3.28)***	**1.90 (1.08, 3.32)***
Number of years since last inpatient treatment (Mean	1.45 (.70)	1.45 (.92, 2.27)	1.48 (.92, 2.38)
SD)	3.21 (.90)	.75 (.48, 1.17)	.74 (.47, 1.16)
Reason for re-admission			
Did not accept abstinence approach	11 (16.67)	.92 (.26, 3.20)	1.38 (.35, 5.46)
Did not want to follow post-treatment approaches	34 (51.51)	2.17 (.79, 5.95)	1.84 (.59, 5.68)
Relapse	12 (18.18)	.35 (.11, 1.17)	.38 (.11, 1.29)
Discharged from treatment requested by a relative/carer	13 (7.56)	**.01 (.00, .03)****	**.01 (.00, .02)****
Continuing care post inpatient treatment			
Referral to mental health services	33 (19.02)	.95 (.47, 1.91)	1.05 (.51, 2.10)
Referral to addiction services	93 (54.01)	.87 (.51, 1.50)	.83 (.47, 1.47)
Referral to children & adolescents services[2]	43 (25.00)	1.28 (.70, 2.33)	1.24 (.66, 2.30)
Psychological variables			
History of mental health disorder before treatment admission	19 (11,5)	.51 (.19, 1.31)	.49 (.19, 1.61)
Report of mental health disorder at treatment admission [3]	43 (25,00)	1.12 (.59, 2.12)	1.26 (.66, 2.41)
Educational variables			
Higher educational level (primary school=0)	97 (58.79)	**.68 (.49, .95)***	**.62 (.44, .89)***
Out of school[4]	150 (89.82)	.80 (.34, 1.90)	.81 (.34, 1.94)
Out of school due substance use	74 (49.33)	.88 (.44, 1.72)	.85 (.43, 1.68)
Out of school due aggression	11 (7.33)	**3.42 (1.10, 10.61)***	**3.42 (1.01, 9.87)***
Criminal variables			
History of involvement with criminal justice	103 (59.88)	1.24 (.71, 2.16)	1.47 (.83, 2.61)
History of attending youth offending unit	39 (37.86)	.78 (.38, 1.60)	.71(.34, 1.51)
Involvement in drug trafficking to sustain drug use	65 (37.87)	1.06 (.58, 1.92)	1.16 (.62, 2.18)
Involvement in thief to sustain drug use	38 (22.10)	.88 (.44, 1.75)	.99 (.49, 2.01)
Family			
Live with			
Mother with/without siblings	71 (41.52)	**.56 (.32, .97)***	.62 (.35, 1.12)
Father with/without siblings	13 (7.60)	1.72 (.67, 4.42)	1.58 (.62, 4.50)
Grandparents with/without siblings	16 (9.36)	1.32 (.54, 3.19)	1.21 (.49, 2.99)
Both parents	36 (21.05)	.80 (.39, 1.62)	.83 (.40, 1.70)
Out of home[5]	35 (20.47)	**1.91(1.01, 3.65)***	1.59 (.81, 3.15)
Substance use problem among family members	112 (74.67)	**2.38 (1.20, 4.76)***	**2.15 (1.06, 4.37)***
Close relative substance user (mother/father/siblings)	85 (75.89)	**2.71 (1.08, 6.80)***	**2.61 (1.02, 6.65)***
Substance Use variables			
Alcohol use	152 (88.37)	.62 (.23, 1.84)	.82 (.24, 2.79)
Alcohol use daily	44 (28.94)	1.31 (.68, 2.51)	1.22 (.63, 2.35)
Tabaco use	135 (78.49)	1.35 (.69, 2.62)	1.29 (.66, 2.50)
Tabaco use daily	124 (91.85)	.99 (.99, 1.01)	.99 (.99, 1.00)
Cannabis use	167 (97.09)	.87 (.17, 4.52)	.93 (.17, 4.97)
Cannabis use daily	128 (76.64)	1.65 (.62, 4.39)	1.60 (.61, 4.26)
Cocaine use	139 (80.81)	**2.31 (1.13, 4.72)***	**2.19 (1.06, 4.53)***
Cocaine use daily	100 (71.94)	.87 (.42, 1.80)	1.26 (.49, 2.16)
Crack-cocaine use	50 (29.07)	1.25 (.69, 2.26)	1.27 (.70, 2.31)
Crack cocaine use diary	36 (72.00)	.81 (.24, 2.72)	.81 (.22, 2.94)
Onset of substance use (Mean SD)	12,03(1.72)	.80 (.59, 1.07)	.81 (.60, 1.10)

Note. Numbers in bold significant p values *p<.05, **p<.001. [a] Model adjusted for gender and age. [1] Involuntary includes both family and judicial order. [2] Children & Adolescents services including mental health services target to this population. [3] Mental health disorders not necessarily associated with substance use. [4] Abandonment/expulsion/permanent exclusion/withdrawing/kicked out of school. [5] Residing in orphaned/juvenile retention institution/homeless.

admission to inpatient treatment, being out of school due to aggressive behaviours, living out of family home and cocaine use.

After controlling for participants age and gender, the following variables remained associated with length of time in treatment: entering treatment involuntarily, re-admission to inpatient treatment, requests of discharge from treatment by a relative/carer, education level, left school due to aggressive behaviours and use of cocaine.

Discussion

This study shows that substance use problems in a cohort of Brazilian adolescents attending inpatient substance use treatment in a psychiatric hospital is associated with a wide range of problems. The majority of participants were out of school, had previous involvement with the criminal justice system, entered treatment involuntary and came from substance using families. Re-admission to inpatient substance use treatment was common as was involvement in drug trafficking. Although the majority of adolescents lived with one/both biological parents, nearly a quarter of the sample lived out of the family home (i.e., in the streets and criminal rehabilitation centers). Nearly all participants reported using alcohol and tobacco. Cannabis was the most used illicit substance. Nearly all participants also reported to use cocaine. The use of crack-cocaine was common and, of those who reported using this substance, nearly three-quarters consumed it daily. The average age of substance use onset was 12 year old. Our results extend findings from studies conducted elsewhere suggesting that adolescents receiving inpatient treatment have severe substance use problems, high rates of relapse as well as family, school and legal problems (Battjes et al., 2003; Chung & Maisto, 2006).

On average, adolescents in our study received inpatient treatment for 3 months (61 to 90 days), which is a significantly higher number than the international recommendation of up to 30 days for adolescents (Paino, Aletraris & Roman, 2015). Reasons for this is unclear, but the fact that Lacan's hospital is partly supported by philanthropic funding allows for more flexibility regarding length of time than those services run by the Brazilian Public Health System. Moreover, 80.0% of our sample entered treatment involuntary (due to referrals and pressures from families or the criminal justice system). Lack of motivation and readiness for treatment might have imposed additional barriers to begin to change adolescents' behaviours and engage in treatment (Battjes et al., 2003; Battjes et al., 2004; Mensinger, Diamond, Kaminer & Wintersteen, 2006; Paino et al., 2015). Higher length of time in treatment in our study was associated with being female, entering treatment involuntary, re-admission to inpatient treatment, lower levels of schooling, not living with the biological mother, living out of the family home, having a substance using relative in the family and use of cocaine. Prior studies have shown that adolescents who stayed in residential treatment longer were likely to have more favorable outcomes (Chung & Maisto, 2006; Knudsen, 2009). It is not clear, however, whether the direction of this association is the same among adolescents receiving inpatient treatment in a psychiatric hospital. It is important to note that the substance use treatment delivered at Lacan's hospital focus on substance use problems only. Approaches designed to integrate other elements of the social context of the adolescents including, for example, educational support is lacking at the service. It is well established in the literature that disengagement and school failure might increase social rejection at school, which in turn might increase associations with off-school deviant peer groups, substance use, low academic achievement, and developing problems with law later in life. (Bachman et al., 2008; Henry, Knight & Thornberry, 2012; Li & Lerner, 2011) Moreover, drug-using peers and academic challenges have been identified as relapse-risk factors for youth after drug treatment (Clark & Winters, 2002; Svensson, 2000). Our findings draw attention to the importance of considering variation in terms of educational needs as well as psychological problems and family functioning of the adolescents. An important avenue for future studies would be to investigate the relevance of these risk factors with post-drug treatment outcomes in adolescents. Information about these risk factors holds promise for conducting comprehensive assessments that might influence timing and type of interventions to be delivered.

Another finding that requires further investigation is the average of 3 years for those who had attended inpatient treatment in the past to be re-admitted to substance use treatment. Studies of relapse involving adolescent who have been admitted to inpatient programmes suggest that one out of three adolescents who relapse to any pattern of substance use post-treatment, return to heavy use or to pre-treatment level of substance involvement through 1 to 2 year follow-up (Myers, Brown & Mott, 1995; Winters, Stinchfield, Opland, Weller & Latimer, 2000). While our variable only allows speculation regarding the relapse characteristics, it signals the need to assess relapse points in adolescents' post-treatment recovery and possible mechanisms that may underlie these change points. Empirical work is needed to determine how development specific life events, contextual influences and life stage issues may influence substance use relapse among adolescents in Brazil. The integration of relapse into treatment frameworks should be map onto the process by which relapse occurs (Chung & Maisto, 2006) and procedures for consistent monitoring of adolescents trajectories aftercare should be put in place.

Our findings also highlight the need for robust national guidelines on a continued care model for adolescents in Brazil. Our data suggests a lack of consistence on referral

to continued care post-inpatient substance use treatment, as some adolescents are referred to addiction services, others for mental health services and some for children and adolescents' services. The evidence that the majority of participants who have been re-admitted to inpatient treatment due to problems following outpatient treatment, demonstrates the urgency for approaches focusing on concrete behavioral issues aimed at improving linkage, retention and adherence to continued care among adolescents. This could include, for example, defining which type of service adolescents with substance use problems should be referred to, development of a multifaceted treatment approach delivered by qualified staff that addresses all aspects of the adolescents life (e.g., school, home, and public activities) (Kelly, Myers & Brown, 2000; Winters et al., 2014) and provide outreach approaches to continued care that facilitates adolescents and their families involvement in the programmes (e.g. home visits and telephone calls).

Limitations of our study include the relatively small sample size, which might have affected the representative of our findings and the association between variables in the regression analysis. Comparisons between length of time in treatment and each type of substance used were not possible due to considerable overlap between groups according to type of substance used. Although reports of mental health disorder were recorded, it was not possible to obtain accurate details regarding the diagnosis due to reporting bias on the electronic records. For example, the initial clinical assessment was conducted by consultant clinical psychiatrics specialised in adult populations. This meant common problems usually reported in children/adolescents such as behavioural and emotional problems, were under reported. In addition, the fact that participants were only recruited from one psychiatric hospital means that results cannot be generalized to adolescents receiving inpatient substance use treatment across the country. Lastly, the relationships we observed between variables and length of time in treatment are only correlational and do not provide the basis to identify the source or direction of influence.

Conclusion

The findings highlight the multiple and complex profile of adolescents with substance use problems in Brazil. Our findings point to the need to develop approaches for cross system collaboration, which include mental health, educational and justice services. Given the high length of time receiving inpatient treatment and lack of a model of continuing care post-inpatient treatment, this study provides evidence that warrant consideration in the design of protocols to support adolescents trying to negotiate their problematic profiles during their recovery.

Conflict of interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

Bachman, J., O'Malley, P. M., Schulenberg, J. E., Johnston, L., Freedman-Doan, P. & Messersmith, E. E. (2008). *The Education–Drug Use Connection: How Successes and Failures in School Relate to Adolescent Smoking, Drinking, Drug Use, and Delinquency.* New York: Lawrence Erlbaum Associates. http://www.psc.isr.umich.edu/pubs/abs/4465.

Bastos, F. I. & Bertoli, N. (2014). *Pesquisa Nacional sobre o uso de crack: Quem são os usuários de crack e/ou similares do Brasil? Quantos são nas capitais brasileiras?* Rio de Janeiro: Fundação Oswaldo Cruz. https://www.icict.fiocruz.br/sites/www.icict.fiocruz.br/files/Pesquisa%20Nacional%20sobre%20o%20Uso%20de%20Crack.pdf.

Battjes, R. J., Gordon, M.S., O'Grady, K.E., Kinlock, T.W. & Carswell, M.A (2003). Factors that predict adolescent motivation for substance abuse treatment. *Journal of Substance Abuse Treatment, 24,* 221-32. doi:10.1016/S0740-5472(03)00022-9.

Battjes, R. J., Gordon, M.S., O'Grady, K.E. & Kinlock T. W. (2004). Predicting retention of adolescents in substance abuse treatment. *Addictive Behaviours, 29,* 1021-1027. doi:10.1016/j.addbeh.2004.02.054.

Bertrand, K., Richer I., Brunelle, N., Beaudoi, I., Lemieux A. & Menard J. (2013). Substance abuse treatment for adolescents: How are family factors related to substance use change? *Journal of Psychoactive Drugs, 45*, 28-38. doi:10.1080/02791072.2013.763560.

Broadfiled D. (2017). *Drug Misuse: Findings from the 2016/17 Crime Survey for England and Wales Statistical Bulletin 11/17*. London: Home Office. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/642738/drug-misuse-2017-hosb1117.pdf.

Castellanos-Ryan, N., O'Leary-Barrett, M., Sully, L. & Conrod, P. (2013). Sensitivity and specificity of a brief personality screening instrument in predicting future substance use, emotional, and behavioral problems: 18-month predictive validity of the Substance Use Risk Profile Scale. *Alcoholism: Clinical and Experimental Research, 37,* E281-E290. doi:10.1111/j.1530-0277.2012.01931.x.

Carlini, E. L. A., Noto, A. R., Sanchez, Z. M., Carlini, C. M. A., Locatelli, D. P. & Abeid, L. R. (2010). *VI Levantamento Nacional sobre o Consumo de Drogas Psicotrópicas entre Estudantes do Ensino Fundamental e Médio das Redes Pública e Privada de Ensino nas 27 Capitais Brasileiras*. São Paulo: Centro Brasileiro de Informações sobre Drogas Psicotrópicas, SENAD - Secretaria Nacional de Políticas sobre Drogas.

Chung, T. & Maisto, S. A (2006). Relapse to alcohol and other drug use in treated adolescents: Review and reconsideration of relapse as a change point in clinical course. *Clinical Psychology Review, 26,* 149-161. doi:10.1016/j.cpr.2005.11.004.

Clark, D. & Winters, K. C. (2002). Measuring risks and outcomes in substance use disorders prevention research. *Journal of Consulting and Clinical Psychology, 70*, 1207–1223. doi:10.1037/0022-006X.70.6.1207.

Coatsworth, J. D., Santisteban, D. A., McBride, C. K. & Szapocznik J. (2001). Brief strategic family therapy versus community control: Engagement retention, and an exploration of the moderating role of adolescent symptom severity. *Family Process, 40*, 313-332. doi:10.1111/j.1545-5300.2001.4030100313.x.

Cornelius, J. R., Maisto, S. A., Pollock, N. K., Martin, C. S., Salloum, I. M. & Lynch, K. G. (2003). Rapid relapse generally follows treatment for substance use disorders among adolescents. *Addictive Behaviors*, *28*, 381–386. doi:10.1016/S0306-4603(01)00247-7.

Dennis, M. & Scott, C. K. (2007). Managing addiction as a chronic condition. *Addiction Science & Clinical Practice, 4,* 45-55.

Kelly, J. F., Myers, M.G. & Brown, S.A. (2000). A multivariate process model of adolescent 12-Step attendance and substance use outcome following inpatient treatment. *Psychology of Addictive Behaviors, 14,* 376-389.

Henry, K. L., Knight, K. E. & Thornberry, T. P. (2012). School disengagement as a predictor of dropout, delinquency, and problem substance use during adolescence and early adulthood. *Journal of Youth Adolescent, 41*, 156-166. doi:10.1007/s10964-011-9665-3.

Knudsen, H.K. (2009). Adolescent-only substance abuse treatment: Availability and adoption of components of quality. *Journal of Substance Abuse & Treatment, 36*, 195-204. doi:10.1016/j.jsat.2008.06.002.

Li, Y. & Lerner, R. M. (2011). Trajectories of school engagement during adolescence: Implications for grades, depression, delinquency, and substance use. *Developmental Psychology, 47*, 233-247. doi:10.1037/a0021307.

Lopes, G. M., Nobrega, B. A., Del Prette, G. & Scivoletto, S. (2013). Use of psychoactive substances by adolescents: current panorama. *Revista Brasileira de Psiquiatria, 35,* S51-S61. doi:10.1590/1516-4446-2013-S105.

Madruga, C., Laranjeira, R., Caetano, R., Pinsky, I., Zaleski, M. & Ferri, C. P. (2012). Use of licit and illicit substances among adolescents in Brazil — A national survey. *Addictive Behaviours, 37, 1171-* 1175. doi:10.1016/j.addbeh.2012.05.008.

Malta, D. C., Mascarenhas, M. D. M., Porto, D. L., Duarte, E. A., Sardinha, L. M., Barreto, S. M. & Neto, O. L. M. (2011). Prevalência do consumo de álcool e drogas entre adolescentes: Análise dos dados da Pesquisa Nacional de Saúde Escolar. *Revista Brasileira de Epidemiologia, 14,* 136–146.

Mensinger, J. L., Diamond, G. S., Kaminer Y. & Wintersteen, M. B. (2006). Adolescent and therapist perception of barriers to outpatient substance abuse treatment. *American Journal on Addictions, 15,* 16–25.

Miech, R. A., Johnston, L. D., O'Malley, P. M., Bachman, J. G. & Schulenberg, J. E. (2016). *Monitoring the future national survey results on drug use, 1975–2015: Volume I, secondary school students*. Ann Arbor, MI: Institute for Research for Social Research, The University of Michigan.

Myers, M. G., Brown, S. A. & Mott, M. A. (1995). Preadolescent conduct disorder behaviors predict relapse and progression of addiction for adolescent alcohol and drug abusers. *Alcohol Clinical Experiment Research, 19,* 1528 – 1536. doi:10.1111/j.1530-0277.1995.tb01019.x.

Paino, M., Aletraris, L. & Roman, P. M. (2015). Organizational predictors and use of evidence-based practices in adolescent substance abuse treatment. *Substance Abuse, 36,* 462–469. doi:10.1080/08897077.2014.960959.

Plettinckx, E., Antoine, J., Blanckaert, P., De Ridder, K., Vander Laenen, F., Laudens, F.,… Gremeaux, L. (2014*). Belgian National Report on drugs 2014, New Developments and Trends*. Brussels: Belgian Monitoring Center for Drugs and Drugs Addiction. http://www.emcdda.europa.eu/system/files/publications/1004/BAR2014%20Final%20EMCDDA%20Version.pdf.

Roxburgh, A. & Burns, L. (2013). *Drug-related hospital stays in Australia 1993–2013*. Sydney: National Drug and Alcohol Research Centre. https://ndarc.med.unsw.edu.au/sites/default/files/ndarc/resources/NIDIP%20Bulletin%20-%20Drug-related%20hospital%20stays%20in%20Australia%201993-2013.pdf.

Serrano, M. B., Al-Halabí, S., Burón, P., Garrido, M., Díaz-Mesa, E.M., Galván, G.,… Bobes J. (2018). Predictive factors of alcohol consumption in adolescents: Data from 1-year follow-up prospective study. *Adicciones.* Advance publication online. doi:10.20882/adicciones.998.

Substance Abuse and Mental Health Services Administration. (2013). *Results from the 2012 national survey on drug use and health: Summary of national findings*. Rockville, MD: National Institutes of Health.

Svensson, R. (2000). Risk factors for different dimensions of adolescent drug use. *Journal of Child & Adolescent Substance Abuse, 9*, 67–90. doi:10.1300/J029v09n03_05.

Sussman, S., Skara, S. & Ames, S. L. (2009). Substance abuse among adolescentes. *Substance Use & Misuse, 43,* 1802-1828. doi:10.1080/10826080802297302.

Vasters, G.P. & Pillon S. (2011). O uso de drogas por adolescentes e suas percepções sobre adesão e abandono de tratamento especializado. *Revista Latino-Americana de Enfermagem, 19*. doi:10.1590/S01041169201100020001 3.

NIDA. (2014). *Principles of Adolescent Substance Use Disorder Treatment: A Research-Based Guide*. Rockville, MD: National

Institutes of Health. https://d14rmgtrwzf5a.cloudfront.net/sites/default/files/podata_1_17_14.pdf.

Winters, K. C., Botzet, A. M., Stinchfield, R., Gonzales-Castaneda, R., Finch, A. J., Piehler, T. F.,… Hemze, A. (2018). Adolescent substance abuse treatment: A review of evidence-based research. In C. G. Leukefeld & T. P. Gullotta (Eds.). *Adolescent Substance Abuse. Evidence-Based Approaches to Prevention and Treatment.* (pp. 141-171). New York, NY: Springer Science

Winters, K. C., Stinchfield, R. D., Opland, E., Weller, C. & Latimer, W. W. (2000). The effectiveness of the Minnesota Model approach in the treatment of adolescent drug abusers. *Addiction, 95,* 601-612. doi:10.1046/j.1360-0443.2000.95460111.x.

Winters, K. C., Tanner-Smith, E. E., Bresani, E. & Meyers K. (2014). Current advances in the treatment of adolescent drug use. *Adolescent Health, Medicine Therapeutics, 5,* 199-210. doi:10.2147%2FAHMT.S48053.

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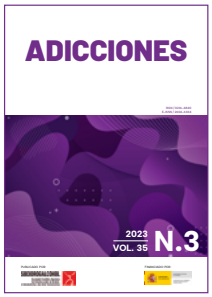

ORIGINAL

Tecnotest: A screening tool for technological addictions and gambling disorder

Tecnotest: Desarrollo de una herramienta de screening de adicciones tecnológicas y juego

Marta Marcos*; Mariano Chóliz*.

* Departamento de Psicología Básica, Facultad de Psicología, Universidad de Valencia.

Abstract

One of the most pressing social and scientific issues, as reflected in the current priority lines of the National Drugs Plan (PNSD), is the development of screening tools for the early detection of addictions, particularly behavioral addictions, due to the impact that these problems are having on the growth of addictions in recent years, especially in adolescents and young people. Goal. The main goal of this research was to develop a screening tool for technological addictions (video games, mobile and social networks) and gambling for early detection in people suffering this kind of behavioral addiction. Procedure. With technologies, in the absence of agreed clinical criteria, those participants who perceived themselves as having problems and, in addition, had received treatment for it, were selected. Regarding gambling, the diagnostic criteria of the DSM-5 were used. The three items that scored the highest Positive Predictive Values (PPV) in each of the four validated tests were selected. These indicators serve to distinguish those who use the technologies and/or gamble in a functional way and do not have any problems from those who already have an addictive problem with video games, mobile, social networks or gambling. Results. This paper shows the finished screening tool with its main psychometric properties, which can be used by professionals working with adolescents in order to detect people who could have some addictive problem, in which case the psychologist can refer them to a specialized healthcare resource.

Keywords: technological addictions, gambling, screening, teenagers, assessment

Resumen

Una de las demandas sociales y científicas más acuciantes, que se plasma en las actuales líneas prioritarias del Plan Nacional sobre Drogas (PNSD) es el desarrollo de herramientas de *screening* para la detección temprana de adicciones, singularmente adicciones sin sustancia, debido al impacto que estas están teniendo en el desarrollo de adicciones desde hace unos años, especialmente en adolescentes y jóvenes. Objetivo. El objetivo principal de esta investigación fue el desarrollo de una herramienta de *screening* de adicciones tecnológicas (videojuegos, móvil y redes sociales) y al juego para vincular la detección temprana con la intervención y la prevención en el campo de las adicciones conductuales. Método. *Participantes*. Participaron en el estudio 1.813 estudiantes de entre 11 y 19 años de 13 comunidades autónomas. *Instrumentos*. Se desarrolló una encuesta con cuatro pruebas validadas sobre adicciones tecnológicas y al juego. *Procedimiento.* Para la construcción de la herramienta de *screening* se seleccionaron los tres elementos que obtuvieron mayor Valor Predictivo Positivo (VPP) de cada una de las cuatro pruebas validadas para diferenciar entre quienes utilizaban las tecnologías y/o jugaban de un modo social y no tenían ningún problema de aquellos que ya tenían un problema adictivo. Resultados. Se obtuvo una herramienta de uso de las tecnologías y juego que consta de 24 ítems (12 ítems de cribado de las cuatro tecnologías y 12 de uso de las mismas) con sus principales propiedades psicométricas (fiabilidad, estructura factorial). Discusión. La escala tiene unas adecuadas propiedades psicométricas y es congruente teóricamente. Se presenta la herramienta definitiva de *screening*, la cual queda a disposición de las/os psicólogas/os para la detección temprana de personas que puedan padecer alguna de estas adicciones, en cuyo caso podrían ser derivados a los recursos sanitarios especializados.

Palabras clave: adicciones tecnológicas, adicción al juego, screening, adolescentes, evaluación

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■ **Send correspondence to:**
Marta Marcos y Mariano Chóliz. Departamento de Psicología Básica, Facultad de Psicología, Universidad de Valencia. Avda. Blasco Ibáñez, 21, 46010, Valencia. Tfno. 96 386 41 00 - Ext. 51900. Email: marta.marcos@uv.es, mariano.choliz@uv.es

The term addiction refers not only to disorders resulting from the use of toxic substances, but also certain behaviours with a tendency to become addictive, just like substance use (Chóliz, Echeburúa & Labrador, 2012; Echeburúa, 1999; Jiménez-Murcia & Farré, 2015). This has been recognized by both the APA in the DSM-5 diagnostic manual for mental illnesses (APA, 2013) and by the WHO in the most recent ICD-11 (WHO, 2018). As far as DSM-5 is concerned, only gambling disorder is included in the category "Substance-related and other addictive disorders", while online gaming disorder appears in Section III as a psychological problem requiring further study for its eventual classification in the category of addictive disorders, something that seems plausible given that there is evidence on the subject (Ferguson, Coulson & Barnett, 2011; Martín-Fernández et al., 2017) and that, in fact, the diagnostic criteria that appear in the DSM-5 for video gaming disorder are practically the same as those for gambling disorder. The WHO indeed already includes video gaming disorder within the same classification of addictive disorders, while in addition distinguishing in both gambling and video gaming disorders between the subcategories of predominantly online and those offline or unspecified.

With regard to mobile phones and social networks, irrespective of whether they are mental disorders as classified in the APA and WHO manuals, there is clinical and scientific evidence and a broad social consensus about of the existence of addictive psychological problems linked to the use of ICTs (Block, 2008; Chóliz, 2010; Echeburúa, Labrador & Becoña, 2009; Petry & O'Brien, 2013). Whether they are considered mental disorders or psychological problems is currently the subject of debate (Carlisle, Carlisle, Polychronopoulos, Goodman-Scott & Kirk-Jenkins, 2016; Kuss & Griffiths, 2017; Northrup, Lapierre, Kirk & Rae, 2015), but there is no doubt that there are people who, in their use of technologies, display the main characteristics of what is defined as addiction (tolerance, presence of withdrawal syndrome, difficulty in controlling behaviour, obsessive use, etc). The main technology addictions are the Internet/social networks (Tsai & Lin, 2003; Young, 1998) and mobile phones (Billieux, Van der Linden, d´Acremont, Ceschi & Zermatten, 2007; Chóliz, 2010), as well as video games (Griffiths, Kuss & King 2012; Kuss & Griffiths, 2012), already mentioned above and considered a mental disorder, especially by the WHO.

The reasons why ICTs may be linked to addictions depend both on their structural characteristics and on the conditions in which their use is becoming prevalent. Indeed, as ICT development advances and excessive use and being permanently online are induced, there are a great many people who develop problems similar to the symptoms caused by substance related addictive disorders such as: a) the need for increasing use of technology to achieve the same benefits as at the beginning (tolerance); b) negative emotional reactions when the technology cannot be used or when a considerable time passes without being able to use it (withdrawal syndrome); c) excessive use of technologies that interferes with all aspects of a person's life; d) difficulties in quitting technology despite being aware of the negative consequences of this behaviour; e) mood modification as a learned escape strategy for coping with the difficulties inherent in one's life (Baggio et al., 2018; Griffiths, 1995; Stepien, 2014).

Technology can also exacerbate other addictions, however, as is the case with online gambling as a type of gambling disorder. In this case, the characteristics of Internet gaming would exacerbate the effects of an activity – gambling – that is already addictive in itself. Furthermore, not only is online gambling very attractive to the player, but there are currently structural and environmental variables which favour excessive gambling and gambling addiction (Chóliz & Marcos, 2018; Griffiths, 2003). Some of the most relevant are: Widespread *availability*, easy *accessibility* or almost *instant* reward, at the click of a button (Welte, Barnes, Wieczorek, Tidwell & Hoffman, 2007). In addition to these characteristics, there is the *intimacy* in which it is played and the *comfort* of not having to go to a casino to play, which eliminates the barriers and *social restrictions* present in face-to-face interaction. Addictive behaviour can thus develop easily and with few constraints, with an addictive potential greater than traditional gambling (Chóliz, Marcos & Lázaro-Mateo, 2019; Griffiths, 2003, 2012; Griffiths, Parke, Wood & Parke, 2006; Monaghan, 2009; Petry, 2006). New forms of gambling through technologies are aimed at young people and adolescents, who are the most frequent users and, furthermore, especially vulnerable to the onset and maintenance of any addiction (Gladwin, Figner, Crone & Wiers, 2011).

We are thus at a time when technological addictions have become a psychological problem of an addictive nature to which health professionals need to pay the necessary attention, both in helping people who have this problem, as well as those who are vulnerable to it by providing the preventive resources required. To do this, the problem must necessarily be identifiable in its early stages so that appropriate preventive action may be taken; moreover, in cases where technology addiction has set in, the subjects must be referred to the corresponding resource for adequate evidence-based treatment that can reverse the psychological problem in time. Early detection of pathologies makes interventions more effective and more serious disorders preventable.

The main aim of this research is the development of a screening tool for technology and gambling addiction that teachers, educators and clinicians can use for the early detection of technological and gambling addictions. This scale uses the main items that discriminate between

the functional use of technologies and the presence of an addictive disorder to any of them, hidden in a generic scale of technology use. The specific objectives are to analyze the differences in gambling addiction, risky gambling and technology addiction (video games, mobile phones and social networks) according to sex and age group (underage adolescents and 18- to 19-year-olds).

Method

Participants

The questionnaire was completed by 2,529 students from 13 autonomous communities in Spain. A total of 1,923 adolescents between the ages of 11 and 19 were selected for the study, of which 110 participants were eliminated for responding with an impossible gaming pattern, claiming to play all games (both face-to-face and online), or scoring the maximum score on all NODS items, an extremely unlikely eventuality given the way the items are expressed. The final sample was made up of 1,813 adolescents, of which 928 (51.2%) were female and 885 (48.8%) were male. In terms of age, 1,638 (90.3%) were minors and 175 (9.7%) were aged 18 or 19 years. Regarding the type of school, 1,043 (58.5%) went to public and 770 (42.5%) to private schools.

Measuring instruments

A battery of empirically validated items related to the problem of technology addictions was administered:

Test of Mobile Dependence (TMD)

The TMD (Chóliz, 2012) assesses addiction to instant messaging (WhatsApp, Telegram, etc.). A Cronbach's alpha internal consistency index of .94 was obtained in the sample under study. Its factorial structure comprises 22 items grouped into four factors: Tolerance and withdrawal, control difficulties, abuse and associated problems, and spending.

Internet Addiction Test (AdiTec-I)

The AdiTec-I (Chóliz, Marco & Chóliz, 2016) assesses addiction to virtual social networks (Facebook, Instagram, Twitter, etc.). In the sample applied, a Cronbach's alpha internal consistency index of .94 was obtained. Its factorial structure is made up of 23 items grouped into four factors: abuse, withdrawal, perturbation and lack of control, and avoidance.

Test of Dependence on Video games (TDV).

The TDV (Chóliz & Marco, 2011) assesses addiction to video games. The sample yielded a Cronbach's *alpha* internal consistency index of .95. Its factorial structure is made up of 25 items grouped into 4 factors: Compulsive gambling, withdrawal, tolerance and interference with other activities, and associated problems and avoidance.

Gambling Addiction Test (NODS)

The NODS (Gerstein et al., 1999), consists of 17 items from a semi-structured interview for the diagnosis of gambling disorder based on DSM-IV-TR criteria (APA, 2000). Scores range from 0 to 9. The NODS was adapted to the current DSM-5 by eliminating the criteria of obtaining money illegally to continue playing.

Additional items for technology addictions

Additional items for mobile use, social networks and video games were added. The added items refer to new modes of use linked to ICT developments and are used as possible screening indicators if they are predictive.

Sociodemographic variables

Seven items corresponding to the descriptive data of the sample were added: Sex, age, school, current school year, educational stage, population and province.

Clinical indicators

In the absence of external addiction criteria for technology addictions (video games, mobile phones, social networks), two questions were introduced after the respective questionnaires (TDV, TMD, ADITEC-I) to establish a clinical group: a) "Do you think you have a problem due to the excessive use of… (video games, mobile phones, social networks)?" and b) "Have you received advice or help for the excessive use of… (video games, mobile phones, social networks)?".

Procedure

An online survey was designed which included the three diagnostic questionnaires on technological addictions and the questionnaire for assessing gambling disorder, as well as the additional items on technology use. The survey was hosted on an Internet domain (http://www.tecnotest.es) and was answered by adolescents during school hours in different schools in 13 autonomous communities. School staff supervised the appropriate implementation of the survey, helping adolescents to resolve any possible doubts they might have. The assessment of each technology was preceded by a short introductory text, in which anecdotes and curiosities were told about them to prevent the survey becoming tedious and items becoming confused. To avoid biases in the responses, such as irradiation, the order of the different technology and gambling sections was mixed.

The anonymity and voluntary nature of the participants was respected at all times. Parental authorization was provided to schools for underage students. The data collection methodology was approved by the Ethics Committee of the University of Valencia with the procedure number: *H1550813462400*.

The screening questionnaire was constructed following the stages described by Muñiz and Fonseca-Pedrero

(2019) for test development, given the need to develop a tool that allows technology and gambling addictions to be detected by professionals from various disciplines. Unlike questionnaires built from scratch, the items selected for a first analysis were part of diagnostic questionnaires which have already been published and which have good psychometric properties. A pilot study was carried out to verify that the survey could be answered without difficulty or fatigue, and that the order of administration of the questionnaires was counterbalanced. After the statistical analyses, the definitive questionnaire was obtained by selecting the items with the highest predictive value. Finally, psychometric analyses were carried out to describe the factorial structure and the reliability of the tool in a way similar to other game questionnaires (Grande-Gosende, Martínez-Loredo & Fernández-Hermida, 2019).

Analysis

Different data analyses were carried out depending on the aims of the study.

Psychometric analysis of the instruments used to construct the scale

Internal consistency analyses were performed and the omega internal consistency coefficient (McDonald, 1999) was calculated for the NODS, TDV, TMD and ADITEC-I scales.

Correlation analysis

The Pearson correlation coefficient between each of NODS, TDV, TMD and ADITEC-I scales was analyzed.

Difference of means

Analysis of the difference of means of the scores obtained on the technology addiction scales (TDV, TMD and ADITEC-I) were carried out as dependent variables, based on the following independent variables: a) *Sex*; b) *Age*. Following the recommendations of Sanders and Williams (2019), two age groups were established: Adolescents aged between 11 and 17 years (minors) and 18- to 19-year-olds; c) *Established external criteria*: a) clinical group (people who acknowledged having a technology addiction problem with video games, mobile phones and social networks and had received help for it) and b) control group (users who did not report needing help with technology use).

Difference analysis in percentage of participants with gambling problems

Pathological gambling and risky gambling were established as dependent variables. The independent variables were: a) *Sex* and b) *Age group* (minors vs. young adults). In the case of gambling addiction, no external criterion was established since the NODS is a diagnostic questionnaire for pathological gambling. A *pathological gambling* diagnosis is considered when the four DSM-5 criteria for gambling disorder are met (tolerance, withdrawal syndrome, distress when attempting to quit gambling, gambling to recover losses, etc.) (APA, 2013), while the presence of one to three criteria was considered *risky gambling*.

Sensitivity and specificity analysis of the items

The Positive Predictive Value (PPV) of the items on the diagnostic scales and other addiction criteria was calculated for each of the technologies with the aim of discriminating users who have an addiction problem (to gambling or technologies) from those who do not. The procedure in Johnson et al. (1997) was followed to establish the PPV. The Negative Predictive Value (NPV) was also calculated. The three items with the highest NPV were selected to pad out the use of technologies and games questionnaire in order to mask the screening items.

Psychometric analysis of the TecnoTest scale

The factorial structure of the scale was calculated, as well as its reliability, using the *omega* internal consistency coefficient, which is the most indicated for Likert response questionnaires (Gadermann, Guhn & Zumbo, 2012).

For data analysis, version 20 of the *IBM SPSS Statistics* program was used.

Results

Reliability analysis

Regarding scale reliability, the coefficients of internal consistency, Cronbach's *alpha* and McDonald's *omega* were as follows: NODS (α = .96; ω = .92), TDV (α = .97; ω = .95), TMD (α = .93; ω = .94) and ADITEC-I (α = .96; ω = .94).

Correlations between scales

The correlations between the questionnaires on technology addictions and gambling are presented in Table 1.

Table 1
Pearson correlations between scales

	NODS	TMD	TDV	ADITEC-I
NODS	--	**.11****	**.14****	**.11****
TMD		--	**.12****	**.84****
TDV			--	**.11****
ADITEC-I				--

$^{**}p < .01$.

Means difference analysis of addictions

Gambling addiction

Problems caused by gambling (pathological gambling and high-risk gambling) are reflected in categorical variables (percentage of cases), for which the Chi square test was used

to contrast hypotheses. The differences based on sex and age in problems caused by gambling are described in Table 2.

Table 2
Percentage of pathological gambling and risky gambling according to sex and age

	Pathological Gambling		Risky Gambling	
	N	%	N	%
Male	93	9.9	191	20.4
Female	54	5.6	109	11.2
11-17 years	139	8.1	270	30
18-19 years	8	4.3	30	16.3

Statistically significant differences were found between men and women in the frequency of both pathological gambling ($X^2 = 12.82$; $p < .001$, $Phi = .08$), and risky gambling ($X^2 = 30.30$; $p < .001$; $Phi = .12$). Statistically significant differences were found between minors and young adults in pathological gambling ($X^2 = 3.24$; $p < .05$; $Phi = .04$).

Technology addictions

Regarding the scores obtained in the questionnaires on technology addictions (video games, mobile phones and social networks), the assumption of homoscedasticity was verified with the Levene test, which was significant for all technologies. A non-parametric hypothesis contrast test was thus applied, specifically the Mann-Whitney U test for independent samples. Descriptive data are presented in Table 3.

Table 3
Scores on the TMD, TDV and ADITEC-I scales according to sex and age

	TDV		TDM		ADITEC-I	
	$\bar{X}$	*SD*	$\bar{X}$	*SD*	$\bar{X}$	*SD*
Male	35.24	24.09	21.70	17.01	22.72	23.70
Female	11.01	16.32	30.75	18.56	35.33	25.97
11-17 years	23.83	24.13	25.93	18.37	28.77	25.78
18-19 years	14.21	18.44	29.89	18.12	32.58	24.36

Table 4
NODS items with the highest PPV and NPV

	Sensitivity	Specificity	PPV	NPV
Have you lied to family or friends several times about how much you play or how much money you have lost?	.495	.995	.991	.663
Have you ever borrowed money from relatives or others because of serious financial problems due to gambling?	.484	.991	.981	.657
Have there ever been periods when you needed to bet increasing amounts of money to feel the same excitement?	.538	.989	.980	.682
Have there ever been periods of two weeks or more when you were thinking about gambling for a long time, or planning to gamble?	.835	.872	.867	.841
Have you ever tried to stop gambling or control what you are gambling?	.758	.838	.824	.776
While gambling, have you tried to stop or give up gambling, without succeeding?	.725	.928	.910	.772

Table 5
TDV items with the highest PPV and NPV

	Sensitivity	Specificity	PPV	NPV
I play video games a lot longer now than when I started.	.824	.649	.701	.786
Once I have started, I find it very difficult to stop playing, even if I have to because my parents or friends are calling me or I have to go somewhere.	.800	.790	.792	.798
I have stopped going out with friends or doing things with them because now we arrange to meet online and play.	.563	.936	.898	.682
When I'm playing, I lose track of time.	.895	.662	.726	.863
The first thing I do when I get home after class or work is play my video games.	.588	.911	.868	.689
I have pretended to be sick to avoid going to class or doing homework to be able to play.	.318	.956	.880	.584

Table 6
TMD items with the highest PPV and NPV

	Sensitivity	Specificity	PPV	NPV
People have told me or warned me about using WhatsApp too much.	.565	.865	.807	.665
I have argued with a relative for spending too much on things related to mobile.	.370	.898	.784	.588
I spend more time than I would like using my mobile.	.947	.579	.692	.917
I went to bed later or slept less because of receiving or sending messages.	.760	.567	.637	.703
When I get bored, I open WhatsApp or any other message program.	.808	.435	.589	.694
I can't just use the messaging applications (Whatsapp, Line, Telegram, etc.) like I used to; I need to use them more and more.	.500	.857	.778	.632

Table 7
ADITEC-I items with higher PPV and NPV

	Sensitivity	Specificity	PPV	NPV
When I'm on social media, I lose track of time.	.667	.661	.663	.665
I feel a constant need to update my status or profile photo on my social networks.	.375	.903	.795	.591
It is important for me to get "likes" in my status or photos because I feel bad if I don't.	.542	.856	.790	.651
I think I use social media too much.	.808	.618	.679	.763
I generally spend more time on social media than I originally planned.	.750	.657	.686	.724
I've lost control of social media.	.522	.877	.809	.647

Table 8
Descriptive statistics of the TecnoTest

Item	Mean	SD	Skew	Kurtosis
1	.12	.32	2.35	3.54
2	.02	.13	7.72	57.70
3	.12	.33	2.28	3.21
4	.13	.33	2.23	2.99
5	.12	.32	2.36	3.55
6	.06	.25	3.53	1.50
7	.08	.27	3.11	7.69
8	.05	.21	4.24	16.03
9	.40	.49	.41	-1.84
10	.25	.44	1.13	-.72
11	.29	.45	.94	-1.11
12	.02	.14	6.69	42.85
13	.39	.49	.46	-1.79
14	.10	.30	2.61	4.84
15	.16	.36	1.89	1.59
16	.02	.13	7.46	53.65
17	.52	.50	-.09	-1.99
18	.04	.20	4.72	2.28
19	.03	.17	5.64	29.84
20	.10	.29	2.75	5.54
21	.29	.45	.94	-1.11
22	.32	.47	.77	-1.42
23	.25	.43	1.17	-.63
24	.04	.20	4.48	18.05

Men scored significantly higher than women on the Video Game Dependence Test ($\mathcal{Z}_{(1,\ 1903)}$ = -23.65; $p < .001$; $\eta^2 = .27$), while women presented higher scores on the Test of Mobile Dependence ($\mathcal{Z}_{(1,\ 1903)}$ = -11.05; $p < .001$; $\eta^2 = .07$) and in the Social Media Dependency Test ($\mathcal{Z}_{(1,1903)}$ = -11.61; $p < .001$; $\eta^2 = .07$). Regarding differences between the age groups, minors obtained higher scores on the TDV ($\mathcal{Z}_{(1,1903)}$ = -5.15; $p < .001$; $\eta^2 = .01$), while adolescents aged 18 and 19 years scored highest on mobile dependence ($\mathcal{Z}_{(1,\ 1903)}$ = -3.02; $p < .01$; $\eta^2 = .01$) and social networks ($\mathcal{Z}_{(1,\ 1903)}$ = -2.59; $p < .01$; $\eta^2 = .01$).

Sensitivity and specificity analysis

Screening for gambling addiction

The results obtained regarding the sensitivity, specificity and PPV and NPV ratios for each item are shown in Table 7. The three items with the highest PPV and NPV scores are presented in Table 4.

Screening for dependence on video games

The results obtained regarding the sensitivity, specificity and PPV and NPV ratios for each item are shown in Table

Table 9
Factor loads of the TecnoTest factor items

	FI	FII	FIII	FIV
9. I usually turn off or silence my mobile when I go to bed so as not to use it in bed.	.847			
21. When I use social networks, I am aware of the time I am spending on them.	.841			
22. When it comes to using social media, I only use it for what I need.	.834			
11. I am able to control the amount of time I spend on social media.	.825			
13. I am usually able to control myself when it comes to the amount of time I spend on the mobile.	.798			
17. I can overcome boredom without using my mobile.	.745			
3. People have told me or warned me about using my mobile phone too much.	.685			
20. I have argued with a family member for spending too much on things related to the mobile.	.563			
4. I can't just use the messaging applications (Whatsapp, Line, Telegram, etc.) like I used to; I need to use them more and more.	.558			
15. I can easily quit the video game if something comes up that I have to do.		.805		
10. I play about the same amount of time now as when I started playing video games.		.768		
23. When I am playing, I am aware of the time I am spending on the video game.		.758		
8. I have stopped going out with friends or doing things with them because now we arrange to meet online and play video games.		.630		
6. The first thing I do when I get home after class or work is play my video games.		.583		
19. I have pretended to be sick to avoid going to class or doing homework in order to play my video games.		.456		
24. I can stop playing or gambling without feeling bad about it.			.805	
16. I have borrowed money from family members or others at some point because of serious financial problems due to gambling.			.757	
18. I have been able to stop playing whenever I have wanted to.			.641	
12. There have been periods when I needed to bet increasing amounts of money to feel the same excitement.			.602	
1. I don't normally worry about gambling nor do I think about gambling or betting.			.503	
2. I have repeatedly lied to my family or friends about how much money I have gambled or lost through gambling or betting.			.461	
7. I feel a constant need to update my status or profile photo on my social networks.				.771
15. It is important for me to get "likes" in my status or photos because I feel bad if I don't.				.686
14. I've lost control of social media.				.606

8. The three items with the highest PPV and NPV scores are presented in Table 5.

Screening for mobile dependence

The results obtained regarding the sensitivity, specificity and PPV and NPV ratios for each item are shown in Table 9. The three items with the highest PPV and NPV scores are presented in Table 6.

Screening for dependence on social networks

The results obtained regarding the sensitivity, specificity and PPV and NPV ratios for each item are shown in Table 10. The three items with the highest PPV and NPV scores are presented in Table 7.

The final TecnoTest scale has a total of 24 items, with 12 items for addiction screening, corresponding to those with the highest PPV and 12 normal items with the purpose of masking the screening items.

Table 8 shows the main descriptives of the scale.

Psychometric analysis of the TecnoTest

Once the TecnoTest scale was constructed, psychometric analysis was performed, specifically on its factorial structure and internal consistency.

Factorial analysis of the scale

The KMO indicator (Kaiser-Meyer-Olkin) and Barlett's test of sphericity showed good suitability for factor analysis. (KMO= .826; $\chi^2_{(276)} = 3238.87$; $p < .001$). Factor analyses were carried out with the Varimax rotation and principal component factor extraction method. All items obtained a corrected discrimination index greater than

.5. Factor analysis yielded four factors. The first, which explains 27.24% of the variance, comprises items 3, 4, 9, 11, 13, 17, 20, 21 and 22. It contains all the items on mobile addiction, as well as three of the largest social media NPVs. The internal consistency indices were α = .92; ω = .92. The second factor explains 12.09% of the variance and comprises items 6, 8, 10, 15, 19 and 23. It contains the six video game addiction items and yielded internal consistency indices of α = .81; ω = .83. The third factor explains 10.46% of the variance and comprises the six gambling addiction items: 1, 2, 12, 16, 18 and 24. The internal consistency indices were α = .66; ω = .80. The fourth factor, explaining 6.18% of the variance, is made up of items 5, 7 and 14, which are the three items with the highest PPV of addiction to social networks. The internal consistency indices were α = .72; ω = .73.

Table 9 shows the factor loadings of each of the TecnoTest items.

Table 10 shows the correlations between the different factors.

Table 10
Correlations between the TecnoTest factors

	FI	FII	FIII	FIV
Factor I. Mobile addiction	-	.13	.19	.54
Factor II. Video game addiction			.23	.27
Factor III. Gambling addiction				.17
Factor IV. Social media addiction				-

Discussion

Gambling and technology addiction are the latest addictions in adolescence and require precision tools for assessment to enable preventive intervention in the early stages. The main aim of this study was therefore to construct a screening tool that would allow the early detection of adolescents with technology and gambling addictions and have the ability to discriminate those who use technologies in a functionally appropriate manner or play in a non-pathological way from those who have developed an addictive disorder or are at risk of doing so. To this end, analyses of the predictive values of all items on validated diagnostic scales were performed to obtain the Positive Predictive Value (PPV) and Negative Predictive Value (NPV) coefficients of all items used to measure the addictions under study. This is the normal procedure used by other researchers when creating scales to screen for gambling addiction (Chóliz, Echeburúa & Ferre, 2017; Fernández-Montalvo, Echeburúa & Báez, 1995; Volberg, Munck & Petry, 2011). The intention is to select the items with the greatest predictive power for detecting people with addiction problems to some of the technologies or games and to reject those which, despite their use, probably do not predict well.

The final instrument, called Tecnotest, comprises 24 items, 12 of which (three for each of the addictions analyzed) have the highest PPV and are used for screening, while the other 12 (three for each of the four addictions) with the highest NPV are used as filling to mask the test objective. So that the questionnaire would not have a negative character and to avoid social desirability, these items with higher negative predictive value (NPV) were inverted.

The items found to have higher PPV in detecting each of the addictions are characteristic of some of the addiction criteria. In the case of gambling addiction, the items with the highest PPV refer to the criteria of: a) tolerance; b) lying about the degree of involvement in gambling and c) trusting that others will solve the problems caused by gambling. Subjects appear to have reached a point where they need to gamble more and more to achieve the desired effects, causing inevitable losses since the game is organized so that the company running it wins in the long run, not the players. They admit to themselves that their pattern of gambling is dysfunctional, recognizing that they lie about their gambling, but they are not aware that they should stop, and they need others to finance their gambling, which is the only way they have learned to pay off the debts they incur.

With regard to video game addiction, the items with the highest PPV refer to the following DSM-5 criteria for Internet Gaming Disorder: a) spending time on video games, which become the dominant everyday activity; b) loss of interest in previous hobbies and entertainment; and c) jeopardizing or losing a significant relationship, job, or educational or employment opportunity due to participation in video games. In other words, video games become the most important thing in the adolescent's life, above and beyond their responsibilities and previous hobbies. Their lives revolve around video games, to which they dedicate all their time, even if it is detrimental to their personal adjustment and social adaptation.

Regarding addiction to mobile phones, the main criteria are: a) associated problems and spending; b) tolerance and c) withdrawal. Dependence on mobile phones is characterized by the need to use instant messaging applications more frequently (and probably urgently), which interferes with other tasks and activities and involves excessive spending, to the point of incurring the disapproval of family or friends.

Finally, with regard to social network addiction, the dimensions reflected by the items on the scale are: a) excessive use; b) presence of withdrawal syndrome and c) lack of control. The most discriminating items of social network addiction refer to the excessive use of social networks, the result of an uncontrollable need to obtain social approval to feel good. This makes it very difficult to stop using them, reflecting a loss of control over them.

The scale shows adequate factorial structure since the factorial loads of the items group them into the four anticipated factors: addiction to mobiles, video games,

gambling and social networks. Each of the four factors contains the three items with the highest PPV that were selected as discriminating for each of the addictions, so we can conclude that coherent factorial structure is maintained. However, Factor I, corresponding to mobiles, also contains the filler items (those with the highest NPV) for social networks, which shows that both addictions (mobile and social networks) share common elements in their use. The fact that the items with the highest PPV selected for social network screening constitute a separate factor is an indicator that mobile phone and social network addictions are probably epistemologically distinct, although the use of mobiles and social networks share common actions or elements.

The limited relationship between the factors, other than between mobile and social network addiction, is corroborated by the fact that the scores on the diagnostic tests of technology addictions of the initial survey show little correlation, except for the case of TMD and AdiTec-I. This would corroborate the hypothesis that comorbidity between behavioural addictions is not frequent, since they all involve a high degree of absorption and a limiting of action in other behaviours, so that the person focuses almost exclusively on the activity they are dependent on. For this reason, it is difficult for addictions that require different resources and psychological processes to be shared, such as gambling, video games or the use of mobile phones. In the research presented here, the correlation between the scores on the diagnostic questionnaires is very low, a finding that is in line with those obtained by other authors, indicating that there is no relationship between gambling disorder and other technology addictions (Delfabbro, Lambos, King & Puglies, 2009; Forrest, King & Delfabbro, 2006; King, Ejova & Delfabbro, 2012). The only exception may be between mobile phones and social networks, insofar as they not only share devices, but also involve similar activities; mobile phones are characterized by instant communication with one or more people, and social networks also involve communication and sharing experiences, although its defining characteristic is participation in a virtual community. These would be the only behavioural addictions to show a certain degree of comorbidity, while the rest of the combinations (gambling, video games and mobile/social networks) do not seem to share comorbidity.

Finally, and although the objective of the research was not to assess the incidence of technology addictions and gambling, the use of diagnostic tests to obtain the items making up the screening questionnaire has allowed us to analyze technology and gambling addictions in the participants. The results have been consistent with the scientific literature, both in the case of gambling and technology addictions. Men show a higher percentage of gambling disorder and risky gambling, with statistically significant differences, since gambling, especially online, is mainly a male activity. This, together with the fact that online gambling is more addictive than traditional gambling, makes teenage boys more vulnerable to gambling addiction (Chóliz et al., 2019; Wardle et al., 2010).

These differences are also present in the case of video games. The greater incidence of video game addiction is reflected both in the TDV scores and in the percentage of men in the clinical group. The fact that men have a greater problem with video games than women is congruent with the scientific literature (Desai, Krishnan-Sarin, Cavallo & Potenza, 2010; Ko, Yen, Chen, Chen & Yen, 2005). However, in the case of mobile phones and social networks, it is women who have higher prevalence rates of addiction than men, which is again consistent with results from other researchers (Billieux, Van der Linden & Rochat, 2008). In this case, however, it cannot be a result of the fact that women are more exposed to mobile phones and social networks since both girls and boys use mobile phones daily and have profiles on social networks. It is more likely due to the role that ICTs have in interpersonal communication and even the establishment of links through them, with social interaction and cooperation as the most relevant activities for personal adjustment, while men use technologies mainly to demonstrate skill, compete and win (Andreassen et al., 2016). The fact that the use of technologies motivates women and men differently and that this is a relevant variable in the issue of addictions is, without doubt, a substantial difference with regard to the analysis of technology addictions from a gender perspective.

The present work has a series of limitations that must be taken into account. The first is a consequence of the current state of epistemological imprecision regarding addiction to mobile phones and social networks since, although they display the main diagnostic criteria of behavioural addiction, it is still to be clarified whether they are mental disorders, which is how they are diagnosed with DSM-5 and ICD-11 or psychological problems which, although they can be considered dysfunctional and maladaptive, may not be appropriately classified as mental disorders (González & Pérez-Álvarez, 2007). Likewise, according to the results of the present study, it seems that both share central characteristics, which would make differential diagnosis difficult, something that is essential when establishing an accurate diagnosis. It would be necessary to be able to define what psychological process or processes underlie both addictions or cause them. The path of these addictions is probably similar to that of video game disorder, currently found in Section III of the DSM-5, referring to "Conditions that need further study", although the current ICD-11 already considers it as a mental disorder independent of gambling disorder, these being the only behavioural addictions recognized by the WHO as a mental disorder.

Regarding age distribution, most participants are aged between 14 and 16 years, although the age range of the study is 11 to 19 years. We understand, therefore, that the differences between age groups should be viewed with caution. The sample could have been reduced to that age range so that the resulting questionnaire was used only in early adolescence, but we consider it appropriate to expand below and above that range to select from early adolescence, since all of them already use the technologies. The study of these addictions in adults is also useful since all limitations to the use of technologies and especially gambling disappear.

The screening tool presented here aims to be useful for professionals as an instrument with which to detect adolescents who may have a problem of addiction to some of the technologies (mobile, social networks, video games) or gambling. It is not so much a diagnostic test, but a screening test, the main objective of which is to guide preventive or therapeutic action if necessary, that is, to link assessment tools with intervention techniques with evidence-based efficacy (Chóliz & Marcos, 2020).

Ethics Committee Approval

All procedures in this study involving human participants were performed in accordance with the standards of the Ethics Committee of the University of Valencia and the Declaration of Helsinki of 1964 and subsequent modifications. This work was approved by the Ethics Committee of the University of Valencia, procedure number: *H1550813462400*.

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Conflict of interests

The authors declare that they have no conflicts of interest. The authors adhere to the Auckland Code of Ethics for Gambling Research (2018).

References

American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR*. Washington, DC: American Psychiatric Association.

American Psychiatric Association (2013). *Diagnostic and Statistical Manual of Mental Disorders, DSM-5*. Arlington: American Psychiatric Publishing.

Andreassen, C. S., Billieux, J., Griffiths, M. D., Kuss, D. J., Demetrovics, Z., Mazzoni, E. & Pallesen, S. (2016). The relationship between addictive use of social media and video games and symptoms of psychiatric disorders: A large-scale cross-sectional study. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors, 30*, 252-262. doi:10.1037/adb0000160.

Baggio, S., Starcevic, V., Studer, J., Simon, O., Gainsbury, S. M., Gmel, G. & Billieux, J. (2018). Technology-mediated addictive behaviors constitute a spectrum of related yet distinct conditions: A network perspective. *Psychology of Addictive Behaviors, 32*, 564-572. doi:10.1037/adb0000379.

Billieux, J., Van der Linden, M. & Rochat, L. (2008). The role of impulsivity in actual and problematic use of the mobile phone. *Applied Cognitive Psychology: The Official Journal of the Society for Applied Research in Memory and Cognition*, *22*, 1195-1210. doi:10.1002/acp.1429.

Billieux, J., Van der Linden, M., d'Acremont, M., Ceschi, G. & Zermatten, A. (2007). Does impulsivity relate to perceived dependence on and actual use of the mobile phone? *Applied Cognitive Psychology*, *21*, 527-537. doi:10.1002/acp.1289.

Block, J. J. (2008). Issues for DSM-V: Internet addiction (2008). *American Journal of Psychiatry, 165*, 306-307. doi:10.1176/appi.ajp.2007.07101556.

Carlisle, K. L., Carlisle, R. M., Polychronopoulos, G. B., Goodman-Scott, E. & Kirk-Jenkins, A. (2016). Exploring internet addiction as a process addiction. *Journal of Mental Health Counseling, 38*, 170-182. doi:10.17744/mehc.38.2.07.

Chóliz, M. (2010). Mobile phone addiction: A point of issue. *Addiction, 105*, 373–374. doi:10.1111/j.1360-0443.2009.02854.x.

Chóliz, M. (2012). Mobile-phone addiction in adolescence: The test of mobile phone dependence (TMD). *Progress in Health Sciences, 2,* 33-44. doi:10.2166/wst.2006.036.

Chóliz, M., Echeburúa, E. & Ferre, F. (2017). Screening tools for technological addictions: A proposal for the strategy of mental health. *International Journal of Mental Health and Addiction*, *15*, 423-433. doi:10.1007/s11469-017-9743-1.

Chóliz, M., Echeburúa, E. & Labrador, F. J. (2012). Technological addictions: Are these the new addictions. *Current Psychiatric Reviews, 8*, 290–291. doi:10.2174/1573400012803520540.

Chóliz, M., Marco, C. & Chóliz, C. (2016). *ADITEC, evaluación y prevención de la adicción a internet, móvil y videojuegos*. Madrid: TEA Ediciones.

Chóliz, M., Marcos, M. & Lázaro-Mateo, J. (2019). The risk of online gambling. A study of gambling disorder prevalence rates in Spain. *International Journal of Mental*

Health and Addiction,11, 1-14. doi:10.1007/s11469-019-00067-4.

Chóliz, M. & Marco, C. (2011). Patrón de uso y dependencia de videojuegos en infancia y adolescencia. *Anales de Psicología, 27*, 418-426.

Chóliz, M. & Marcos, M. (2018). *Cuando jugar es un problema.* Valencia: Psylicom.

Chóliz, M. & Marcos, M. (2020). *Tratamiento psicológico de la adicción al juego online.* Madrid: Pirámide.

Delfabbro, P., Lambos, C., King, D. & Puglies, S. (2009). Knowledge and beliefs about gambling in Australian secondary school students and their implications for education strategies. *Journal of Gambling Studies*, *25*, 523-539. doi:10.1007/s10899-009-9141-0.

Desai, R. A., Krishnan-Sarin, S., Cavallo, D. & Potenza, M. N. (2010). Video game playing in high school students: Health correlates, gender differences and problematic gaming. *Pediatrics*, *126*, 1414-1424. doi:10.1542/peds.2009-2706.

Echeburúa, E. (1999). *¿Adicciones sin drogas?: Las nuevas adicciones: Juego, sexo, comida, compras, trabajo, Internet.* Bilbao: Desclée de Brouwer.

Echeburúa, E., Labrador, F. J. & Becoña, E. (2009). *Adicción a las nuevas tecnologías en adolescentes y jóvenes*. Madrid: Pirámide.

Ferguson, C. J., Coulson, M. & Barnett, J. (2011). A meta-analysis of pathological gaming prevalence and comorbidity with mental health, academic and social problems. *Journal of Psychiatric Research*, *45*, 1573-1578. doi:10.1016/j.jpsychires. 2011.09.005.

Fernández-Montalvo, J., Echeburúa, E. & Báez, C. (1995). El Cuestionario Breve de Juego Patológico (CBJP): Un nuevo instrumento de "screening". *Análisis y Modificación de Conducta, 21,* 211-223.

Forrest, C. J., King, D. L. & Delfabbro, P. H. (2016). The gambling preferences and behaviors of a community sample of Australian regular video game players. *Journal of Gambling Studies*, *32*, 409-420. doi:10.1007/s10899-015-9535-0.

Gadermann, A. M., Guhn, M. & Zumbo, B. D. (2012). Estimating ordinal reliability for Likert-type and ordinal item response data: A conceptual, empirical, and practical guide. *Practical Assessment, Research and Evaluation*, *17*, 1-13. doi:10.7275/n560-j767.

Gerstein, D., Hoffmann, J., Larison, C., Engelman, L., Murphy, S., Palmer, A.,… Hill, M. A. (1999). *Gambling impact and behavior study.* Report to the National Gambling Impact Study Commission. National Opinion Research Center at the University of Chicago, Chicago, National Opinion Research Center.

Gladwin, T. E., Figner, B., Crone, E.A. & Wiers, R.W. (2011). Addiction, adolescence, and the integration of control and motivation. *Developmental Cognitive Neuroscience*, *1*, 364-376. doi:10.1016/j.dcn.2011.06.008.

González, H. & Pérez-Álvarez, M. (2007). *La invención de los trastornos mentales.* Madrid: Alianza Editorial.

Grande-Gosende, A., Martínez-Loredo, V. & Fernández-Hermida, J. R. (2019). Gambling Motives Questionnaire validation in adolescents: Differences based on gambling severity and activities. *Adicciones, 31,* 212-220. doi:10.20882/adicciones.1057.

Griffiths, M. (1995). Technological addictions. *Clinical Psychology Forum, 76*, 14–19.

Griffiths, M. D. (2003). Internet gambling: Issues, concerns and recommendations. *CyberPsychology & Behavior, 6,* 557-568. doi:10.1089/ 109493103322725333.

Griffiths, M. D. (2012). Internet gambling, player protection, and social responsibility. In R. J. Williams, R. Wood and J. Parke (Eds.), *Routledge International Handbook of Internet Gambling* (pp. 227-249). U.K: Routledge.

Griffiths, M. D., Kuss, D. J. & King, D. L. (2012). Video game addiction: Past, present and future. *Current Psychiatric Reviews, 8*, 308–318. doi:10.2174/157340012803520414.

Griffiths, M. D., Parke, A., Wood, R. & Parke, J. (2006). Internet gambling: An overview of psychosocial impacts. *UNLV Gaming Research & Review Journal, 10*, 27-39. doi:10.4018/978-1-59140-993-9.ch033.

Jiménez-Murcia, S. & Farré, J. J. (2015). *Adicción a las nuevas tecnologías: ¿La epidemia del siglo XXI?* Barcelona: Siglantana.

Johnson, E. E., Hamer, R., Nora, R. M., Tan, B., Eisenstein, N. & Engelhart, C. (1997). The Lie/Bet Questionnaire for screening pathological gamblers. *Psychological Reports, 80,* 83-88. doi:10.2466/pr0.1997.80.1.83.

King, D. L., Ejova, A. & Delfabbro, P. H. (2012). Illusory control, gambling, and video gaming: An investigation of regular gamblers and video game players. *Journal of Gambling Studies*, *28*, 421-435. doi:10.1007/s10899-011-9271-z.

Ko, C. H., Yen, J. Y., Chen, C. C., Chen, S. H. & Yen, C. F. (2005). Gender differences and related factors affecting online gaming addiction among Taiwanese adolescents. *The Journal of Nervous and Mental Disease*, *193*, 273-277. doi:10.1097/01.nmd.0000158373.85150.57.

Kuss, D. J. & Griffiths, M. D. (2012). Internet gaming addiction: A systematic review of empirical research. *International Journal of Mental Health and Addiction*, *10*, 278-296. doi:10.1007/s11469-011-9318-5.

Kuss, D. J. & Griffiths, M. D. (2017). Social networking sites and addiction: Ten lessons learned. *International Journal of Environmental Research and Public Health, 14*, 311. doi:10.3390/ijerph14030311.

Martín-Fernández, M., Matalí, J. L., García-Sánchez, S., Pardo, M., Lleras, M. & Castellano-Tejedor, C. (2017). Adolescentes con trastorno por juego en Internet (IGD): Perfiles y respuesta al tratamiento. *Adicciones, 29*, 125-133. doi:10.20882/adicciones.890.

McDonald, R. P. (1999). *Test theory: A unified treatment*. Mahwah, NJ: Lawrence Erlbaum.

Monaghan, S. (2009). Internet gambling—Not just a fad. *International Gambling Studies, 9,* 1-4.

Muñiz, J. & Fonseca-Pedrero, E. (2019). Diez pasos para la construcción de un test. *Psicothema, 31,* 7-16. doi:10.7334/psicothema2018.291.

Northrup, J. C., Lapierre, C., Kirk, J. & Rae, C. (2015). The internet process addiction test: Screening for addictions to processes facilitated by the internet. *Behavioral Sciences, 5*, 341-352. doi:10.3390/bs5030341.

Petry, N. M. (2006). Internet gambling: An emerging concern in family practice medicine? *Family Practice, 23*, 421-426. doi:10.1093/fampra/cml005.

Petry, N. M. & O'brien, C. P. (2013). Internet gaming disorder and the DSM-5. *Addiction*, *108*, 1186-1187. doi:10.1111/add.12162.

Sanders, J. & Williams, R. (2019). The relationship between video gaming, gambling, and problematic levels of video gaming and gambling. *Journal of Gambling Studies, 35,* 559-569. doi:10.1007/s10899-018-9798-3.

Stepien, K. (2014). Internet addiction. The phenomenon of pathological internet use - problems of interpretation in the definition and diagnosis. *Internal Security, 6*, 79-90. doi:10.5604/20805268.1157164.

Tsai, C. C. & Lin, S. S. (2003). Internet addiction of adolescents in Taiwan: An interview study. *CyberPsychology & Behavior, 6*, 649–652. doi:10.1089/109493103322725432.

Volberg, R. A., Munck, I. M. & Petry, N. M. (2011). A quick and simple screening method for pathological and problem gamblers in addiction programs and practices. *The American Journal on Addictions*, *20*, 220-227. doi:10.1111/j.1521-0391.2011.00118.x.

Wardle, H., Moody, A., Spence, S., Orford, J., Volberg, R., Jotangia, D.,... Dobbie, F. (2011). *British gambling prevalence survey 2010,* London: National Centre for Social Research. http://www. gamblingcommission. gov.uk/ PDF/British%20Gambling% 20Prevalence% 20Survey, 202010.

Welte, J. W., Barnes, G. M., Wieczorek, W. F., Tidwell, M-C. O. & Hoffman, J.H. (2007). Type of gambling and availability as risk factors for problem gambling: A Tobit regression analysis by age and gender. *International Gambling Studies, 7*, 183-198. doi:10.1080/14459790701387543.

World Health Organization (2018). ICD-11. International Classification of Diseases, 11th revision. https://icd. who.int.

Young, K. S. (1998). Internet addiction: The emergence of a new clinical disorder. *Cyberpsychology & Behavior*, *1*, 237-244. doi:10.1089/cpb.1998.1.237.

ANNEXES

TecnoTest

This is a questionnaire about technology use (videogames, mobile phones and social networks) and gambling. Please indicate if the following statements have applied to you **DURING THE PAST YEAR.** There are no true or false, good or bad answers. Please answer honestly. Thank you for your collaboration.

Sex: Age:

		YES	NO
1	I don't normally worry about gambling nor do I think about gambling or betting.	O	O
2	I have repeatedly lied to my family or friends about how much money I have gambled or lost through gambling or betting.	O	O
3	People have told me or warned me about using my mobile phone too much.	O	O
4	I can't just use the messaging applications (Whatsapp, Line, Telegram, etc.) like I used to; I need to use them more and more.	O	O
5	It is important for me to get "likes" in my status or photos because I feel bad if I don't.	O	O
6	The first thing I do when I get home after class or work is play my video games.	O	O
7	I feel a constant need to update my status or profile photo on my social networks.	O	O
8	I have stopped going out with friends or doing things with them because now we arrange to meet online and play video games.	O	O
9	I usually turn off or silence my mobile when I go to bed so as not to use it in bed.	O	O
10	I play about the same amount of time now as when I started playing video games.	O	O
11	I am able to control the amount of time I spend on social media.	O	O
12	There have been periods when I needed to bet increasing amounts of money to feel the same excitement.	O	O
13	I can usually control myself when it comes to the amount of time I spend on the mobile.	O	O
14	I've lost control of social media.	O	O
15	I can easily quit the video game if something comes up that I have to do.	O	O
16	I have borrowed money from family members or others at some point because of serious financial problems due to gambling.	O	O
17	I can handle boredom without using my mobile.	O	O
18	I have been able to stop playing whenever I have wanted to.	O	O
19	I have pretended to be sick to avoid going to class or doing homework in order to play my video games.	O	O
20	I have argued with a relative about spending too much on things related to mobile phones.	O	O
21	When I use social networks, I am aware of the time I am spending on them.	O	O
22	When it comes to using social media, I only use it for what I need.	O	O
23	When I play, I am aware of the time I am spending on the video game.	O	O
24	I can stop playing or gambling without feeling bad about it.	O	O

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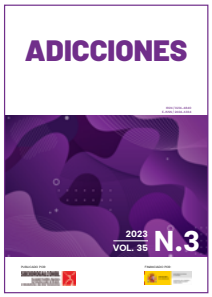

ORIGINAL

Financed research from Government Delegation grants for the National Plan on Drugs: Research assessment and scientific impact

Repercusión científica de las ayudas de la Delegación del Gobierno para el Plan Nacional sobre Drogas: Publicaciones derivadas e impacto científico

Rafael Aleixandre-Benavent*,***; Víctor Agulló-Calatayud*,****; Adolfo Alonso-Arroyo*,**; Francisco-Jesús Bueno-Cañigral*****; Lourdes Castelló-Cogollos*,****; Rut Lucas-Domínguez*,**; David Melero-Fuentes******; Andrea Sixto-Costoya*,**; Antonio Vidal-Infer*,**; Juan-Carlos Valderrama-Zurián*,**.

* Unidad de Investigación e Información Social y Sanitaria-UISYS. CSIC-Universitat de València.

** Departamento de Historia de la Ciencia y Documentación. Universitat de València.

*** Ingenio. CSIC-Universitat Politècnica de València.

**** Departamento de Sociología y Antropología Social. Universitat de València.

***** Servicio de Drogodependencias (PMD/UPCCA-València). Concejalía de Salud y Consumo. Ajuntament de València.

****** Facultad de Psicología. Instituto de Documentación y Tecnologías de la Información. Universidad Católica de Valencia San Vicente Mártir.

Abstract

Addictive disorders are a serious health problem to which large amounts of research resources are devoted. This study aims to analyze the evolution and scientific impact of the publications derived from the funding of research projects by the Spanish National Plan on Drugs (PNSD). The list of grants awarded was provided by the PNSD. Derived publications were obtained by asking the principal investigators of the grants and searching in the Web of Science and Scopus. Bibliometric indicators and evolutive trends of scientific production per project were calculated. On average, the PNSD conferred 15 annual grants to research projects, with an annual amount close to one million euros (€944,200.64) and an average amount per grant of just over €60,000, being higher in basic research and in alcohol. 71,9% of the grants had derived publications and almost half of them produced between one and three publications, with basic research being the most prolific. The international journal in which most articles were published was *Psychopharmacology* (50) and among Spanish journals, *Adicciones* stood out (28). A high level of co-authorship and international collaboration was identified. Most of the PNSD-funded projects produced research articles, many of them in journals belonging to the first and second quartiles of the *Journal Citation Reports*. The results of this study have revealed the scientific impact of the PNSD research projects funding and may contribute to determining future funding priorities.

Keywords: substance-related disorders, funding support, research projects, bibliometrics, publications resulting

Resumen

Los trastornos adictivos son un grave problema de salud al que se destinan gran cantidad de recursos de investigación. El propósito de este trabajo es analizar la evolución e impacto científico de las publicaciones derivadas de las ayudas a proyectos de investigación financiados por el Plan Nacional Sobre Drogas (PNSD). La relación de ayudas concedidas fue proporcionada por el PNSD. Las publicaciones derivadas se obtuvieron preguntando a los investigadores principales de las ayudas y buscando en Web of Science y Scopus. Se calcularon indicadores bibliométricos y tendencias evolutivas de la producción científica por proyecto. Por término medio, el PNSD concedió 15 ayudas anuales a proyectos de investigación, con un importe anual cercano al millón de euros (944.200,64€) y un importe medio por ayuda de algo más de 60.000€, siendo mayor en la investigación básica y en alcohol. El 71,9% de las ayudas tuvieron publicaciones derivadas y casi la mitad produjeron entre una y tres publicaciones, siendo la investigación básica la más prolífica. La revista extranjera en la que más artículos se publicaron fue *Psychopharmacology* (50) y entre las españolas destacó *Adicciones* (28). Se identificó un alto índice de coautoría y de colaboración internacional. La mayoría de los proyectos financiados por el PNSD produjeron artículos de investigación y muchos de ellos en revistas del primer y segundo cuartil del *Journal Citation Reports*. Los resultados de este estudio han permitido conocer la repercusión científica de las ayudas a proyectos de investigación del PNSD y puede contribuir a determinar futuras prioridades de financiación.

Palabras clave: trastornos por abuso de sustancias, ayudas económicas, proyectos de investigación, bibliometría, publicaciones derivadas

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■ **Send correspondence to:**
Juan-Carlos Valderrama-Zurián. UISYS (Universitat de València). Plaza Cisneros, 4, 46003-Valencia.
Email: juan.valderrama@uv.es

Almost five decades ago, drug use and its consequences became one of the main concerns in Spanish society. The problem sparked debates at political, health and social levels, calling for a government response that came at the Council of Ministers on July 24, 1985, the date on which the National Plan on Drugs was brought into being to promote and coordinate the drug addiction policies of public administrations. In its declaration of principles, Section 4 referred to research on drug addiction in the following terms as "permanent research that must be strengthened both with regard to the knowledge of reality in a way that facilitates the planning and development of actions consistent with it, and in applied research, which enables new experiences of prevention and treatment to be defined. Similarly, in the field of research in Spain, there is an urgent need to develop standardized methods that make it possible to compare and complete the results obtained, in different studies and at different times" (Royal Decree 1677/1985).

Thirty-five years have passed since that declaration of principles, and with hindsight it can be said that drug addiction research has been a firmly established reality in Spain for a long time, as observed in several bibliometric studies analyzing Spanish research in the field (Aleixandre, 1999; Álvarez & del Río, 2003; Ballesteros, Torrens & Valderrama, 2006; González-Alcaide, Calafat, Becoña, Thijs & Glänzel, 2016; Rodríguez de Fonseca et al., 2006). One of the main achievements is the consolidation of an annual round of research project funding by the National Plan on Drugs. Grants are awarded on the basis of the quality criteria of the projects presented in concurrent competition, and this has led to state subsidy of a very considerable number of projects, as well as greater monitoring and control by the administration of how well goals are met by the principal investigators (Plan Nacional sobre Drogas, s.f.a). Other types of subsidy have also been established, such as, for example, financial aid to private non-profit organizations for implementing addiction programs paid for by the Confiscated Assets Fund resulting from operations against illicit drug trafficking and other related crimes under Law 17/2003; grants for implementing supra-community programs on addictions (Ministerio de Sanidad, Servicios Sociales e Igualdad, 2019); help for local corporations who can charge the cost of developing drug prevention programs to the Confiscated Assets Fund (Plan Nacional sobre Drogas, s.f.b).

An important aspect of research assessment is quantifying the performance of such public or privately funded research. The aim of this study is to ascertain which projects were financed by the PNSD from 2000 to 2016 and to assess the academic performance of the grants through the bibliometric analysis of the publications derived from these projects in scientific journals.

Methods

Obtaining project data

The list of grants for research projects funded from 2000 to 2016 by the PNSD was obtained on the website http://www.pnsd.mscbs.gob.es/delegacionGobiernoPNSD/convocatoriaSubvenciones/ongs/proyecInvestig.htm. The following information was collected from the projects: name of the principal investigator (PI), institution, amount and year of grant. In the case of 77 grants for projects prior to 2004, information was available regarding the institution to which the PI belonged but not on the researcher's identity since names were not registered. The projects were classified according to: a) substances covered, classified as alcohol, hallucinogens, cannabis, cocaine, synthetic drugs, opiates, psychostimulants, tobacco, and drugs in general; b) type of research, divided into basic, clinical-psychiatry, documentation, genetics, general medicine, public policies, prevention, radiology, public health, social services, treatment, emergency services.

Search for publications derived from grants

In order to identify the derived publications, the PIs of each grant were emailed with a request for the bibliographic references of the publications derived from the funded projects. When these references were not provided by the PIs, searches were made in the Web of Science (WoS) Core Collection and Scopus, combining the keywords from the project title with the surnames of the PIs. These sources are the two reference databases commonly used in the evaluation of scientific activity and in determining bibliometric indicators, especially those based on the citations received by published papers (Bar-Ilan, Levene & Lin, 2007; Marx, Schier & Wanitschek, 2001).

In the 77 grants in which the main researcher was not listed, the derived output was identified from the project title. A bibliographic search was also carried out in the WoS and Scopus "Funding Entity" field. The search equation included the terms ("Spanish national drug*" OR "pnd" OR "pnsd" OR "plan nacional de drogas" OR "plan nacional sobre drogas" OR "plan nacional en drogas" OR "plan nacional drogas" OR "national drug plan" OR "National Plan on Drugs" OR ((Nacional OR Plan OR National) AND (drug* or droga*)) and the articles and reviews were filtered out. The results obtained were cross-checked by four of the authors, specialists in the field of addictive disorders and scientific documentation, to determine whether each paper retrieved really corresponded to the project to which it was assigned. For an article to be considered as a derived publication, two criteria had to be met: a) the PI the project had to be one of the authors of the article; b) the date of publication of the article had to be after or in the same year as the grant award. The searches for derived articles were carried out from September to December 2019 and all papers derived from the research projects found in the

databases on December 31, 2019 were included. Thus, there was a wait of at least less 3 years after the last PNSD call for projects included in this work; this amount of time is considered sufficient for the results of the investigations to be published and to minimize possible losses, according to Kingwell et al (2006). The number of citations for each derived publication was consulted on April 6, 2020 to ensure the most updated information possible.

Data extraction and indicators

The following information was extracted from each derived article: authors, article title, journal, number of citations received and year of publication. These data were completed with the following supplementary information about the journals from the 2018 edition of the *Journal Citation Reports* (jcr.clarivate.com): country of publication and five-year impact factor.

The following indicators were then obtained: trends in the number of annual grants, annual total investment and average amount per grant; substance studied under the project and type of research funded; annual development of subsidies depending on whether or not publications were derived; gap in years between grants awarded and publications derived; annual number of articles published in Spanish and foreign journals; institutions benefiting from the aid and number of articles published; journals in which the articles were published, number of citations received, author collaboration rates, existence of national and international collaboration and map showing collaboration between the countries of the authors' institutions. Citation analysis was used to assess the academic impact of published papers in a given subject field (Moed, 2009; Waltman, 2016); this has become a useful and widely used tool since the frequency with which papers are cited can be considered an objective parameter of their quality (Bornmann & Leydesdorff, 2014; Byrne & Chapman, 2005; Mahabee-Gittens, Gordon, Melink & Merianos, 2017; Marx et al., 2001; Tanner-Smith & Polanin, 2016; van Wesel, 2015).

Statistical analysis was carried out using SPSS version 26 (IBM, Armonk, NY, USA). Descriptive and frequency analyses were performed, with the chi-square ($\chi 2$) test for comparing categorical variables and the non-parametric Kruskal-Wallis test (K-W) for quantitative variables of various categories. The level of statistical significance was established at $p<0.05$. For the type of research, the various categories were grouped into three large research areas: basic, health sciences (clinical-psychiatry, genetics, general medicine, radiology, public health, treatment, emergencies) and social sciences (documentation, public policies, prevention, social services).

To represent the network of international collaboration on the derived publications, Pajek software was used, with its Pathfinder scaling algorithm to reduce the dimensional space and the Kamada-Kawai algorithm as the visualization algorithm. This network is shown in the form of a geographical world map. In it, the diameter of the spheres is proportional to the number of different countries with which each country is related and the thickness of the lines represents the number of times that two countries collaborate. The network was established on the basis of a threshold of more than one article published in collaboration.

The data from which the results were extracted, as well as additional tables and figures, are available as supplementary material on Zenodo (Aleixandre-Benavent et al., 2020a; Aleixandre-Benavent et al., 2020b; Aleixandre-Benavent et al., 2020c).

Results

The PNSD has been distributing grants for the development of research projects on addictions since 2000. Table 1 shows the annual distribution of the 253 grants awarded from 2000 to 2016, to a total value of €16,051,410.87. To present homogeneous values for the complete period, subsidies in 2000 and 2001, originally published in pesetas (107,700,000 pesetas in 2000 and 75,250,000 pesetas in 2001), have been converted to euros (at the official 2002 exchange rate of 166,386 pesetas per euro). The year with most grants awarded was 2005 (21 grants), while in 2012 only ten were conferred. On average, around 15 grants were awarded annually, with an average annual amount close to one million euros (€944,200.64) and an average amount per grant of a little over €60,000. As can be seen, neither the number of grants nor their amount follow a rising trend over time as there are annual fluctuations. Although the number of grants increased in the last three years (from 11 grants in 2014 to 17 in 2016), the amount awarded fell by 27% (from €1,117,951 in 2014 to €815,286 in 2016). At the same time, the average amount per grant fell by almost half from 2014 to 2016.

Alcohol was the focus of 36% of the projects, while 22.9% were on drugs in general and 19% on cocaine (Table 1 of supplementary material (SM)), and only one project dealt specifically with hallucinogens (0.4%). Except in one year, projects on alcohol or drugs in general have always been funded. Since 2010, funding has gone mainly to projects on alcohol, ranging from 52.9% of the projects annually in 2016 to 83.3% in 2015. The two projects receiving the most funding were on psychostimulants (€194,087) and cannabis (€193,357), with synthetic drugs projects obtaining the most funding (median: €68,943). Statistically significant differences were found in the amounts granted according to the type of substances investigated (K-W: $\chi 2=20.04$; $p<0.006$) (Figure 1a).

Basic research is the focus of 42.7% of the projects, followed by studies in the area of health sciences, and among them those focused on clinical aspects in the area of psychiatry and psychology. Prevention projects represent

9.5% of all projects. Among the least funded areas, those of social aspects, general medicine, brain radiological studies, emergency services and public policies stand out (Table 2, SM). Differences were found in the amounts awarded to the research areas (K-W: $\chi 2=20.7$; $p<0.001$), with the projects in the basic area receiving more funding (Figure 1b).

Figure 2 provides an overview of year-on-year changes in the projects with derived articles in terms of absolute numbers. At the beginning of the period (2000-2004) there is almost parallel development between grants with and without derived publications, followed by the rise in the number of grants with derived publications as of 2005. The year in which all projects saw at least one publication was 2012 (100%), while the year with the lowest percentage (43.8%) was 2000.

Figure 1 SM shows the number of published articles derived from the 182 grants leading to scientific publications. Of the total grants (n=253), 84 (33.2%) generated one, two or three derived publications, with grants leading to a single derived publication predominating (32 grants; 12.6%), followed by grants with two publications (31 grants, 12.3%) and grants with three publications (22 grants; 8.7%). Grants with more than 14 publications represent 4.4%. The total number of derived publications was 1,019, although 31 of them were funded by two PNSD grants. Projects in the basic research area have a higher median number of derived publications than those in health sciences and social sciences (K-W: $\chi 2=14.99$; $p<0.002$) (Table 2). In terms of the substances covered by the research projects, it is psychostimulants that present the greatest number of derived publications. Statistically significant differences were found in the number of publications derived from the projects on cocaine or alcohol with respect to those on drugs in general (Table 2). The median number of publications derived from projects on opioids is one article, which is the same median for projects on tobacco and drugs in general.

It is also relevant to know the time elapsed between grant award and publication (Figure 2, SM). Most papers were published three years (21.5%) and four years (19%) after the award. The percentage of articles published within the same year the project was funded was 3.3%. The rate of publication six years after the grant was 11.2%.

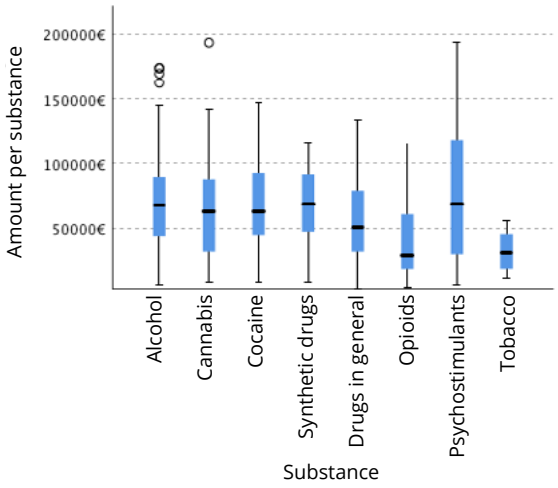
The number of articles published annually in Spanish and foreign journals is presented in Table 3 of SM. Of the 1,019 articles, 937 (92%) were published in foreign journals and 82 (8%) in Spanish journals.

Table 3 shows the journals in which five or more studies derived from the grants were published. The journals receiving the largest number of papers were Psychopharmacology (n=50), followed by Drug and Alcohol Dependence (n=38)

Table 1
Annual changes in the amounts in euros granted by the Spanish National Plan on Drugs for the development of research projects on addictions

Year	Nº grants	Total invested (€)	Mean amount granted (€)	Standard deviation (€)	5% trimmed mean (€)	Min. (€)	Max. (€)
2000	16	647,290.04	40,455.63	21,524.54	39,508.20	10,818.21	87,146.76
2001	16	452,261.61	28,266.35	19,095.57	27,433.70	3,005.06	68,515.38
2002	17	866,124.92	50,948.52	40,555.07	48,998.36	4,000	133,000
2003	20	1,380,925.31	69,046.27	44,164.66	65,316.02	11,150	194,087
2004	14	655,510	46,822.14	47,827.73	40,526.38	13,611	193,357
2005	21	1,158,149	55,149.95	36,242.69	54,224.42	11,400	115,630
2006	13	893,366	68,720.46	23,318.05	68,466.90	35,000	107,005
2007	14	1,089,010	77,786.43	44,316.25	77,809.43	8,000	147,160
2008	13	772,610	59,431.54	31,602.93	58,615.60	10,550	123,000
2009	15	975,700	65,046.67	33,703.78	64,829.63	16,000	118,000
2010	16	1,214,490	75,905.63	33,028.72	74,228.47	20,000	162,000
2011	15	1,134,821	75,654.73	22,673.36	74,621.09	43,915	126,000
2012	10	918,200	91,820	38,422.15	90,661.11	35,300	169,200
2013	13	939,060	72,235.38	38,981.04	71,598.26	15,793	140,146
2014	11	1,117,951	101,631.91	37,484.70	100,064.68	57,836	173,638
2015	12	1,020,656	85,054.67	26,264.88	83,401.24	54,844	145,027
2016	17	815,286	47,958	19,905.50	47,914.56	12,698	84,000
Total	253	16,051,410.87	63,444.31	37,514.36	61,172.43	3.005.06	194.087

Figure 1a
Amount per substance researched. Kruskal-Wallis test (p<0.006)



Nota. As only one project on hallucinogens was funded, it was excluded from the analysis.

Figure 1b
Distribution of amounts granted by research area

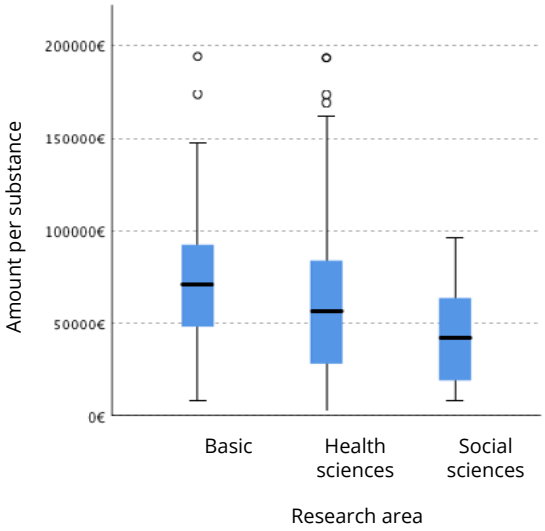
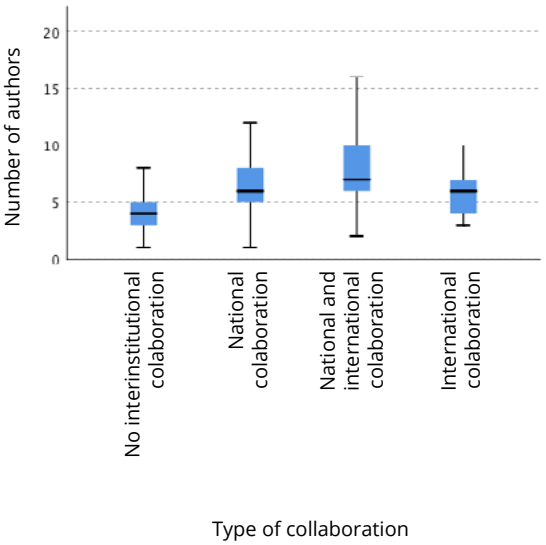


Figure 1c
Distribution of the number of authors by type of collaboration. Kruskal-Wallis test (p<0.001)



and Addiction Biology (n=35). The first Spanish journal was Addictions (n=28). In the number of citations in WoS, the ranking is headed by Drug and Alcohol Dependence (n=1,243). The journal with the highest "citations per paper" indicator in WoS was Biological Psychiatry (C/P=74.25). Of the 52 journals in which five or more papers were published, 26 (50%) were in the first quartile of JCR and 17 (32.7%) in the second quartile, with 603 papers published in journals in top two quartiles.

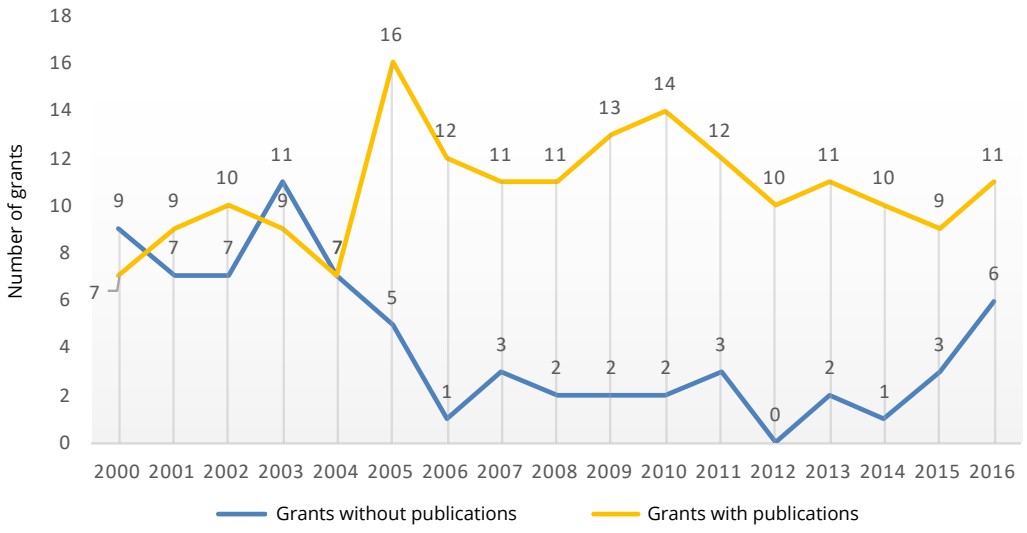
The 70 beneficiary institutions of Spanish National Plan on Drugs funding are presented in Table 4. Of these, 14 did not report any derived publications. Those receiving the most aid during the period analyzed were the Complutense University of Madrid (n=21), followed by the Fundación Instituto Mar de Investigaciones Médicas (IMIM) (n=18), the Consejo Superior de Investigaciones Científicas (Higher Council for Scientific Research) (n=15) and the universities of Santiago de Compostela (n=13) and València (n=12). The five institutions that received the highest total amount were the same as those mentioned above. In absolute number of studies derived from the grants, the Complutense University of Madrid (n=79) stands out, followed by Pompeu Fabra University (n=63) and the University of València (n=60). The indicator "number of papers per grant" is higher for the Marqués de Valdecilla Public Foundation (n=27), followed by the Jiménez Díaz Foundation Health Research Institute (n=18) and the Andalusian Public Foundation for Research in Biomedicine and Health (FIMABIS) in Malaga (n=17). Finally, the indicator "grant per paper" (€/P) was €261,197.46 for the Biomedical Research Foundation of the 12 de Octubre University Hospital, since only one publication was derived from five funded projects, and €110,920 for the Foundation for Health Training and Research of the Region of Murcia.

Regarding the number of citations, the institutions with the most citations for papers by its authors were the Consejo Superior de Investigaciones Científicas, Centro de Investigación Príncipe Felipe at the Fundación de la Comunidad Valenciana, and the Complutense University of Madrid with 2,591, 2,182 and 2,104 citations, respectively. The Centro de Investigación Príncipe Felipe at the Fundación de la Comunidad Valenciana remains among the top three institutions with respect to the number of citations per paper (n=68) and number of papers per grant (n=727).

Table 2
Derived publications according to research area and type of substance

	Number of derived publications				
Research area	**Min.**	**Max.**	**Median**	**5% trimmed mean**	**Kruskal-Wallis test**
Basic	0	19	4	4.58	
Health sciences	0	27	2	3.02	χ^2=14.99 p<0.002
Social sciences	0	15	1	1.93	
Substance					
Alcohol	0	19	3	4.37	
Cannabis	0	27	2.5	4.11	
Cocaine	0	24	3	4.38	
Synthetic drugs	0	11	2	3.57	χ^2=19.13 p<0.009
Drugs in general	0	18	1	1.94	
Opioids	0	17	1	2.20	
Psychostimulants	0	13	4	5.94	
Tobacco	0	7	1	1.97	

Figure 2
Annual change in the number of grants from the Spanish National Plan on Drugs with and without derived publications



Derived articles written in collaboration comprised 99.7% of all papers. The 5% trimmed mean of the number of authors of the articles derived from the funded projects stands at 6.5 authors per paper. The average number of authors per paper is higher in health sciences (7.15) than in basic sciences (6.27) and social sciences (5.23) (K-W: χ2=40.61; p<0.001). As regards collaboration between institutions, this occurred in 17.2% of the articles, and a foreign institution was involved in 28.8% of the papers. International collaboration is higher in health sciences (33.8%) compared to other areas (χ2=14.3; p<0.002). Differences were observed in the number of authors per paper according to the type of collaboration (K-W: χ2=174.2; p<0.001) (Figure 1c). The papers where authors from various national and international institutions collaborated had a greater number of authors per paper.

The authors collaborated with researchers from 89 countries. The collaboration map shown in Figure 3 has a threshold of two or more articles in collaboration, thus generating a network of 29 participating countries. It can be seen that the country with which Spain collaborates the most is the United States (n=112), followed by the United Kingdom (n=57) and Australia (n=43).

Table 3

Journals with more than 5 derived articles and number of citations (sorted by number of derived articles and total number of citations)

Journal	Country	Nº Derived Articles	Total Nº of Citations	Citations/ Article in WoS	FI 5 years	Quartiles
Psychopharmacology	Germany	50	1,075	21.5	3.3	Q2
Drug and Alcohol Dependence	Switzerland	38	1,243	32.71	3.989	Q1
Addiction Biology	England	35	581	16.6	4.02	Q1
Neuropharmacology	England	34	807	23.74	4.494	Q1
Plos One	United States	32	673	21.03	3.337	Q2
Adicciones*	Spain	28	225	9.78	2.221	Q1
British Journal of Pharmacology	England	23	643	27.96	5.755	Q1
Journal of Psychopharmacology	England	23	332	14.43	4.434	Q1
Neuropsychopharmacology	England	22	1,104	50.18	6.705	Q1
European Neuropsychopharmacology	Netherlands	19	332	17.47	4.394	Q1
Journal of Neurochemistry	England	16	829	51.81	4.371	Q1
International Journal of Neuropsychopharmacology	England	15	223	14.87	4.39	Q1
Neuroscience	England	14	430	30.71	3.504	Q2
Alcoholism-clinical and Experimental Research	United States	14	328	23.43	3.276	Q2
Progress in Neuro-psychopharmacology & Biological Psychiatry	England	14	235	16.79	4.159	Q1
European Journal of Pharmacology	Netherlands	12	194	16.17	3.12	Q2
Gaceta Sanitaria	Spain	12	140	11.67	1.918	Q2
Psychiatry Research	Netherlands	12	128	10.67	2.67	Q2
Scientific Reports	England	11	54	4.91	4.525	Q1
Alcohol and Alcoholism	England	10	556	55.6	2.882	Q2
Pharmacology Biochemistry and Behavior*	England	10	266	29.55	2.867	Q2
Schizophrenia Research*	Netherlands	10	233	25.88	4.583	Q1
Addictive Behaviors	England	10	220	22	3.325	Q1
Behavioural Pharmacology	United States	10	196	19.6	1.869	Q3
Neuroscience Letters	Netherlands	10	155	15.5	2.228	Q3
Behavioural Brain Research	Netherlands	10	154	15.4	3.021	Q2
Neurobiology of Disease	England	9	434	48.22	5.304	Q1
Neuroscience and Biobehavioral Reviews	England	9	393	43.67	9.42	Q1
Addiction	England	9	202	22.44	6.45	Q1
Frontiers in Behavioral Neuroscience	Switzerland	9	145	16.11	3.454	Q2
Biological Psychiatry	United States	8	594	74.25	11.275	Q1
European Addiction Research	Switzerland	8	67	8.38	2.532	Q2
Frontiers in Psychiatry	Switzerland	8	41	5.13	n/a	Q2
Journal of Psychiatric Research	England	7	225	32.14	4.475	Q1
Physiology & Behavior	United States	7	136	19.43	2.848	Q2
Biochemical Pharmacology	United States	7	50	7.14	4.637	Q1
Substance Use & Misuse	United States	7	42	6	1.584	Q4
Journal of Affective Disorders	Netherlands	7	39	5.57	4.16	Q1
Psicothema	Spain	6	104	17.33	2.057	Q2
European Journal of Neuroscience	England	5	240	48	3.023	Q3
Alcohol	United States	5	220	44	2.528	Q3
Cerebral Cortex	United States	5	218	43.6	6.149	Q1
Brain Behavior and Immunity	United States	5	215	43	6.616	Q1
Psychological Medicine	United States	5	196	39.2	6.313	Q1
Brain Research	Netherlands	5	151	30.2	2.937	Q2
Current Pharmaceutical Design	United Arab Emirates	5	144	28.8	2.832	Q3
Hormones and Behavior	United States	5	68	13.6	4.041	Q1
International Journal of Environmental Research and Public Health	Switzerland	5	55	11	2.948	Q1
Journal of Substance Abuse Treatment	United States	5	52	10.4	2.753	Q2
Actas Españolas de Psiquiatría	Spain	5	40	8	1.318	Q3
International Journal of Drug Policy	Netherlands	5	40	8	4.45	Q3
Trastornos Adictivos**	Spain	5	-	-	n/a	n/a

Note. *In these journals the number of citations per article was calculated from the number of articles included in the Main Collection of WoS. *Adicciones* (n=23); *Pharmacology Biochemistry and Behavior* (n=9); *Schizophrenia Research* (n=9).
***Trastornos Adictivos* was not included in the Main Collection of Web of Science nor in *Journal Citation Reports*.

Table 4
Beneficiary institutions of the Spanish National Plan on Drugs and number of derived articles (alphabetical order)

Beneficiary institution	Nº of grants	Nº of derived articles	Total cost	Derived articles per grant	Cost per article	Citations	Citations/ article	Citations/ grant
Agència de Salud Pública de Barcelona	5	16	€304,787	3	€19,049.19	390	24	78
Agencia Laín Entralgo	1	0	€57,000	0	No publication	0	0	0
Asociación Colaboración Cochrane Iberoamericana	1	0	€20,000	0	No publication	0	0	0
Consejo Superior de Investigaciones Científicas	15	57	€1,328,112.53	4	€23,300.22	2,591	45	173
Escuela Andaluza de Salud Pública	1	0	€80,000	0	No publication	0	0	0
Fundació Clínic per a la Recerca Biomèdica	3	7	€196,047	2	€28,006.71	69	10	23
Fundació Institut de Recerca de l'Hospital Universitari Vall d'Hebron	4	31	€270,055	8	€8,711.45	704	23	176
Fundació Institut d'Investigació en Ciencias de la Salut Germans Trias I Pujol	4	23	€287,643	6	€12,506.22	54	2	14
Fundació Privada Institut de Recerca Biomèdica	1	10	€99,000	10	€9,900	297	30	297
Fundación Andaluza para la Atención a las Drogodependencias	2	5	€124,770	3	€24,954	140	28	70
Fundación Biomédica Galicia Sur	1	0	€33,925	0	No publication	0	0	0
Fundación Canaria de Investigación Sanitaria (FUNCANIS)	1	0	€12,698	0	No publication	0	0	0
Fundación de la Comunidad Valenciana Centro de Investigación Príncipe Felipe	3	32	€252,250	11	€7,882.81	2,182	68	727
Fundación Hospital Alcorcón	2	0	€31,400	0	No publication		0	0
Fundación Hospital Carlos Haya	2	2	€88,815.74	1	€44,407.87	173	87	87
Fundación IDICHUS	1	2	€83,037	2	€41,518.50	10	5	10
Fundación IMABIS	4	36	€335,000	9	€9,305.56	820	23	205
Fundación Instituto Mar de Investigaciones Médicas (IMIM)	18	51	€1,650,740.90	3	€32,367.47	1,256	25	70
Fundación Miguel Servet	1	14	€23,000	14	€1,642.86	262	19	262
Fundación para la Formación e Investigación Sanitaria de la Región de Murcia	1	1	€110,920	1	€110,920	0	0	0
Fundación para la Investigación Biomédica del Hospital Universitario 12 de Octubre	5	1	€261,197.46	0	€261,197.46	0	0	0
Fundación para la Investigación Biosanitaria de Andalucía Oriental Alejando Otero (FIBAO)	1	2	€8,000	2	€4,000	50	25	50
Fundación para la Investigación Sanitaria en Castilla la Mancha	2	1	€28,525	1	€28,525	129	129	65
Fundación Parc Científic de Barcelona	1	0	€70,100	0	No publication	0	0	0
Fundación Progreso y Salud	1	2	€53,650	2	€26,825	17	9	17
Fundación Pública Andaluza para la Investigación de Málaga en Biomedicina y Salud (FIMABIS)	2	33	€192,573	17	€5,835.55	190	6	95
Fundación Pública Marqués de Valdecilla	1	27	€61,000	27	€2,259.26	680	25	680
Fundación Universitaria San Pablo CEU	6	11	€359,481	2	€32,680.09	54	5	9
Fundación Valenciana de Investigaciones Biomédica	2	1	€90,752.83	1	€90,752.83	0	0	0
Fundación Vasca de Innovación e Investigación Sanitaria	2	13	€210,695	7	€16,207.31	191	15	96
Hospital General Gregorio Marañón	2	6	€176,000	3	€29,333.33	158	26	79
Hospital Universitario de Canarias	1	0	€13,611	0	No publication		0	0
Hospital Universitario de Salamanca	1	3	€48,450	3	€16,150	38	13	38
Hospital Universitario Ramón y Cajal	1	3	€14,350	3	€4,783.33	51	17	51
Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau	10	10	€301,849.35	1	€30,184.94	117	12	12

Table 4

Beneficiary institutions of the Spanish National Plan on Drugs and number of derived articles (alphabetical order)(cont.)

Beneficiary institution	Nº of grants	Nº of derived articles	Total cost	Derived articles per grant	Cost per article	Citations	Citations/ article	Citations/ grant
Institut d'Investigacions Biomèdiques August Pi i Sunyer	1	6	€82,980	6	€13,830	63	11	63
Instituto de Investigación Sanitaria Fundación Jiménez Díaz	1	18	€70,773	18	€3,931.83	54	3	54
Instituto de Salud Carlos III	2	8	€114,314	4	€14,289.25	237	30	119
Universidad Autónoma de Madrid	2	22	€335,284	11	€15,240.18	195	9	98
Universidad Castilla la Mancha	1	4	€91,300	4	€22,825	87	22	87
Universidad Complutense de Madrid	21	79	€1,774,464.05	4	€22,461.57	2,104	27	100
Universidad de A Coruña	1	0	€27,805	0	No publication	0	0	0
Universidad de Alcalá	2	4	€74,882	2	€18,720.50	14	4	7
Universidad de Almería	1	2	€37,000	2	€18,500	9	5	9
Universidad de Cantabria	2	3	€131,775	2	€43,925	133	44	67
Universidad de Deusto	1	0	€57,000	0	No publication	0	0	0
Universidad de Granada	6	30	€240,636.30	5	€8,021.21	888	30	148
Universidad de Huelva	1	3	€22,769	3	€7,589.67	2	1	2
Universidad de la Rioja	1	0	€73,916	0	No publication	0	0	0
Universidad de León	3	4	€143,886.22	1	€35,971.55	5	1	2
Universidad de Lleida	1	0	€31,853.64	0	No publication	0	0	0
Universidad de Málaga	2	0	€71,949	0	No publication	0	0	0
Universidad de Murcia	3	10	€116,234.17	3	€11,623.42	71	7	24
Universidad de Navarra	3	18	€208,683	6	€11,593.50	401	22	134
Universidad de Oviedo	6	37	€287,914	6	€7,781.46	441	12	74
Universidad de Salamanca	6	9	€191,330.97	2	€21,259	126	14	21
Universidad de Santiago de Compostela	13	51	€904,235.99	4	€17,730.12	850	17	65
Universidad de Sevilla	4	16	€221,422	4	€13,838.88	485	30	121
Universidad de Valladolid	1	1	€26,444.53	1	€26,444.53	0	0	0
Universidad del País Vasco	3	13	€97,871.35	4	€7,528.57	225	17	75
Universidad Miguel Hernández	6	28	€321,616.52	5	€11,486.30	742	27	124
Universidad Nacional de Educación A Distancia	5	24	€398,380.31	5	€16,599.18	389	16	78
Universidad Rey Juan Carlos	1	0	€24,500	0	No publication	0	0	0
Universitat Autònoma de Barcelona	3	29	€301,892.38	10	€10,410.08	552	19	184
Universitat de Barcelona	10	50	€639,986	5	€12,799.72	915	18	92
Universitat de les Illes Balears	5	19	€256,437	4	€13,496.68	238	13	48
Universitat de València	12	60	€554,979.27	5	€9,249.65	707	12	59
Universitat Jaume I	7	39	€287,823.52	6	€7,380.09	787	20	112
Universitat Pompeu Fabra	7	63	€549,636.85	9	€8,724.39	1,171	19	167
Total	253	1,050	€16,051,410.87	4	€15,287.06	22,514		

Note. NG: Number of Grants; NS: Number of studies; SG: Number of studies published per grant; €/S: amount in euros per published study. The same study can be financed by two grants.

Discussion

This study has made it possible to ascertain and investigate relevant aspects related to research funding on addictive disorders in Spain by the Spanish National Plan on Drugs and its academic profitability in terms of scientific publications and their impact. On average, the PNSD awarded 15 grants per year for research projects, to an annual value of close to one million euros. Almost three quarters of the grants had derived publications, the vast majority of them in foreign magazines. *Adicciones* was the Spanish journal in which the largest number of articles were published. A high degree of international collaboration was identified and most of the derived articles were from the basic research field.

Public funding for research on addictive disorders competes with other government funding priorities aiming to improve the health of the population. In Spain, funding for research projects in this area comes from the European Union, the Spanish Government, the Spanish Autonomous Communities, the pharmaceutical industry, foundations and non-governmental organizations, as in other areas of health sciences and social sciences and within the framework of what has come to be known as a multilevel R&D&I model (Fernández-Formoso, Pérez-Ortega, Sanz-Martiul and Blázquez-Herranz, 2010). However, in the area of addictive disorders, the Spanish Government is the main source of funding through the PNSD rounds since 2000 of the Acción Estratégica en Salud del Instituto de Salud Carlos III (s.f.) and the Plan Estatal de Investigación Científica y Técnica y de Innovación (Ministerio de Ciencia e Innovación, s.f.a, s.f.b), previously known as the Plan Nacional I+D+I (R&D&I).

The analysis of publications derived from funded projects has been the object of study in some biomedical areas (Lewison & Dawson, 1998; Sun, Steinberg & Jagsi, 2013) as, for example, in nutrition (Thomson, 2007), genomics (Schiermeier, 1999), rehabilitation (DeLisa & Rosenthal, 2005; Zwingmann, Buschmann-Steinhage, Gerwinn & Klosterhuis, 2004), stem cell research (Campbell, 2005) and cardiology (Aleixandre et al., 2011; Rodríguez-Padial et al., 2019). However, we have not found studies analyzing the performance of publications funded by investment from official bodies or scientific associations and foundations in the area of addictive disorders. Most of the studies on funding refer to the subsidising of treatments (Chalmers, Ritter, Berends & Lancaster, 2016; Mark, Levit, Vandivort-Warren, Coffey & Buck, 2007; Stewart & Horgan, 2011) and harm reduction (Atun & Kazatchkine, 2010; Bridge et al., 2016; Kulesza, Teachman, Werntz, Gasser & Lindgren, 2015; World Health Organization, 2012).

With regard to the grants awarded by the PNSD, our analysis has shown that the funded projects are fundamentally in the area of basic sciences, an area in which a greater number of projects are presented and on which greater funding is conferred, while the number of projects in the social sciences is lower and they are also awarded less.

Figure 3
Collaborating network of countries of derived article authors

A study on the funding practices of the Research Council of Norway's Programs for Mental Health found that the projects it funded were mainly focused on biological, genetic and neurological areas, while those dedicated to community health and living conditions were less frequent (Andersen, Borg, Karlsson & Larsen, 2016).

As Becoña (2016) has stated, funding by the National Institute on Drug Abuse in the United States and Spanish institutions has, for a variety of reasons, probably focused on brain disease and the biologistic perspective, with more research required in the area of prevention and other models of action. It is possible that the methodological standardization used in the basic sciences results in greater approval and funding when projects are assessed. It would therefore be advisable to establish correction factors in the calls for projects to make more room for those from other areas of knowledge that also have more difficulties in other national funding rounds. Moreover, it should be noted that despite recognizing the importance of PNSD funding, the percentage of gross domestic product (GDP) dedicated to research in Spain (1.21% of GDP) is far behind the investment levels in large European countries such as France, which allocates 2.19%, or Germany (3.04%), and even China (2.13%) and the United States (2.80%) (World Bank, 2019).

Previous studies analyzing publications derived from research projects in other areas have shown mixed results. Thus, in two studies on the performance of cardiology projects funded by the Spanish Society of Cardiology in two different time periods, derived publication were found in 59.4% of the projects in one case (Aleixandre et al., 2011) and 37% in the other (Rodríguez-Padial et al., 2019). In our study, 71.9% of the grants had derived publications, a percentage that is quite close to the first of the above. However, it is likely that there are methodological differences that may explain the differences, based on whether only those derived articles acknowledging the funding in the manuscript are counted or whether all papers are counted, both with or without explicit recognition of funding. Nevertheless, the fact that the percentage of derived publications obtained in our study is higher than in an area as consolidated as cardiology shows the importance of the research on addictive disorders. The number of derived publications is higher in the area of basic research, an area that receives the most funding per project.

The largest number of funded projects is on alcohol, drugs in general, and cocaine. This is linked to the fact that alcohol is the most widely used drug, both in the general population and in adolescents, and because social science research usually focuses on all drugs, as for example in studies on neurobiological substrates and on prevention. The significant number of projects on cocaine is related to the high number of articles published by Spanish researchers on this drug (Khalili et al., 2018). Currently, with the increase in cannabis use, the appearance of synthetic cannabinoids and the opening of the international debate on the medical or recreational use of cannabis and the consequences of its legalization (Cerdá et al., 2020; Matielo, et al., 2018; Smart & Pacula, 2019), it would be advisable to promote research on this drug, especially taking into account the 58% decrease in funded projects related to cannabis when comparing the first half of the period studied (23 projects) to the second half (11 projects).

As has been seen, the grants were distributed among research groups from a wide variety of beneficiary institutions, including universities, hospitals, research institutes, and public and private foundations throughout the country. The profitability in terms of derived publications from these institutions has been inconsistent, and it should be taken into account that other variables that could relativize this profitability, such as the size of the research teams or researchers requesting help through various institutions to which they may be attached, have not been considered.

The fact that 92% of the derived publications were published in foreign journals is a sign of the internationalization of Spanish research on addictive disorders and also confers high visibility. Furthermore, as a sign of their quality, almost 80% of the most productive journals have impact factors that place them in the first or second quartile in their corresponding subject areas of the *Journal Citation Reports*. It is important to highlight that the internationalization of research is inextricably linked to factors such as the allocation of financial investment and human resources to research (González, Valderrama & Aleixandre, 2012; Moya Anegón et al., 2008; Peters, 2006). The subject areas of the journals in which most papers were published are substance abuse disorders, neurosciences and neurology, psychiatry and pharmacology, areas in which numerous articles on addictive disorders and their treatment are normally published (Tran et al., 2019). However, there is a shortage of publications in journals in the areas of general medicine, public health and education; these are fundamental areas in the approach to addictive disorders. The fact that papers published in the journal *Drug and Alcohol Dependence* received the greatest number of citations had already been observed in an earlier study on the scientific map of addiction treatment (Blobaum, 2013).

The average number of authors per study of 6.5 is higher than that revealed as part of the study on 50 years of Spanish research on addictive disorders funded by the National Plan on Drugs (Aleixandre-Benavent et al., 2020d) and was also higher than that found in another study on eating disorders, where the average was 4.39 authors per study (Valderrama-Zurián et al., 2017). Publications derived from research projects in health sciences have a greater average number of authors per paper than those from basic science or social science projects.

The study of collaboration in the derived publications shows that 82.8% of the papers were carried out in national or international collaboration and that this collaboration was reflected in a greater number of authors per study. Collaboration in the derived publications involved 87 countries, principally the United States. These data show that Spanish research on drug addiction is carried out with researchers from all continents and that the possibility of financing training in the United States is endorsed by the National Institute on Drugs of Abuse (NIDA) has had an important impact. The potential influence of the creation in 2002 of the Red de Trastornos Adictivos (RTA, Addictive Disorders Network) as part of the Ministry of Health initiative to promote research networks should also be highlighted (Rodríguez de Fonseca et al., 2006). Both the high degree of collaboration between authors and the high percentage of studies carried out in international collaboration in the derived articles are consistent with previous results showing that articles funded in the area of addictive disorders present a higher author per paper average, a greater degree of international collaboration and a greater number of citations per article (Valderrama-Zurián, Castelló-Cogollos, Melero-Fuentes, Aleixandre-Benavent & Bueno-Cañigral, 2019).

Limitations

This study has some limitations that should be taken into account. First, it is possible that some research may have been overlooked if the grant's principal investigators did not report publication, or if they were published in journals not indexed in the WoS Main Collection or Scopus. However, the databases consulted in this study are today considered the gold standard, enjoying significant international prestige and being the most used in bibliometric studies, especially those analyzing citation and scientific impact indicators (Moed, 2009). Secondly, it is possible that some authors have followed a strategy of fragmented publication to make their projects more academically profitable, a practice that would only be possible to identify through a careful review of potentially fragmented publications, which is an aspect beyond the scope of our study. There may also be an excess or default "funding bias". The excess bias is when some authors include acknowledgement in their study of a funded project, regardless of whether the study is actually associated with that project, with the aim of increasing the productivity of the projects in reports, or even continue acknowledging it many years after funding with no apparent connection. Conversely, the default "funding bias" happens when the authors omit acknowledgment in a funded paper. Third, it is possible that by not knowing who the PI was of the projects funded during the period 2000-2003, there was an under-representation of the publications derived from these projects. Finally, it is clear that the projects awarded in recent years had less time to publish their results, which may have produced a lower percentage of derived publications and citations.

Despite these limitations, the results of our analysis provide information of interest to ascertain the current state of research in addictive disorders, the aspects that may deserve greater attention and those with the greatest issues. The information obtained may be useful for making strategic decisions aimed at correcting the weaknesses detected or continuing to finance the most relevant aspects identified.

Conclusions

The results of this study have revealed the return on financial investment in PNSD research projects in terms of scientific publications and can help determine future funding priorities. The publication rate, and the fact that most of the studies were published in journals found in the top quartiles of the JCR, widely read and of great international impact, show that Spanish research teams carry out rigorous and high quality research, usually collaborating in national and international networks and generally optimizing the resources they obtain. Furthermore, this return provides a strong incentive for the PNSD to continue and to ensure that funding for research on addictive disorders is maintained or increased.

Future studies could follow the development of grants by the PNSD and other public or private sources and their academic performance in terms of publications, as well as their impact on society through knowledge transfer.

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Delegación de Gobierno para el Plan Nacional sobre Drogas (2016 round. Proyecto 2016/028). Ministerio de Sanidad Consumo y Bienestar Social.

Servicio de Drogodependencias (PMD/UPCCA-València). Concejalía de Sanidad y Consumo. Ajuntament de València.

References

Aleixandre Benavent, R. (1999). Investigación española en drogodependencias. ¿Hacia dónde vamos? *Trastornos Adictivos, 1*, 227-233.

Aleixandre-Benavent, R., Agulló-Calatayud, V., Alonso-Arroyo, A., Castelló-Cogollos, L., Lucas-Domínguez, R., Melero-Fuentes, D.,… Valderrama-Zurián, J. C. (2020a). Financed projects from Government Delegation grants for the National Plan on Drugs (Spain), 2000-2016. doi:10.5281/zenodo.3778579.

Aleixandre-Benavent, R., Agulló-Calatayud, V., Alonso-Arroyo, A., Castelló-Cogollos, L., Lucas-Domínguez,

R., Melero-Fuentes, D.,… Valderrama-Zurián, J. C. (2020b). Financed researchs from Government Delegation grants for the National Plan on Drugs (Spain), 2001-2019. doi:10.5281/zenodo.3778642.

Aleixandre-Benavent, R., Agulló-Calatayud, V., Alonso-Arroyo, A., Castelló-Cogollos, L., Lucas-Domínguez, R., Melero-Fuentes, D.,… Valderrama-Zurián, J. C. (2020c). Tables and figures of the supplementary material from research: Financed researchs from Government Delegation grants for the National Plan on Drugs: Research assessment and scientific impact. doi: 10.5281/zenodo.4030455.

Aleixandre-Benavent, R., Agulló-Calatayud, V., Alonso-Arroyo, A., Castelló-Cogollos, L., Lucas-Domínguez, R., Melero-Fuentes, D.,… Valderrama-Zurián, J. C. (2020d). La evolución de la investigación española en drogodependencias presente en publicaciones científicas. http://pnsd.uisys.es.

Aleixandre Benavent, R., Alonso Arroyo, A., Anguita Sánchez, M., Bolaños Pizarro, M., Heras, M., González Alcalde, G.,… Morell Cabedo, S. (2011). Evolución y repercusión científica de las becas de investigación de la Sociedad Española de Cardiología y la Fundación Española del Corazón (2000-2006). *Revista Española de Cardiología, 64*, 904-915. doi:10.1016/j.recesp.2011.03.024.

Álvarez, F. J. & del Río, M. C. (2003). Current initiatives in drug abuse research in Spain. *Addiction, 98*, 861. doi:10.1046/j.1360-0443.2003.04511.x.

Andersen, A. J. W., Borg, M., Karlsson, B. E. & Larsen, I. B. (2016). More of the same? A study of the funding practices of The Research Council of Norway's Programs for Mental Health in the period 1995 to 2015. *Scandinavian Psychologist, 3*. doi:10.15714/scandpsychol.3.e13.

Atun, R. & Kazatchkine, M. (2010). The Global Fund's leadership on harm reduction: 2002–2009. *International Journal of Drug Policy, 21*, 103-106. doi:10.1016/j.drugpo.2010.01.002.

Ballesteros, J., Torrens, M. & Valderrama Zurián, J.C. (coords.) (2006). Manual introductorio a la investigación en drogodependencias. Valencia: Sociedad Española de Toxicomanías.

Banco Mundial (2019). Gasto en investigación y desarrollo (% del PIB). https://datos.bancomundial.org/indicador/GB.XPD.RSDV.GD.ZS.

Bar-Ilan, J., Levene, M. & Lin, A. (2007). Some measures for comparing citation databases. *Journal of Informetrics, 1*, 26-34. doi:10.1016/j.joi.2006.08.001.

Becoña, E. (2016). Adicción: No sólo un mal funcionamiento cerebral. Papeles del Psicólogo, 37, 118-125.

Blobaum, P. M. (2013). Mapping the literature of addictions treatment. *Journal of the Medical Library Association, 101*, 101-109. doi:10.3163/1536-5050.101.2.005.

Bornmann, L. & Leydesdorff, L. (2014). Scientometrics in a changing research landscape. *EMBO Reports, 15*, 1228-1232. doi:10.15252/embr.201439608.

Bridge, J., Hunter, B. M., Albers, E., Cook, C., Guarinieri, M., Lazarus, J. V.,… Wolfe, D. (2016). The Global Fund to Fight AIDS, Tuberculosis and Malaria's investments in harm reduction through the rounds-based funding model (2002–2014). *International Journal of Drug Policy, 27*, 132-137. doi:10.1016/j.drugpo.2015.08.001.

Byrne, F. & Chapman S. (2005). The most cited authors and papers in tobacco control. *Tobacco Control, 14*, 155-160. doi:10.1136/tc.2005.011973.

Campbell, A. (2005). Ethos and economics: Examining the rationale underlying stem cell and cloning research policies in the United States, Germany, and Japan. *American Journal of Law & Medicine, 31*, 47-86. doi:10.1177/009885880503100102.

Cerdá, M., Mauro, C., Hamilton, A., Levy, N. S., Santaella-Tenorio, J., Hasin, D., … Martins, S. S. (2020). Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry, 77*, 165. doi:10.1001/jamapsychiatry.2019.3254.

Chalmers, J., Ritter, A., Berends, L. & Lancaster, K. (2015). Following the money: Mapping the sources and funding flows of alcohol and other drug treatment in Australia. *Drug and Alcohol Review, 35*, 255-262. doi:10.1111/dar.12337.

DeLisa, J. A. & Rosenthal, M. (2005). Funding for rehabilitation medicine. *American Journal of Physical Medicine & Rehabilitation, 84*, 991-998. doi:10.1097/01.phm.0000187849.87038.33.

Fernández-Formoso, J. A., Pérez-Ortega, J. M., Sanz-Martiul, E. & Blázquez-Herranz, M. (2010). Para que nada ni nadie se quede sin investigar: la Acción Estratégica en Salud (AES) en el contexto del fomento y promoción de la I+D+i biosanitarias. *Emergencias, 22*, 460-469.

González Alcaide, G., Valderrama Zurián J. C. & Aleixandre Benavent, R. (2012). Análisis del proceso de internacionalización de la investigación científica española. *Revista Española de Documentación Científica, 35*, 94-118.

González-Alcaide, G., Calafat, A., Becoña, E., Thijs, B. & Glänzel, W. (2016). Co-citation analysis of articles published in substance abuse journals: Intellectual structure and research fields (2001–2012). *Journal of Studies on Alcohol and Drugs, 77*, 710-722. doi:10.15288/jsad.2016.77.710.

Instituto de Salud Carlos III (s.f.). Acción Estratégica en Salud. https://www.isciii.es/QueHacemos/Financiacion/Paginas/Accion-Estrategica-en-Salud.aspx.

Khalili, M., Rahimi-Movaghar, A., Shadloo, B., Mojtabai, R., Mann, K. & Amin-Esmaeili, M. (2018). Global scientific production on illicit drug addiction: A two-decade analysis. *European Addiction Research, 24*, 60-70. doi:10.1159/000487590.

Kingwell B.A., Anderson G.P., Morris, M.E. Duckett S.J., Hoole, E.A., Rothwell-Short, J. & Wilson,

A.J. (2006). Evaluation of NHMRC funded research completed in 1992, 1997 and 2003: gains in knowledge, health and wealth. *Medical Journal of Australia, 184*, 282-286. doi:10.5694/j.1326-5377.2006.tb00238.x.

Kulesza, M., Teachman, B. A., Werntz, A. J., Gasser, M. L. & Lindgren, K. P. (2015). Correlates of public support toward federal funding for harm reduction strategies. *Substance Abuse Treatment, Prevention, and Policy, 10*. doi:10.1186/s13011-015-0022-5.

Lewison, G. & Dawson, G. (1998). The effect of funding on the outputs of biomedical research. *Scientometrics, 41*, 17-27. doi:10.1007/bf02457963.

Ley 17/2003, de 29 de mayo, por la que se regula el Fondo de bienes decomisados por tráfico ilícito de drogas y otros delitos relacionados, Boletín Oficial del Estado núm. 129 (2003). https://www.boe.es/buscar/act.php?id=BOE-A-2003-10828.

Mahabee-Gittens, E. M., Gordon, J. S., Melink, K. F. & Merianos, A. L. (2017). Top 100 cited articles in recent tobacco research. *Journal of Behavioral Health, 6*, 16-25.

Mark, T. L., Levit, K. R., Vandivort-Warren, R., Coffey, R. M. & Buck, J. A. (2007). Trends in spending for substance abuse treatment, 1986–2003. *Health Affairs, 26*, 1118-1128. doi:10.1377/hlthaff.26.4.1118.

Marx, W., Schier, H. & Wanitschek, M. (2001). Citation analysis using online databases: Feasibilities and shortcomings. *Scientometrics, 52*, 59-82. doi:10.1023/a:1012798911792.

Matielo, C., Sarzi, D., Justolin, B., Lemos, R., Camargo, F. & Stefenon, V. (2018). A bibliometric analysis of cannabis publications: Six decades of research and a gap on studies with the plant. *Publications, 6*, 40. doi:10.3390/publications6040040.

Ministerio de Ciencia e Innovación (s.f.a). Plan Estatal de Investigación Científica y Técnica y de Innovación 2017-2020. http://www.ciencia.gob.es/portal/site/MICINN/menuitem.7eeac5cd345b4f34f09dfd1001432ea0/?vgnextoid=83b192b9036c2210VgnVCM1000001d04140aRCRD.

Ministerio de Ciencia e Innovación (s.f.b). Planes Nacionales I+D+i Anteriores. http://www.ciencia.gob.es/portal/site/MICINN/menuitem.29451c2ac1391f1febebed1001432ea0/?vgnextoid=79dbec05f2a7d210VgnVCM1000001d04140aRCRD.

Ministerio de Sanidad, Servicios Sociales e Igualdad (2019). Ayudas para la realización de programas supracomunitarios sobre adicciones en el año 2019. https://www.ayudas-subvenciones.es/subvencion/17851/ayudas-para-la-realizacion-de-programas-supracomunitarios-sobre-adicciones-en-el-ano-2019.

Moed, H. F. (2009). New developments in the use of citation analysis in research evaluation. *Archivum Immunologiae et Therapiae Experimentalis, 57*, 13-18. doi:10.1007/s00005-009-0001-5.

Moya Anegón, F. de, Chinchilla Rodríguez, Z., Benavent Pérez, M., Corera-Álvarez, E., González Molina, A. & Vargas Quesada, B. (2008). Indicadores bibliométricos de la actividad científica española 2008. Madrid: Fundación Española para la Ciencia y la Tecnología (FECYT).

Peters, M. A. (2006). The rise of global Science and the emerging political economy of international research collaborations. *European Journal of Education, 41*, 225-244.

Plan Nacional sobre Drogas (s.f.a). Convocatoria de ayudas para el desarrollo de proyectos de investigación sobre adicciones. http://www.pnsd.mscbs.gob.es/delegacionGobiernoPNSD/convocatoriaSubvenciones/ongs/proyecInvestig.htm.

Plan Nacional sobre Drogas (s.f.b). Programas de Corporaciones Locales. http://www.pnsd.mscbs.gob.es/delegacionGobiernoPNSD/convocatoriaSubvenciones/ongs/programasCorpora.htm.

Real Decreto 1677/1985, de 11 de septiembre, de Coordinación Interministerial para la ejecución del Plan Nacional sobre Drogas, Boletín Oficial del Estado núm. 226. (1985). https://www.boe.es/buscar/doc.php?id=-BOE-A-1985-19702.

Rodríguez de Fonseca, F., Aleixandre, R., Camí, J., Navarro, M., Torrens, M., Iraurgi, J.,… Molina, M. (2006). La investigación en drogodependencias. *Trastornos Adictivos, 8*, 115-132.

Rodríguez-Padial, L., Fernández Lozano, I., Hidalgo Urbano, R., Silva Melchor, L., Evangelista Massip, A., Anguita Sánchez, M. & Íñiguez Romo, A. (2019). Evolución e impacto bibliométrico de las becas de la Sociedad Española de Cardiología/Fundación Española del Corazón en el periodo 2007-2012. *Revista Española de Cardiología, 72*, 1012–1019. doi:10.1016/j.recesp.2018.08.013.

Schiermeier, Q. (1999). Berlin places genomics among top funding priorities. Nature, 402, 568-568. doi:10.1038/45036.

Smart, R. & Pacula, R. L. (2019). Early evidence of the impact of cannabis legalization on cannabis use, cannabis use disorder, and the use of other substances: Findings from state policy evaluations. *The American Journal of Drug and Alcohol Abuse, 45*, 644-663. doi:10.1080/00952990.2019.1669626.

Stewart, M. T. & Horgan, C. M. (2011). Health services and financing of treatment. *Alcohol Research & Health, 33*, 389-394.

Sun, G. H., Steinberg, J. D. & Jagsi, R. (2013). Funding for Biomedical Research. *JAMA, 309*, 1228-1229.

Tanner-Smith, E. E. & Polanin, J. R. (2016). Brief alcohol intervention trials conducted by higher prestige authors and published in higher impact factor journals are cited more frequently. *Journal of Clinical Epidemiology, 75*, 119-125. doi:10.1016/j.jclinepi.2016.01.028.

Thomson, C. A. (2007). Funding Nutrition Research: Where's the Money? *Nutrition in Clinical Practice, 22*, 609-617. doi:10.1177/0115426507022006609.

Tran, B. X., Hoang, C. L., Tam, W., Phan, H. T., Vu, G. T., Latkin, C.,… Ho, R. C. M. (2019). A global bibliometric analysis of antiretroviral treatment adherence: implications for interventions and research development (GAPRESEARCH). *AIDS Care, 32*, 637-644. doi:10.1080/09540121.2019.1679708.

Valderrama-Zurián, J. C., Castelló-Cogollos, L., Melero-Fuentes, D., Aleixandre-Benavent, R. & Bueno-Cañigral, F. J. (2019). Bibliometric differences between funding and non-funding papers on substance abuse scientific research. In: G. Catalano, C. Daraio, M. Gregori, H. F. Moed & G. Ruocco (Eds.), 17th International Conference on Scientometrics and Informetrics (pp. 2622-2623). Roma: Edizioni Efesto.

Valderrama-Zurián, J.-C., Aguilar-Moya, R., Cepeda-Benito, A., Melero-Fuentes, D., Navarro-Moreno, M.-Á., Gandía-Balaguer, A. & Aleixandre-Benavent, R. (2017). Productivity trends and collaboration patterns: A diachronic study in the eating disorders field. *PLoS One, 12*, e0182760. doi:10.1371/journal.pone.0182760.

van Wesel, M. (2015). Evaluation by Citation: Trends in Publication Behavior, Evaluation Criteria, and the Strive for High Impact Publications. *Science and Engineering Ethics, 22*, 199-225. doi:10.1007/s11948-015-9638-0.

Waltman, L. (2016). A review of the literature on citation impact indicators. *Journal of Informetrics, 10*, 365-391. doi:10.1016/j.joi.2016.02.007.

World Health Organization (2012). WHO, UNODC, UNAIDS technical guide for countries to set targets for universal access to HIV prevention, treatment and care for injecting drug users - 2012 revision. https://apps.who.int/iris/bitstream/handle/10665/77969/9789241504379_eng.pdf;jsessionid=707AED61E667AFF1BCE59B4E5F2CDD13?sequence=1.

Zwingmann, C., Buschmann-Steinhage, R., Gerwinn, H. & Klosterhuis, H. (2004). Förderschwerpunkt "Rehabilitationswissenschaften": Ergebnisse - Umsetzung - Erfolge und Perspektiven. *Die Rehabilitation, 43*, 260-270. doi:10.1055/s-2004-828393.

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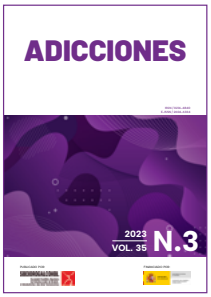

ORIGINAL

Methodology used to estimate alcohol-attributable mortality in Spain, 2001-2017

Metodología utilizada para estimar la mortalidad atribuible a alcohol en España, 2001-2017

Marta Donat*,**; Luis Sordo**,***; Juan Miguel Guerras**,****; Julieta Politi****; José Pulido**,***; Gregorio Barrio *,**.

* Escuela Nacional de Sanidad. Instituto de Salud Carlos III, Madrid.
** Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBERESP).
*** Departamento de Salud Pública y Materno-infantil, Facultad de Medicina, Universidad Complutense de Madrid.
**** Centro Nacional de Epidemiología. Instituto de Salud Carlos III, Madrid.

Abstract

The objective is to describe and discuss methods and assumptions to estimate the mortality attributable to alcohol in Spain in 2001-2017. The annual mean number of deaths attributable to alcohol (DAAs) was estimated based on 19 groups of alcohol-related causes of death (18 partially attributable and one directly attributable), and 20 alcohol population-attributable fractions (PAFs), resulting from combining sex, 5 age groups, and the periods 2001-2009 and 2010-2017, for each cause group. Deaths from causes were obtained from the Spanish National Institute of Statistics. For partially attributable causes, Spain-specific PAFs were calculated using the Levin formula with alcohol exposure data from health surveys and sales statistics, and relative risks from international meta-analyses. Annual prevalences of ex-drinkers and seven levels of daily alcohol consumption were considered. The underestimation of self-reported daily average consumption with respect to the sales statistics was corrected by multiplying by a factor of 1.58-3.18, depending on the calendar year. DAA rates standardized by age and standardized proportions of general mortality attributable to alcohol, according to sex, age group, calendar period, type of drinker and autonomous community were calculated. Sensitivity analyses were performed to assess how the DAA estimates changed when changing some methodological options, such as the ex-drinker criterion or the introduction of a latency period.

Keywords: alcohol, attributable mortality, Spain, methodology

Resumen

El objetivo es describir y discutir los métodos y asunciones para estimar la mortalidad atribuible a alcohol en España en 2001-2017. Se estimó el nº medio anual de muertes atribuibles a alcohol (MAAs) basándose en 19 grupos de causas de muerte relacionadas con alcohol (18 parcialmente atribuibles y uno directamente atribuible), y 20 fracciones atribuibles poblacionales al alcohol (FAPs) para cada grupo de causas, resultantes de combinar sexo, 5 grupos de edad, y los períodos 2001-2009 y 2010-2017. Las muertes por causa se obtuvieron del Instituto Nacional de Estadística. Para las causas parcialmente atribuibles se calcularon FAPs específicas para España, usando la fórmula de Levin con datos de exposición al alcohol procedentes de encuestas de salud y estadísticas de ventas, y riesgos relativos procedentes de metanálisis internacionales. Se consideraron las prevalencias anuales de exbebedores y de siete niveles de consumo diario de alcohol. Se corrigió la subestimación del consumo medio diario autoinformado con respecto a las estadísticas de venta, multiplicando por un factor de 1,58-3,18, dependiendo del año-calendario. Se calcularon tasas de MAA y porcentajes de la mortalidad general atribuibles a alcohol estandarizados por edad, según sexo, grupo de edad, periodo-calendario, tipo de bebedor y comunidad autónoma. Se realizaron análisis de sensibilidad observando cómo cambiaban las estimaciones de MAA al hacerlo algunas opciones metodológicas, como el criterio de exbebedor o la introducción de un período de latencia.

Palabras clave: alcohol, mortalidad atribuible, España, metodología

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■ **Send correspondence to:**
Luis Sordo. Departamento de Salud Pública y Materno-Infantil. Facultad de Medicina. Universidad Complutense de Madrid.
Email: lsordo@ucm.es

Alcohol use is one of the main preventable risk factors for morbidity, mortality and disability in many countries (Global Burden of Disease [GBD], 2018a; Institute for Health Metrics and Evaluation [IHME], 2020). People who drink alcohol, especially high-risk drinkers or people with alcohol use disorder, have a much higher mortality risk than the general population (Roerecke & Rehm, 2013). However, alcohol use begins to raise the risk of death long before levels of consumption considered to be high risk are actually reached, or before an alcohol use disorder develops (Stockwell et al., 2016).

In estimating deaths attributable to alcohol (DAA), essential synthetic indicators are used to compare the impact of alcohol consumption across regions, periods and subgroups, to determine the need for public health interventions, to assess them and allocate resources (World Health Organization [WHO], 2009). The World Health Organization defines DAA as the algebraic sum of deaths caused and preceded by alcohol use that would not have occurred in a counterfactual scenario without historical consumption of this substance. In theory, they should be estimated by comparing the actual risk of death with the hypothetical risk in a counterfactual scenario without historical alcohol consumption (WHO, 2018a).

However, such estimates require information from multiple sources, which often have considerable gaps, so that different authors tend to make methodological choices and assumptions which do not always match, and/or turn to data that are not always possible to extrapolate from alcohol use in other times or regions. Among other aspects, methodological choices may be made based on the inclusion of alcohol-related causes of death, studies or meta-analyses providing risk functions relating the amount of alcohol consumed to mortality from each cause, whether or not risk of DAA is considered in ex-drinkers or that associated with binge drinking and the definitions of these terms, the number of subgroups for which the alcohol-related population attributable fractions (PAFs) used in the calculations are obtained, whether or not a latency period is considered between alcohol use and death, and whether or not the underestimation of average self-reported drinking in the surveys is corrected with respect to more valid sources.

For these reasons, quite dissimilar estimates are sometimes published for the same country, producing a great deal of uncertainty when the results are used in decision-making. Spain is also affected by this situation, with estimates by authors or national or international institutions of the annual number of DAA in the population aged 15 years and over ranging from 8,558 in 1999-2004 (Fierro, Ochoa, Yánez, Valderrama & Álvarez, 2008) to 37,000 in 2016 (GBD, 2018b), and the proportion of general mortality attributable to alcohol from 2.1% to 9.0%, respectively. However, the lowest estimate was only partially based on empirical consumption data obtained from Spanish surveys, and these data were not corrected for underestimation of self-reported average consumption in population-based surveys (Fierro et al., 2008). Regarding estimates by foreign or international institutions (GBD, 2018a; IHME, 2020; WHO, 2020), these use international data sources, so their data are based on the population distribution of average consumption and alcohol consumption patterns non-specific to Spain. In addition, some methodological details are opaque or difficult to comprehend, which makes it impossible to apply them to obtain different results from those published, for example, with reference to different subgroups of interest.

It therefore seems necessary that a country like Spain should have detailed procedures to allow the estimation of DAA based on data on the population distribution of alcohol consumption collected directly from the Spanish population. This would allow routine estimates of the risk of DAA to be made rapidly, including series on changes over time and inter-regional comparisons (for example, between autonomous communities) and between sociodemographic subgroups. Beyond the global estimates that may exist, many countries, especially those with an Anglo-Saxon tradition, have their own methodologies of this type for making such routine estimates.

The objective of this article is thus to describe and discuss a methodology specific to Spain with which to estimate its alcohol-attributable mortality, which will be applied in a later article to obtain estimates during the period 2001-2017.

Description of methodology

General methodological approach

Deaths caused and preceded by alcohol use that would not have occurred in a counterfactual scenario without historical use of the substance are considered DAA. To estimate the total number of DAA, the specific cause approach is used. For this purpose, a series of causes or groups of causes considered to be related to alcohol use are selected, deaths attributable to alcohol for each of these causes (DAA_c) are estimated and the results of all those selected are added together.

$$DAA = \sum DAA_c$$

The number of DAA_c is estimated by multiplying the number of deaths from this cause (N_c), extracted from mortality statistics, by its corresponding PAF (PAF_c), which is the proportion of deaths from this cause attributable to exposure to alcohol and which could be avoided if the population stopped consuming this substance completely, and expresses the proportional contribution of alcohol use to population mortality from this cause. The PAF is obtained through an algorithm incorporating the relative

risks (RR) with respect to abstainers and the population prevalences of different categories of alcohol use.

$$DAA_c = (N_c)\,(PAF_c)$$

For each cause, the process is stratified for different population subgroups of sex, age and calendar-period, with the aim of achieving a balance that allows PAF_c to be obtained which are specific enough to give greater validity to the results while maintaining a reasonable level of precision. Specifically, for each cause, PAF_c are obtained for the 20 subgroups based on combining both sexes, five age groups (15-24, 25-44, 45-64, 65-74 and ≥75) and two calendar periods (2001-2009 and 2010-2017). This means that independent estimates are obtained for each of the 20 subgroups and subsequently summed. The estimation applies to the population aged 15 years and over.

Thus, the total number of deaths attributable to alcohol is the sum of the deaths attributed to different causes. The process therefore involves: (1) identifying and quantifying the different related causes of death, (2) establishing an attributable fraction for each cause and population subgroup, and (3) adding the results for absolute totals and rates.

Causes of death related to alcohol

Two types of alcohol-related causes of death are selected: 1) causes directly or completely attributable to alcohol, such as alcohol use disorder, where alcohol is always considered a necessary cause, and 2) other causes of alcohol-related death, in which alcohol is a contributing but not the sole factor; these comprise 18 groups, for example oesophageal cancer. The selection of causes is based on the most recent reviews and meta-analyses focused on assessing the risk of developing or dying from certain diseases associated with alcohol use (Corrao, Bagnardi, Zambon & Arico, 1999; Rehm et al., 2017; Samokhvalov, Irving & Rehm, 2010; Sherk, Stockwell, Rehm, Dorocicz & Shield, 2017), and in the selections made in the estimates of other countries (Connor, Kydd, Rehm & Shield, 2013; Jones & Bellis, 2013; Marmet, Rehm, Gmel, Frick & Gmel, 2014; Rey, Boniol & Jougla, 2010). Table 1 shows the codes of the International Classification of Diseases, tenth edition (ICD-10), corresponding to the 19 groups of selected causes. To avoid duplication, the codes corresponding to causes which are part of broader categories already included in a group of partially attributable causes are excluded from the list of codes for the group of causes directly attributable to alcohol. This is the case of alcoholic liver disease (K70), already included in cirrhosis/chronic liver disease, and involuntary alcohol poisoning (X45) or intentional alcohol self-poisoning (X65), included as external causes, among others (Table 1).

Not included as partially attributable causes are a broad group of diseases or health problems probably related to alcohol, such as certain cancers (for example, stomach

Table 1
Groups of causes of death selected to estimate alcohol-attributable mortality in Spain 2001-2017

Groups of causes	ICD-10[3] codes
	Causes partially attributable to alcohol
1. Tuberculosis	A15-A19, B90, K67.3, P37.0
2. Lower respiratory infection/pneumonia	A48.1, A70, J09-J15.8, J16, J20-J21, P23.0-P23.4
3. Cancer of the mouth and pharynx[1]	C00-C13
4. Cancer of the esophagus[1]	C15
5. Colorectal cancer[1]	C18-C21
6. Liver cancer[1]	C22
7. Laryngeal cancer[1]	C32
8. Breast cancer (women)[1]	C50
9. Diabetes mellitus	E10.0-E10.1, E10.3-E11.1, E11.3-E12.1, E12.3-E13.1, E13.3-E14.1, E14.3-E14.9, P70.0-P70.2, R73
10. Epilepsy	G40, G41
11. Hypertensive heart disease	I11
12. Ischemic heart disease	I20-I25
13. Atrial fibrillation/flutter	I48
14. Ischemic stroke	G45, I63, I67.2-I67.3, I67.5-I67.6, I69.3
15. Non-ischemic stroke	I60-I62, I69.0-I69.2, I67.0-I67.1
16. Cirrhosis/chronic liver disease	B18, I85, I98.2,K70, K71.3–K71.5, K71.7, K72.1–K74.6, K75.8–K76.0, K76.6–K76.7, K76.9
17. Pancreatitis	K85-K86
18. External cause	V01-Y98
19. Causes directly attributable to alcohol[2]	E24.4, F10, G31.2, G62.1, G72.1, I42.6, K29.2, O35.4, R78.0

Note. [1] D codes (carcinoma in situ, benign tumour, and tumours of uncertain or unknown behaviour) were not included because a fourth digit is often not available. [2] Causes of death directly attributable to alcohol part of broader categories included in groups of partially attributable causes were not considered, including alcoholic liver disease (K70), involuntary alcohol poisoning (X45), intentional alcohol self-poisoning (X65), intoxication by alcohol with undetermined intention (Y15) and evidence of involvement of alcohol (Y90-Y91). [3] ICD-10: International Statistical Classification of Diseases and Related Health Problems, tenth review.

and pancreatic cancers) since the evidence is considered insufficient to establish the causality of alcohol or to quantify the relative risk (Rehm et al., 2017; WHO, 2018b). HIV disease is excluded, although it is included in some countries (Gmel, Shield & Rehm, 2011; Marmet, Rehm & Gmel, 2016).

The number of deaths from the selected causes is sourced from the mortality register of the Spanish National Institute of Statistics [INE] (INE, 2020).

Population fractions attributable to alcohol

The population fraction attributable to alcohol for a cause or group of causes of death (PAF_c) expresses the relative contribution of alcohol use to total mortality from this cause. In this way, an attributable fraction of one was applied ($PAF_c=1$) for causes of death directly attributable to alcohol, while for causes partially attributable to alcohol, specific PAF_c were calculated for Spain. For the calculation, the Levin formula for categorical data was used, combining prevalence data of different levels of exposure to alcohol with the relative risks of mortality from a given cause (Rehm, Klotsche & Patra, 2007), and to which a term to include the fraction corresponding to ex-drinkers has been added. The formula is shown below:

In this formula, P_{exd} is the prevalence of ex-drinkers, P_i the prevalence for category i of the average amount of alcohol consumed daily during the last 12 months in the population, RR_{exd} is the relative risk of ex-drinkers versus unexposed individuals (abstainers), RR_i the relative risk of the exposed versus abstainers for this cause of death, and category i the amount of alcohol consumed daily. The number of categories i used in the calculations was seven, corresponding to the intervals ≤19, 20-39, 40-49, 50-59, 60-79, 80-99 and ≥100 grammes of pure alcohol/day. For each of the 18 groups of causes of death partially attributable to alcohol, 20 PAFs were calculated, the result of combining sex, five age groups, and the periods 2001-2009 and 2010-2017. It was decided to calculate PAFs for two multi-year periods rather than doing so for each calendar year, which would have provided more valid estimates, because the annual consumption prevalences included in the calculation formula would have been subject to greater variability due to randomness, especially considering that it would have been necessary to estimate them simultaneously by age stratum, sex and amount of alcohol consumed. The calculated PAFs are shown in Table 2.

The above formula makes it possible to segment the numerator in order to study different groups of drinkers (Sherk et al., 2017), for example, ex-drinkers and two groups of current drinkers, with high risk and medium-low risk, defined by certain values of i. Ex-drinkers are those who have not consumed alcoholic beverages in the last year, but have drunk them at least 12 times in some year of their life, following the definition of the United States National Health Survey (Villarroel, Clarke & Schoenborn, 2016). People who have drunk alcohol less than 12 times in any year of their life and have not drunk in the last year are abstainers. Current high-risk drinkers are men (or women) who have consumed an average of ≥60 (or 40) g of pure alcohol/day during the last year, which corresponds to 6 (or 4) standard drink units (SDUs). This criterion was adopted following earlier studies (Marmet et al., 2014; Rehm et al., 2017; Rehm, Rehm, Shield, Gmel & Gual, 2013; Rehm, Shield, Rehm, Gmel & Frick, 2012), including high and very high-risk drinkers according to classifications by the WHO (WHO, 2000) and the European Medicines Agency [EMA] (EMA, 2010; Mann, Aubin & Witkiewitz, 2017). Other people who have drunk alcohol in the last year are considered current low-risk drinkers. When distributing DAA by type of drinker, it is assumed that all deaths directly attributable to alcohol (PAFc = 1) occur in current high-risk drinkers and that there are no deaths from external causes attributable to alcohol among former regular drinkers.

The meaning of the different parameters in the Levin formula used to calculate the PAFs and the way in which they are obtained is detailed below.

Relative risks for different categories of population exposure to alcohol

Relative risk (RR) is a measure of association strength between alcohol exposure and death from a certain cause in a given group, place, and time compared to another group. The RR_i used to calculate the PAF_c can be consulted in Table 3. As reference or counterfactual scenario (RR = 1) they have abstainers, and for current drinkers they are calculated using continuous RR functions from different international meta-analyses, most of which were included in a recent review by Rehm et al. (Corrao et al., 1999; Rehm et al., 2017; Samokhvalov et al., 2010).

As a representative RR_i for each exposure interval (average daily amount of alcohol consumed) for current drinkers of < 100 grams of pure alcohol/day, the figure i corresponding to the midpoint of each interval is used (10, 30, 45, 55, 70 and 90). For current drinkers of ≥ 100 grams of alcohol/day, however, 130 grams of pure alcohol/day is used as representative RR_i, this being the median amount of alcohol consumed by the drinkers of that group included in the population health survey samples in both periods 2001-09 and 2010-17. In addition, in the case of some causes of death, sex-specific RRs were used (diabetes mellitus, hypertensive heart disease, ischemic heart disease, ischemic stroke, non-ischemic stroke, cirrhosis/chronic liver disease, and pancreatitis).

In the case of ex-drinkers, there are no published RRs for all the selected causes of death. For specific causes with available information, RRs are taken from a 2010 meta-analysis (Rehm et al., 2010a), and for those without

Table 2
Population alcohol-attributable fractions for the selected causes, by sex, period and age. Spain, 2001-2017

	Men									
	2001-2009					2010-2017				
	15-24	25-44	45-64	65-74	≥75	15-24	25-44	45-64	65-74	≥75
Cause of death										
1. Tuberculosis	0.427	0.563	0.628	0.576	0.511	0.341	0.440	0.573	0.601	0.474
2. Lower respiratory infection/pneumonia	0.111	0.157	0.188	0.171	0.159	0.084	0.119	0.167	0.185	0.155
3. Cancer of the mouth and pharynx[1]	0.506	0.633	0.691	0.644	0.581	0.414	0.518	0.642	0.668	0.549
4. Cancer of the esophagus[1]	0.529	0.629	0.677	0.635	0.579	0.447	0.540	0.638	0.658	0.558
5. Colorectal cancer[1]	0.139	0.200	0.239	0.215	0.195	0.105	0.149	0.210	0.231	0.186
6. Liver cancer[1]	0.369	0.586	0.670	0.607	0.528	0.286	0.394	0.592	0.631	0.451
7. Laryngeal cancer[1]	0.483	0.497	0.501	0.493	0.460	0.240	0.318	0.418	0.443	0.348
8. Breast cancer (women)[1]	-	-	-	-	-	-	-	-	-	-
9. Diabetes mellitus	-0.056	-0.042	-0.021	-0.018	-0.008	-0.060	-0.058	-0.033	-0.016	-0.011
10. Epilepsy	0.290	0.396	0.455	0.409	0.357	0.225	0.302	0.407	0.434	0.335
11. Hypertensive heart disease	0.210	0.292	0.342	0.305	0.269	0.161	0.221	0.303	0.327	0.254
12. Ischemic heart disease	-0.061	-0.044	-0.026	-0.026	-0.016	-0.049	-0.058	-0.036	-0.017	-0.016
13. Atrial fibrillation/flutter	0.133	0.188	0.224	0.201	0.184	0.101	0.142	0.198	0.218	0.177
14. Ischemic stroke	-0.015	0.040	0.090	0.076	0.074	-0.045	-0.015	0.056	0.087	0.065
15. Non-ischemic stroke	0.157	0.222	0.263	0.234	0.208	0.119	0.166	0.232	0.252	0.198
16. Cirrhosis/chronic liver disease	0.666	0.799	0.844	0.808	0.755	0.576	0.680	0.803	0.824	0.711
17. Pancreatitis	0.411	0.545	0.610	0.558	0.494	0.327	0.424	0.555	0.584	0.459
18. External cause	0.191	0.256	0.297	0.267	0.239	0.144	0.200	0.267	0.288	0.233
	Women									
	2001-2009					2010-2017				
	15-24	25-44	45-64	65-74	≥75	15-24	25-44	45-64	65-74	≥75
Cause of death										
1. Tuberculosis	0.245	0.251	0.246	0.197	0.144	0.220	0.222	0.257	0.219	0.158
2. Lower respiratory infection/pneumonia	0.063	0.070	0.068	0.057	0.051	0.059	0.066	0.073	0.066	0.056
3. Cancer of the mouth and pharynx[1]	0.309	0.315	0.311	0.250	0.186	0.282	0.283	0.324	0.279	0.204
4. Cancer of the esophagus[1]	0.360	0.364	0.355	0.286	0.222	0.339	0.342	0.373	0.325	0.244
5. Colorectal cancer[1]	0.077	0.085	0.083	0.069	0.059	0.072	0.079	0.088	0.079	0.065
6. Liver cancer[1]	0.156	0.163	0.161	0.140	0.079	0.117	0.110	0.152	0.123	0.079
7. Laryngeal cancer[1]	0.425	0.427	0.418	0.375	0.347	0.163	0.169	0.190	0.163	0.121
8. Breast cancer (women)[1]	0.132	0.138	0.135	0.107	0.085	0.121	0.127	0.144	0.124	0.094
9. Diabetes mellitus	-0.243	-0.222	-0.177	-0.107	-0.070	-0.241	-0.230	-0.202	-0.136	-0.081
10. Epilepsy	0.163	0.170	0.166	0.131	0.101	0.149	0.154	0.175	0.150	0.111
11. Hypertensive heart disease	0.191	0.205	0.219	0.185	0.122	0.143	0.143	0.219	0.192	0.132
12. Ischemic heart disease	-0.052	-0.032	-0.014	0.009	0.020	-0.059	-0.042	-0.019	0.004	0.020
13. Atrial fibrillation/flutter	0.075	0.082	0.080	0.066	0.057	0.070	0.077	0.086	0.076	0.062
14. Ischemic stroke	-0.154	-0.136	-0.095	-0.045	-0.044	-0.186	-0.183	-0.122	-0.081	-0.054
15. Non-ischemic stroke	0.191	0.194	0.190	0.147	0.105	0.172	0.172	0.199	0.167	0.116
16. Cirrhosis/chronic liver disease	0.430	0.434	0.429	0.363	0.249	0.380	0.370	0.433	0.373	0.264
17. Pancreatitis	0.234	0.240	0.236	0.189	0.139	0.211	0.213	0.246	0.210	0.152
18. External cause	0.107	0.114	0.112	0.089	0.074	0.100	0.107	0.120	0.105	0.082

Note. The population attributable fractions (PAFs) for the group of causes of death directly attributable to alcohol are always 1 and were not included. To calculate the PAF, the corrected prevalences of consumption were used, raising the average consumption of each participant in the surveys to 80% of the average per capita consumption estimated from the sales statistics. For a more accurate calculation of deaths attributable to alcohol for a given territory or subgroup, PAFs with 5 decimal places are often required, so it is recommended to request the file from the authors.

Table 3
Relative risks of death from the selected causes, by sex and level of exposure to alcohol. Spain, 2001-2017

	Men								Women							
	Average amount of alcohol consumed (g pure alcohol/day)															
	Exd[1].	10	30	45	55	70	90	130	Exd.	10	30	45	55	70	90	130
Cause of death																
1. Tuberculosis	1.38	1.20	1.71	2.24	2.69	3.52	5.04	10.34	1.38	1.20	1.71	2.24	2.69	3.52	5.04	10.34
2. Lower respiratory infection/pneumonia	1.38	1.05	1.15	1.24	1.30	1.40	1.54	1.86	1.38	1.05	1.15	1.24	1.30	1.40	1.54	1.86
3. Cancer of the mouth and pharynx[1]	1.38	1.28	2.03	2.81	3.45	4.65	6.70	12.68	1.38	1.28	2.03	2.81	3.45	4.65	6.70	12.68
4. Cancer of the esophagus[1]	1.38	1.46	2.39	3.21	3.81	4.80	6.29	9.76	1.38	1.46	2.39	3.21	3.81	4.80	6.29	9.76
5. Colorectal cancer[1]	1.38	1.06	1.21	1.23	1.41	1.55	1.76	2.26	1.38	1.06	1.21	1.23	1.41	1.55	1.76	2.26
6. Liver cancer[1]	1.38	1.01	1.16	1.40	1.66	2.29	3.94	17.55	1.38	1.01	1.16	1.40	1.66	2.29	3.94	17.55
7. Laryngeal cancer[1]	1.38	1.16	1.52	1.85	2.10	2.52	3.17	4.77	1.38	1.16	1.52	1.85	2.10	2.52	3.17	4.77
8. Breast cancer (women)[1]	-	-	-	-	-	-	-	-	1.38	1.11	1.36	1.58	1.75	2.04	2.50	3.76
9. Diabetes mellitus	1.18	0.90	0.88	0.93	0.97	1.07	1.16	1.16	1.14	0.68	0.62	0.86	1.18	1.18	1.18	1.18
10. Epilepsy	1.38	1.14	1.45	1.75	1.98	2.38	3.04	4.97	1.38	1.14	1.45	1.75	1.98	2.38	3.04	4.97
11. Hypertensive heart disease	1.38	1.10	1.31	1.50	1.65	1.89	2.26	3.25	1.38	0.89	1.60	2.43	3.16	4.59	7.38	17.76
12. Ischemic heart disease	1.25	0.95	0.84	0.74	0.67	1.00	1.00	1.43	1.54	0.84	0.99	1.15	1.26	1.45	1.74	2.53
13. Atrial fibrillation/flutter	1.38	1.06	1.19	1.30	1.37	1.50	1.68	2.11	1.38	1.06	1.19	1.30	1.37	1.50	1.68	2.11
14. Ischemic stroke	1.33	0.85	0.96	1.07	1.14	1.26	1.43	1.81	1.15	0.65	0.77	1.00	1.22	1.70	2.75	7.81
15. Non-ischemic stroke	1.33	1.07	1.23	1.36	1.46	1.62	1.86	2.45	1.15	1.16	1.55	1.93	2.24	2.79	3.74	6.73
16. Cirrhosis/chronic liver disease	1.31	1.33	2.32	3.53	4.67	7.10	12.42	37.95	6.50	2.82	5.97	8.90	11.20	15.24	21.93	40.87
17. Pancreatitis	1.38	1.19	1.68	2.18	2.60	3.37	4.76	9.53	1.38	0.77	0.66	1.53	3.01	4.80	10.26	10.26
18. External cause	1.38	1.09	1.30	1.48	1.62	1.85	2.21	2.42	1.38	1.09	1.30	1.48	1.62	1.85	2.21	2.42

Exd[1]: ex-drinkers.
Note. The references used to obtain the RRs for each cause of death are Corrao, Bagnardi, Zambon and Arico (1999); Samokhvalov, Irving and Rehm (2010), and Rehm et al. (2017), in the case of current drinkers. For ex-drinkers, references are Rehm et al. (2010a), and Stockwell et al. (2016).

information, the all-cause mortality RR of 1.38 from a Stockwell et al. meta-analysis is applied, corresponding to the joint and completely adjusted model (Stockwell et al., 2016).

Prevalences of population exposure to alcohol

The formula for calculating PAFs involves the prevalence of ex-drinkers and the annual prevalences of different average daily amounts of alcohol consumed. These prevalences are shown in Table 4 by age, sex, and period.

Data sources and how they were obtained are described below.

Ex-drinker prevalences

For the period 2010-2017, these are estimated from figures in the Spanish National Health Survey (ENS) and the European Health Survey in Spain (EESE) corresponding to the period. As the studies providing RRs for mortality in ex-drinkers most likely exclude infrequent ex-drinkers or those just trying out alcohol, it is advisable to correct the prevalences by eliminating this subgroup. To make this correction, the distribution of infrequent and regular ex-drinkers from the United States National Health Survey in the period 2011-14 (Villarroel et al., 2016) is used since there are no data for this from Spanish sources.

For the period 2001-09, the prevalence figures for ex-drinkers obtained from ENS and EESE are very low compared to 2010-17 and to those obtained from other sources for some age subgroups and were thus not considered reliable; instead, they were estimated from the 2010-17 corrected prevalences, assuming a relative change between periods similar to that observed in the Spanish Household Survey on Alcohol and Drugs (Encuesta Domiciliaria sobre Alcohol y Drogas en España, EDADES) (Delegación del Gobierno para el Plan Nacional sobre Drogas [DGPNSD], 2018).

Annual prevalences of average daily consumption of different amounts of alcohol

These are obtained from the individual files of ENS 2001, 2006, 2011 and 2017, and EESE 2009 and 2014 (INE, 2019a; Ministerio de Sanidad, Consumo y Bienestar Social [MSCBS], 2019). To this end, the average self-reported daily amount of alcohol consumed by each participant during the last year is first corrected for underestimation, given the well-known fact that self-reports of alcohol use strongly underestimate real consumption (Sordo et al., 2016). The categories of consumption used for stratifying annual consumption prevalence, in grams of pure alcohol, correspond to the seven categories i mentioned in the PAF_c calculation. The prevalences for the intermediate years without the survey are estimated by linear interpolation.

Table 4
Corrected prevalence of alcohol consumption[1] in the population aged 15 years and over[2], by age, sex, average daily amount of alcohol consumed and period (%). Spain, 2001-2017

		Prevalence (%)									Sample size
Drinker status		**Abstainer[3]**	**Ex-drinker[4]**	**Drinker in the previous year**							
Grams alcohol/day[5]		**0**	**0**	**1-19**	**20-39**	**40-49**	**50-59**	**60-79**	**80-99**	**≥100**	
						2001-2009					
Age	**Sex**										
15-24	Men	22.8	1.8	41.0	17.1	5.5	3.0	4.2	2.3	2.3	3368
	Women	32.2	2.0	51.6	9.5	1.8	0.9	0.7	0.7	0.7	3365
	Total	27.5	1.9	46.3	13.3	3.7	2.0	2.6	1.5	1.5	6733
25-44	Men	14.3	3.2	37.1	19.6	5.3	4.8	5.6	3.1	7.0	11240
	Women	32.4	4.2	48.8	9.7	1.3	1.4	1.2	0.5	0.7	13344
	Total	24.1	3.7	43.4	14.2	3.1	3.0	3.2	1.7	3.6	11111
45-64	Men	15.2	4.9	27.0	19.9	4.7	7.5	6.8	3.9	10.3	9033
	Women	41.4	4.2	38.0	10.8	1.0	2.3	1.2	0.4	0.7	11800
	Total	30.0	4.5	33.2	14.7	2.6	4.6	3.6	1.9	4.7	11199
65-74	Men	20.7	7.8	25.1	19.0	2.4	8.7	6.1	2.4	7.6	3614
	Women	58.6	5.3	23.4	9.1	0.4	1.8	0.7	0.1	0.6	5489
	Total	43.5	6.3	24.1	13.0	1.2	4.5	2.9	1.0	3.4	9103
>=75	Men	26.2	13.2	20.3	18.7	1.5	8.8	3.7	1.6	5.3	2938
	Women	67.8	6.7	15.3	7.7	0.3	1.5	0.3	0.1	0.2	5104
	Total	52.6	9.1	17.1	11.7	0.7	4.2	1.5	0.6	2.1	8042
Total	Men	19.8	6.2	30.1	18.9	3.9	6.6	5.3	2.7	6.5	30193
	Women	46.5	4.5	35.4	9.4	1.0	1.6	0.8	0.4	0.6	39102
	Total	34.9	5.2	33.1	13.5	2.2	3.7	2.8	1.4	3.2	69295
						2010-2017					
Age	**Sex**										
15-24	Men	27.4	1.9	48.3	12.1	3.6	2.0	2.1	0.8	1.8	2195
	Women	32.8	2.2	52.8	8.0	1.6	1.2	0.7	0.4	0.4	2202
	Total	30.1	2.1	50.5	10.1	2.6	1.5	1.4	0.6	1.1	4397
25-44	Men	15.7	3.5	46.0	17.1	5.4	3.5	4.5	1.5	2.8	9749
	Women	32.0	4.5	49.9	9.3	2.1	0.9	0.9	0.2	0.3	10312
	Total	24.1	4.0	48.0	13.1	3.7	2.2	2.6	0.8	1.5	20061
45-64	Men	13.9	5.2	33.5	19.5	5.8	4.5	8.0	2.8	7.0	10753
	Women	35.4	4.5	42.3	11.4	2.3	1.3	1.9	0.4	0.5	11529
	Total	25.0	4.8	38.1	15.3	4.0	2.8	4.8	1.6	3.6	22282
65-74	Men	14.9	8.4	26.0	20.4	5.1	4.6	9.2	3.2	8.4	4051
	Women	49.5	5.7	29.1	10.4	1.6	1.2	2.0	0.1	0.3	5148
	Total	34.3	6.9	27.7	14.8	3.1	2.7	5.2	1.5	3.9	9199
>=75	Men	24.5	14.9	19.8	21.8	4.0	3.8	6.1	1.7	3.4	3597
	Women	64.1	7.2	17.5	8.5	0.6	0.9	1.1	0.1	0.1	6546
	Total	50.1	9.9	18.3	13.2	1.8	1.9	2.9	0.7	1.3	10143
Total	Men	19.3	6.8	34.7	18.2	4.8	3.7	6.0	2.0	4.7	30345
	Women	42.8	4.8	38.3	9.5	1.6	1.1	1.3	0.2	0.3	35737
	Total	32.0	5.7	36.7	13.5	3.1	2.3	3.5	1.0	2.3	66082

Note. [1] Corrected prevalence of alcohol consumption: Prevalences obtained after correcting the underestimation of self-reported consumption in population surveys with respect to alcohol consumption sales statistics. The correction was made by applying an elevation factor to the average daily quantity consumed by each individual participant in the survey up to 80% of the average daily quantity per capita estimated from the sales statistics. [2]Population aged 15 year and older: In reality, the consumption prevalences correspond to the population aged 16 years and over, which is the reference population of the population surveys included in this study. However, the estimates of sales statistics from international organizations usually apply to the population aged 15 years and over; the fractions attributable to alcohol in the population and the estimates of attributable mortality were thus applied to the 15-and-older population. [3]Abstainer: Person who has never drunk alcoholic beverages in their life. [4]Ex-drinker: Person who has not drunk alcoholic beverages in the previous year and has drunk such beverages less than 12 times in any other year of their life. The prevalence was estimated as explained in the Methodology section. 5Alcohol consumed (g/day): Refers to the average amount of pure alcohol consumed daily in grams.

The algorithm used to correct for underestimation is detailed below. For each participant in the survey, average daily consumption in a given year in grams of pure alcohol (Ac), is obtained by multiplying the self-reported average daily consumption during the 12 months prior to the survey (As), by an elevation factor (Ef). This factor is calculated in turn by dividing the best estimate of the average daily population consumption per capita from multiple sources, mainly sales statistics (Ar), by As and multiplying the result by the degree of correction of the desired underestimation (C).

$$Ac = \text{Aa}\left[\frac{Ar}{\text{Aa}}C\right], \text{ donde } \left[\frac{Ar}{\text{Aa}}C\right]=\text{Fe}$$

According to international recommendations (Kehoe, Gmel, Shield, Gmel & Rehm, 2012; Rehm et al., 2010b; Stockwell et al., 2018), C is 0.8; that is, As is corrected up to 80% of Ar. The justification for this procedure is somewhat extensive and is included in Appendix Table 1. The estimates of As, Ar and Ef by calendar year are included in Table 5. As can be seen in this table, the Ef has increased in the most recent years, highlighting the increasing difficulty in capturing real consumption in surveys and further justifying the need to correct self-reported consumption. A specific Ef was calculated for each year with survey results and was applied to all the participants in the survey who had drunk alcohol during the last year, irrespective of their sociodemographic profile and their consumption patterns, because the annual Ar could only be estimated for the country as a whole, without the possibility of stratification by sociodemographic variables.

The methodology for estimating Ar and As has been published (Sordo et al., 2016) and is summarized below.

Estimation of average self-reported alcohol consumption (As)

The surveys used for estimating As can be considered representative of the non-institutionalized population aged ≥ 15 years in Spain. Its characteristics can be seen in Appendix Table 2. The amount of alcohol consumed (*As*) in litres of pure alcohol (lpa) per person-year (py) is estimated following the classical approach (Dawson, 2003) with the algorithm: $As=\sum_{i=1}^{k}\frac{D_i SD_i V_i C_i}{SS}$, where the subscript i represents the different categories of beverages, such as wine/cava, beer/cider, aperitifs/intermediate products (drinks with alcohol content of 1.2-22% ABV, other than fermented ones such as vermouth, sherry, port and pale sherries or amontillados) and spirits/distilled beverages (including mixes made with spirits), D_i is the annual number of days or times each drink is consumed, SD_i the number of SDUs consumed each day or each time, V_i the volume of each SDU in litres, C_i the proportion of alcohol over the total volume of the drink, and SS the effective sample size. Given

Table 5
Elevation factors used for correcting underestimated self-reported annual alcohol consumption. Spain, 2001-2017

	Registered alcohol consumption (Ar)[1]	Self-reported alcohol alcohol consumption (As)[2]	Elevation factor (Ef)[3]
2001	12.5	6.3	1.58
2002	10.8		
2003	11.7		
2004	12.0		
2005	11.3		
2006	11.4	3.8	2.38
2007	11.1		
2008	10.3		
2009	9.9	3.0	2.61
2010	9.6		
2011	9.4	2.6	2.83
2012	9.5		
2013	9.8		
2014	9.6	2.9	2.64
2015	9.6		
2016	9.7		
2017	9.6	2.4	3.18

Note. [1] Registered alcohol consumption (Ar): Average annual per capita consumption in litres of pure alcohol/year by residents in Spain aged 15 years and over, estimated from sales statistics. [2] Self-reported alcohol consumption (As): Average annual per capita consumption of pure alcohol/year in litres by residents in Spain aged 15 years and over, self-reported in population surveys. [3] Elevation factor (Fe): Ef=(Ar/As)*0.8. The multiplication factor used to correct the underestimation of self-reported alcohol use in the population statistics with respect to the estimates from sales statistics. The correction was made only up to 80% of the sales statistics consumption estimate, as recommended (Rehm et al., 2010a; Stockwell et al., 2018; Kehoe et al., 2012). It was applied to the average consumption of each individual participating in the surveys so that the population prevalences of consumption according to the average daily amount consumed could then be obtained.

the great scarcity of empirical data (Rodríguez-Martos, Gual & Llopis Llácer, 1999), the SDU volume of each drink, V_i, is assigned using the upper limits of the volumes reflected in some clinical and public health guidelines (Organización Médica Colegial y Ministerio de Sanidad y Consumo [OMC-MSC], 2006; Sociedad Española de Medicina de Familia y Comunitaria [SEMFYC], 2005): wine (125 ml), beer/cider (250 ml), aperitifs (100 ml), spirits (60 ml), and C_i are applied to each drink on the basis of the Spanish Tax Agency guidelines (5.5%, 11.5%, 15% and 35%, respectively) (Agencia Tributaria [AT], 2015; 2019). In this way, the amounts in grams of pure alcohol per SDU of each drink are: 11.36 (wine), 10.86 (beer/cider), 11.85 (aperitifs), and 16.59 (spirits). For a vague category, such as "regional drinks", it is assumed that an SDU contains 10 g of pure alcohol.

The results of the surveys were weighted to adjust for the imbalance of the sample according to sex, age group, province, size of household, and response rate.

Estimated average registered alcohol consumption (Ar)

The main aggregated data for estimating the average alcohol use registered per capita (Ar) refer to legal sales or supplies of drinks intended for human consumption within Spain with an alcohol content by volume (ABV) of > 1.2%. These figures are corrected to account for unregistered alcohol, consumption/purchase by international travellers, and post-sale alcoholic drink loss. The data for estimating the alcohol consumed/purchased by foreign visitors in Spain and Spanish visitors abroad are obtained from the Spanish Tourism Institute (TURESPAÑA, 2019), INE (INE, 2019b), WHO (registered per capita alcohol consumption by country) (WHO, 2020), Eurostat (Eurostat, 2019) and World Bank (World-Bank, 2019) and the scientific literature (Sordo et al., 2016). The remaining data necessary for correcting the sales statistics is obtained from the scientific literature, including the consumption of contraband beverages or those made with alcohol for other purposes, drinks from unregistered sales or production (for example, self-use), products with an alcoholic content greater than zero and ≤ 1.2% ABV, loss of alcoholic beverages (spilled, spoiled or wasted/unfinished drinks) and beverages used for cooking or for purposes other than direct human consumption (Boniface & Shelton, 2013; Landberg & Norstrom, 2011; Meier et al., 2013; Norstrom & Skog, 2001; Rehm et al., 2010b; Rehm et al., 2007; Trolldal, 2001; WHO, 2020). The characteristics of the main routine sources providing useful aggregate data for estimating per capita alcohol consumption in Spain are included in Appendix Table 3.

Alcohol quantity is expressed in litres of pure alcohol per person-year (lpa/py), using the population resident in Spain each year as the denominator. To obtain figures for the real consumption of alcohol, a multistage process was followed starting with the availability of alcohol for consumption published by the Spanish Tax Agency (TA). The TA calculates availability by adding to the alcohol from legal sales of beverages subject to excise duty on alcohol (beer, spirits and snacks) the alcohol from wine purchases which are self-reported to the Spanish Food Consumption Panel (Panel de Consumo Alimentario). This availability does not include cider, and it has been noted that self-reported wine purchases are underestimated compared to sales (as in the case of beer, where underestimation reaches 45%). A multi-source availability indicator was therefore created by replacing the wine component in TA availability with the Eurostat wine supply statistic and adding the FAO figure for cider supply. Finally, the real average per capita consumption was obtained by adding the alcohol from drinks consumed/purchased abroad by Spanish residents and the remaining unregistered alcohol, and subtracting alcohol loss and alcohol from drinks consumed/bought in Spain by foreign visitors. The specific calculation algorithms can be consulted in a previous study (Sordo et al., 2016).

Alcohol-attributable mortality indicators

The main indicators used to express the results of alcohol-attributable mortality estimates in Spain are: absolute number of DAA and various age-standardized indicators such as DAA rate (RDAA), and the proportional contribution of alcohol to general mortality risk (CAGM), proportional contribution to the total risk of alcohol-attributable mortality of different causes of death (CMAAC), and from high-risk consumption (CMAAR).

RDAA is an indicator of the absolute risk or probability of dying from alcohol use in a given population subgroup. Population rates are expressed per 100,000 person-years (py) and standardized using the direct method with the age structure weights of the 2013 European Standard Population (Eurostat, 2013). The standardized proportional contributions are expressed as percentages and are the result of dividing the RDAA by the all-cause mortality rate (CAGM), the specific RDAA for each cause by the RDAA for all causes (CMAAC), and the RDAA in current high-risk drinkers by the sum of RDAAs in high-risk and medium-low-risk drinkers (CMAAR).

Most of the indicators were calculated by sex, age group (15-34, 35-54, 55-74 years and >= 75 years), autonomous community, calendar period (2001-09 and 2010-17) and type of drinker (ex-regular drinkers, medium-low risk drinkers and high-risk drinkers).

The populations by age group, sex, autonomous community and calendar year for the calculation of the indicators were obtained from the population figures of the Spanish National Statistics Institute (INE, 2019c). To compare the risk of DAA between groups (for example, men and women) or periods (2001-09 and 2010-17), the

ratio and difference of age-standardized rates were applied, transforming the rate ratio into a percentage of change for temporal comparisons.

Sensitivity analysis

Several sensitivity analyses were carried out to observe how the change of some methodological options affected the estimation of the total number of DAA in 2017 (Appendix Table 4). These included introducing prevalences without correction for underestimated consumption, excluding the DAA occurring in ex-drinkers from the calculations, adopting a broader definition of ex-drinker which included both "regular ex-drinkers" and "infrequent ex-drinkers", using the alcohol use prevalences of the period 2001-09 instead of 2010-2017 figures, which is equivalent to introducing a latency period of approximately 12 years with respect to 2017, and estimating the DAA in traffic accidents taking as the PAFc the proportion of drivers and pedestrians who died in such accidents with a blood alcohol level above 0.8 grams/litre during 2015-17, calculated with data extracted from the annual reports of the National Institute of Toxicology and Forensic Sciences during 2001-17 (1,870 drivers and 489 pedestrians) (Instituto Nacional de Toxicología y Ciencias Forenses [INTCF], 2019).

Methodology discussion

This article sets out a detailed methodology for estimating alcohol-attributable mortality in Spain, following as far as possible the most common and updated international recommendations and procedures in the field (IHME, 2020; Rehm et al., 2017; Rehm et al., 2009; Sherk et al., 2017; WHO, 2000, 2018b, 2020). Its application to the period 2001-2017 has made it possible to obtain results by sex, age, calendar period, autonomous community, cause of death and type of drinker, which are quite consistent with other indicators of alcohol problems. In the future, it will in turn allow comparative results to be obtained for other subgroups of interest, such as those defined by educational level or socioeconomic position based on the mortality cohorts from the 2001 and 2011 censuses of the KharonXXI Platform for National Longitudinal Mortality Studies that is being established within the CIBERESP framework.

The two main strengths of the methodology are that the PAFs were calculated from empirical data on population exposure to alcohol from almost all Spanish sources, and that individual survey data on average self-reported alcohol use were corrected for underestimation in relation to other sources of greater validity such as statistics on the sale of alcoholic drinks, following a very painstaking process (Sordo et al., 2016). The methodology also has other strengths, such as the inclusion of DAA linked to ex-drinkers. Finally, the PAFc obtained are quite robust because the distribution of population exposure to alcohol is based on the joint analysis of surveys with a significant sample size (n = 66,082 in 2010-2017 and 69,295 in 2001-2009). This makes it possible to obtain PAFc for the 20 population subgroups mentioned above and to segment the PAFc for each cause of death by type of drinker (ex-drinker, low-risk and high-risk drinker).

Despite its strengths and the fact that great pains were taken to collect all the relevant data available, it is undoubtedly still a work in progress which will require reviewing and improving in the future. In this regard, a number of methodological options may be considered for the proposed model.

A specific cause approach was chosen in preference of all causes because it allows better control of confounding factors, as well as making it possible to estimate the relative weights of different causes or groups of causes of death in the total mortality attributable to alcohol, an aspect of interest to clinical and public health practice (Corrao, Rubbiati, Zambon & Arico, 2002). To design more appropriate prevention and treatment interventions, it is not only a matter of knowing the number of DAA but also the specific causes.

Beyond this general approach, conservative methodological strategies were adopted to avoid overestimating the number of DAA, which makes it highly likely that the figures obtained underestimate the mortality attributable to alcohol in Spain. Among these strategies, the following are worth noting: 1) Only those causes of death for which there is clear evidence linking them to alcohol use and which have valid RR estimates were included (Table 1). This excludes a broad group of diseases with a probable relationship to alcohol. 2) In calculating the amount of alcohol consumed, an alcohol content of 11.5% ABV was applied to wine, which is probably low in the current Spanish context (Alston, Lapsley, Soleas & Tumber, 2013). 3) A restrictive definition of ex-drinker was applied, including only the fraction of these individuals (regular ex-drinkers), which may offer a better fit with the profile of ex-drinkers referred to in the RRs obtained in epidemiological studies. This option, which has probably not been adopted in other studies (Rehm et al., 2010a; Stockwell et al., 2016), considerably reduces estimates of the number of DAA because ex-drinkers have RRs close to high-risk drinkers (Rehm et al., 2010a; Stockwell et al., 2016) given that many stopped drinking due to problems caused by alcohol. In any case, it must be noted that the data to make the correction came from the United States, where the epidemiological situation of alcohol use may not be equivalent to Spain's. For example, alcohol use in Spain has clearly declined during the 21st century, something that has not happened in the United States (Breslow, Castle, Chen & Graubard, 2017; Centers for Disease Control and Prevention [CDC],

2020). The effect of including only regular ex-drinkers or all ex-drinkers in the calculations can be seen in Appendix Table 4. 4) Binge drinking was not specifically addressed due to the lack of corresponding information; however, it is considered that this consumption pattern was already taken into account in the algorithm used to obtain the PAFs in a general way. Nevertheless, the changes in the estimate as a result of considering the effect of this consumption pattern can be seen in Appendix Table 4. 5) The RR_i of some diseases are probably underestimated given that they are calculated in comparison with abstainers, a group that in some studies may also include former regular drinkers (Rehm et al., 2017; Rehm, Shield, Roerecke & Gmel, 2016; Stockwell et al., 2016). However, a sensitivity analysis was carried out for 2017 which considered a latency period of approximately 12 years and the estimate of the number of DAA was only 1.03 times greater than that considered valid in this study (Appendix Table 4).

In addition, there are some general limitations that affect the estimates of alcohol-attributable mortality worldwide. Among them we must mention the scarcity and low quality of the RR_i estimates published for certain causes of death, age groups, sex and average daily consumption. Thus, the RR_i for some severe health problems, for example, traffic accidents, can vary widely by age, so the application of the same RR_i at all ages could result in an underestimation of these deaths in young people and an overestimation in older people (Jones, Bellis, Dedman, Sumnal & Tocke, 2008; Rehm, Patra & Popova, 2006). The DAA estimates for the oldest age groups and some causes of death, such as circulatory diseases, are particularly dependent on the methodological options regarding exposure to alcohol or the RR_i chosen to cmeasure them (Marmet et al., 2016; Sherk, Thomas, Churchill & Stockwell, 2020; Trias-Llimós, Martikainen, Mäkelä & Janssen, 2018). Furthermore, the RR_i used would most likely reflect the strength of the association between average consumption and mortality by cause in countries and time periods with different consumption patterns from those prevalent in Spain in the study period. Finally, it should be noted in this regard that when linking consumption to incidence, RRs do not normally differentiate between morbidity and mortality, so that sometimes reference is made to incidence of disease and not necessarily mortality. However, there is no alternative way to obtain these RR_i . A futher limitation is related to the practice of correcting for underestimation homogeneously across all participants in population surveys. If, as is likely, there are differences in the degree of underestimation according to sociodemographic factors or level of average daily alcohol use, this could bias the estimates of the total number of DAA, as well as its distribution by sociodemographic factors, cause of death and type of drinker.

As indicated, the purpose of this methodology is to serve as the basis for establishing a routine alcohol-attributable mortality indicator in Spain to help monitor the issue, starting with an analysis of the limitations of existing general health information systems. In this regard, statistics on alcohol consumption in population health surveys, as well as alcoholic beverage sales, need to be made more consistent and maintained over time. Frequent changes in the questionnaires of the National Health Survey during the period 2001-2017 in terms of the content and format of the questions on alcohol use, or the uncertainty associated with the data on sales of alcoholic beverages not subject to special tax (wine and cider) published by the TA or international institutions, made it extremely difficult to estimate the population's exposure to alcohol during this period. Adopting international instruments has not necessarily improved the situation because they are often not well adapted to the consumption patterns and types of beverages prevalent in Spain. Likewise, it would be helpful to determine the changes in the practices of certification and codification of causes of death in Spain, especially as regards circulatory diseases, in order to better interpret the findings on the changes in mortality attributable to alcohol by cause.

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Conflict of interests

The authors declare no conflict of interest related to aspects discussed in this article.

References

Agencia Europea de Medicamentos. (2010). *Guideline on the development of medicinal products for the treatment of alcohol dependence*. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-development-medicinal-products-treatment-alcohol-dependence_en.pdf.

Agencia Tributaria. (2015). *Impuestos especiales.* http://www.agenciatributaria.es/AEAT.internet/Inicio/Aduanas_e_Impuestos_Especiales/Impuestos_Especiales/Impuestos_Especiales.shtml.

Agencia Tributaria. (2019). *Impuestos sobre el alcohol y las bebidas alcohólicas, 2015.* https://www.agenciatributaria.es/AEAT.internet/Inicio/La_Agencia_Tributaria/Memorias_y_estadisticas_tributarias/Estadisticas/Estadisticas_por_impuesto/Impuestos_especiales/Impuestos_especiales.shtml.

Alston, J. M. F., Lapsley, J.T., Soleas, G. & Tumber K.P. (2013). The high and rising alcohol content of wine. In. E. P. Giraud-Héraud, M.C. (Ed.), *Wine Economics*. London: Palgrave Macmillan.

Boniface, S. & Shelton, N. (2013). How is alcohol consumption affected if we account for under-reporting? A hypothetical scenario. *European Journal of Public Health, 23*, 1076-1081. doi:10.1093/eurpub/ckt016.

Breslow, R. A., Castle, I. P., Chen, C. M. & Graubard, B. I. (2017). Trends in alcohol consumption among older americans: National health interview surveys, 1997 to 2014. *Alcoholism: Clinical and Experimental Research, 41*, 976-986. doi:10.1111/acer.13365.

Centers for Disease Control and Prevention. (2020). *Alcohol use.* https://www.cdc.gov/nchs/fastats/alcohol.htm.

Connor, J., Kydd, R., Rehm, J. & Shield, K. (2013). *Alcohol-attributable burden of disease and injury in New Zealand: 2004 and 2007. Research report commissioned by the Health Promotion Agency.* https://www.hpa.org.nz/sites/default/files/Attributable%20fractions%20Final.pdf.

Corrao, G., Bagnardi, V., Zambon, A. & Arico, S. (1999). Exploring the dose-response relationship between alcohol consumption and the risk of several alcohol-related conditions: A meta-analysis. *Addiction, 94*, 1551-1573. doi:10.1046/j.1360-0443.1999.9410155111.x.

Corrao, G., Rubbiati, L., Zambon, A. & Arico, S. (2002). Alcohol-attributable and alcohol-preventable mortality in Italy. A balance in 1983 and 1996. *European Journal of Public Health, 12*, 214-223. doi:10.1093/eurpub/12.3.214.

Dawson, D. A. (2003). Methodological issues in measuring alcohol use. *Alcohol Research & Health, 27*, 18-29.

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2018). *EDADES 2017. Encuesta sobre alcohol y otras drogas en España (EDADES), 1995-2017.* http://www.pnsd.mscbs.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/EDADES_2017_Informe.pdf.

Eurostat. (2013). *Revision of the European Standard Population. Report of Eurostat's task force.* https://ec.europa.eu/eurostat/documents/3859598/5926869/KS-RA-13-028-EN.PDF/e713fa79-1add-44e8-b23d-5e8fa09b3f8f.

Eurostat. (2019). *Purchasing power parities (PPPs), price level indices and real expenditures for ESA 2010 aggregates*. https://ec.europa.eu/eurostat/web/products-datasets/-/prc_ppp_ind&lang=en.

Fierro, I., Ochoa, R., Yánez, J. L., Valderrama, J. C. & Álvarez, F. J. (2008). Mortalidad y mortalidad prematura relacionadas con el consumo de alcohol en España entre 1999 y 2004. *Medicina Clínica, 131*, 10-13. doi:10.1157/13123036.

Global Burden of Disease. (2018a). Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet, 392*, 1015-1035. doi:10.1016/S0140-6736(18)31310-2.

Global Burden of Disease. (2018b). Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet, 392*, 1923-1994. doi:10.1016/S0140-6736(18)32225-6.

Gmel, G., Shield, K. D. & Rehm, J. (2011). Developing a method to derive alcohol-attributable fractions for HIV/AIDS mortality based on alcohol's impact on adherence to antiretroviral medication. *Population Health Metrics 9*, 5. doi:10.1186/1478-7954-9-5.

Institute for Health Metrics and Evaluation. (2020). *GBD Results Tool.* http://ghdx.healthdata.org/gbd-results-tool.

Instituto Nacional de Estadística. (2019a). *Encuesta Nacional de Salud. Microdatos.* https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176783&menu=resultados&secc=1254736195295&idp=1254735573175.

Instituto Nacional de Estadística. (2019b). *INEbase. Servicios. Hosteleria y turismo.* https://www.ine.es/dyngs/INEbase/es/categoria.htm?c=Estadistica_P&cid=1254735576863.

Instituto Nacional de Estadística. (2019c). *INEbase. Demografía y población. Cifras de población y censos demográficos. Cifras de población.* https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176951&menu=ultiDatos&idp=1254735572981.

Instituto Nacional de Estadística. (2020). *INEbase Sociedad. Salud. Estadística de defunciones según la causa de muerte. Resultados. 2020.* https://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=1254736176780&menu=resultados&idp=1254735573175#!tabs-1254736194710.

Instituto Nacional de Toxicología y Ciencias Forenses. (2019). *Memorias. Víctimas mortales en accidentes de tráfico.* https://www.mjusticia.gob.es/cs/Satellite/Portal/va/ministerio/organismos-ministerio-justicia/instituto-nacional/memorias.

Jones, L. & Bellis, M. A. (2013). *Updating England-Specific Alcohol-Attributable Fractions.* http://www.cph.org.uk/wp-content/uploads/2014/03/24892-ALCOHOL-FRACTIONS-REPORT-A4-singles-24.3.14.pdf.

Jones, L., Bellis, M. A., Dedman, D., Sumnal, H. & Tocke, C. (2008). *Alcohol-attributable fractions for England. Alcohol-attributable mortality and hospital admissions.* http://www.nwph.net/nwpho/publications/alcoholattributablefractions.pdf.

Kehoe, T., Gmel, G., Shield, K. D., Gmel, G. & Rehm, J. (2012). Determining the best population-level alcohol consumption model and its impact on estimates of alcohol-attributable harms. *Population Health Metrics, 10*, 6. doi:10.1186/1478-7954-10-6.

Landberg, J. & Norstrom, T. (2011). Alcohol and homicide in Russia and the United States: A comparative analysis. *Journal of Studies on Alcohol and Drugs, 72*, 723-730. doi:10.15288/jsad.2011.72.723.

Mann, K., Aubin, H. J. & Witkiewitz, K. (2017). Reduced drinking in alcohol dependence treatment, what is the evidence? *European Addiction Research, 23*, 219-230. doi:10.1159/000481348.

Marmet, S., Rehm, J. & Gmel, G. (2016). The importance of age groups in estimates of alcohol-attributable mortality: Impact on trends in Switzerland between 1997 and 2011. *Addiction, 111*, 255-262. doi:10.1111/add.13164.

Marmet, S., Rehm, J., Gmel, G., Frick, H. & Gmel, G. (2014). Alcohol-attributable mortality in Switzerland in 2011--age-specific causes of death and impact of heavy versus non-heavy drinking. *Swiss Medical Weekly, 144*, w13947. doi:10.4414/smw.2014.13947.

Meier, P. S., Meng, Y., Holmes, J., Baumberg, B., Purshouse, R., Hill-McManus, D. & Brennan, A. (2013). Adjusting for unrecorded consumption in survey and per capita sales data: Quantification of impact on gender- and age-specific alcohol-attributable fractions for oral and pharyngeal cancers in Great Britain. *Alcohol and Alcoholism, 48*, 241-249. doi:10.1093/alcalc/agt001.

Ministerio de Sanidad, Consumo & Bienestar Social. (2019). *Banco de datos.* https://www.mscbs.gob.es/estadEstudios/estadisticas/bancoDatos.htm.

Norstrom, T. & Skog, O. J. (2001). Alcohol and mortality: Methodological and analytical issues in aggregate analyses. *Addiction, 96 (Suppl 1)*, S5-S17. doi:10.1080/09652140020021143.

Organización Médica Colegial y Ministerio de Sanidad y Consumo. (2006). *Guía de buena práctica clínica en uso y abuso de alcohol.* http://www.msssi.gob.es/alcoholJovenes/docs/guiaBPCusoabusoAlcohol07.pdf.

Rehm, J., Baliunas, D., Borges, G. L., Graham, K., Irving, H., Kehoe, T.,...Taylor, B. (2010a). The relation between different dimensions of alcohol consumption and burden of disease: An overview. *Addiction, 105*, 817-843. doi:10.1111/j.1360-0443.2010.02899.x.

Rehm, J., Gmel, G. E., Sr., Gmel, G., Hasan, O. S. M., Imtiaz, S., Popova, S.,...Shuper, P. A. (2017). The relationship between different dimensions of alcohol use and the burden of disease-an update. *Addiction, 112*, 968-1001. doi:10.1111/add.13757.

Rehm, J., Kehoe, T., Gmel, G., Stinson, F., Grant, B. & Gmel, G. (2010b). Statistical modeling of volume of alcohol exposure for epidemiological studies of population health: The US example. *Population Health Metrics, 8*, 3. doi:10.1186/1478-7954-8-3.

Rehm, J., Klotsche, J. & Patra, J. (2007). Comparative quantification of alcohol exposure as risk factor for global burden of disease. *International Journal of Methods in Psychiatric Research, 16*, 66-76. doi:10.1002/mpr.204.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y. & Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet, 373*, 2223-2233. doi:10.1016/S0140-6736(09)60746-7.

Rehm, J., Patra, J. & Popova, S. (2006). Alcohol-attributable mortality and potential years of life lost in Canada 2001: Implications for prevention and policy. *Addiction, 101,* 373-384. doi:10.1111/j.1360-0443.2005.01338.x.

Rehm, J., Rehm, M. X., Shield, K. D., Gmel, G. & Gual, A. (2013). Alcohol consumption, alcohol dependence and related harms in Spain, and the effect of treatment-based interventions on alcohol dependence. *Adicciones, 25*, 11-18.

Rehm, J., Shield, K. D., Rehm, M. X., Gmel, G. & Frick, U. (2012). *Alcohol consumption, alcohol dependence and attributable burden of disease in Europe. Potential gains from effective interventions for alcohol dependence*. http://amphoraproject.net/w2box/data/AMPHORA%20Reports/CAMH_Alcohol_Report_Europe_2012.pdf.

Rehm, J., Shield, K. D., Roerecke, M. & Gmel, G. (2016). Modelling the impact of alcohol consumption on cardiovascular disease mortality for comparative risk assessments: An overview. *BMC. Public Health, 16*, 363. doi:10.1186/s12889-016-3026-9.

Rey, G., Boniol, M. & Jougla, E. (2010). Estimating the number of alcohol-attributable deaths: Methodological issues and illustration with French data for 2006. *Addiction, 105*, 1018-1029. doi:10.1111/j.1360-0443.2010.02910.x.

Rodríguez-Martos, D. A., Gual, S. A. & Llopis Llácer, J. J. (1999). The "standard drink unit" as a simplified record of alcoholic drink consumption and its measurement in Spain. *Medicina Clínica, 112*, 446-450.

Roerecke, M. & Rehm, J. (2013). Alcohol use disorders and mortality: A systematic review and meta-analysis. *Addiction, 108*, 1562-1578. doi:10.1111/add.12231.

Samokhvalov, A. V., Irving, H. M. & Rehm, J. (2010). Alcohol consumption as a risk factor for atrial fibrillation: A systematic review and meta-analysis. *European Journal of Cardiovascular Prevention & Rehabilitation, 17*, 706-712. doi:10.1097/HJR.0b013e32833a1947.

Sherk, A., Stockwell, T., Rehm, J., Dorocicz, J. & Shield, K. D. (2017). *The International Model of Alcohol Harms and*

Policies (InterMAHP). Version 1.0: December 2017. www.intermahp.cisur.ca.

Sherk, A., Thomas, G., Churchill, S. & Stockwell, T. (2020). Does drinking within low-risk guidelines prevent harm? Implications for high-income countries using the international model of alcohol harms and policies. *Journal of Studies on Alcohol and Drugs, 81*, 352-361.

Sociedad Española de Medicina de Familia y Comunitaria. (2005). *Guía rápida para abordar el abuso de alcohol*. https://www.semfyc.es/pfw_files/cma/Informacion/modulo/documentos/abuso-alcohol.pdf.

Sordo, L., Barrio, G., Bravo, M. J., Villalbí, J. R., Espelt, A., Neira, M. & Regidor, E. (2016). Estimating average alcohol consumption in the population using multiple sources: The case of Spain. *Population Health Metrics, 14*, 21. doi:10.1186/s12963-016-0090-4.

Stockwell, T., Zhao, J., Panwar, S., Roemer, A., Naimi, T. & Chikritzhs, T. (2016). Do "moderate" drinkers have reduced mortality risk? A systematic review and meta-analysis of alcohol consumption and all-cause mortality. *Journal of Studies on Alcohol and Drugs, 77*, 185-198. doi:10.15288/jsad.2016.77.185.

Stockwell, T., Zhao, J., Sherk, A., Rehm, J., Shield, K. & Naimi, T. (2018). Underestimation of alcohol consumption in cohort studies and implications for alcohol's contribution to the global burden of disease. *Addiction, 113*, 2245-2249. doi:10.1111/add.14392.

Trias-Llimós, S., Martikainen, P., Mäkelä, P. & Janssen, F. (2018). Comparison of differents approaches for estimating age-specific alcohol-attributable mortality: The cases of France and Finland. *PLoS One, 13*: e0194478. doi:10.1371.journal.pone.0194478.

Trolldal, B. (2001). Alcohol sales figures in 15 European countries: Corrected for consumption abroad and tax-free purchases. *Nordic Studies on Alcohol, 18*, 71-81. doi:10.1177/145507250101801S02.

TURESPAÑA. (2019). *Estadísticas turísticas*. http://estadisticas.tourspain.es/es-ES/turismobase/Paginas/default.aspx.

Villarroel, M. A., Clarke, T. C. & Schoenborn, C. A. (2016). *Tables of adult health behaviors, alcohol use: National Health Interview Survey, 2011–2014., from National Center for Health Statistics*. Center for Disease Control and Prevention (CDC). https://ftp.cdc.gov/pub/Health_Statistics/NCHs/NHIS/SHS/2011-2014_AHB_Table_ALC-1.pdf.

World-Bank. (2019). *International Comparison Program. ICP 2011*. https://datacatalog.worldbank.org/dataset/international-comparison-program-2011.

World Health Organization. (2000). *International guide for monitoring alcohol consumption and related harm. WHO/MSD/MSB/00.4*. http://whqlibdoc.who.int/hq/2000/who_msd_msb_00.4.pdf.

World Health Organization. (2009). *Global health risks. Mortality and burden of disease attributable to selected major risks. WA 105*. Retrieved at http://www.who.int/healthinfo/global_burden_disease/GlobalHealthRisks_report_full.pdf.

World Health Organization. (2018a). *Methods and data sources for global burden of disease estimates, 2000-2016*. https://www.who.int/healthinfo/global_burden_disease/GlobalDALY_method_2000_2016.pdf.

World Health Organization. (2018b). *Global status report on alcohol and health*. https://www.who.int/substance_abuse/publications/alcohol/en/.

World Health Organization. (2020). *Global Information System on Alcohol and Health (GISAH)*. http://apps.who.int/gho/data/node.gisah.GISAH?showonly=GISAH.

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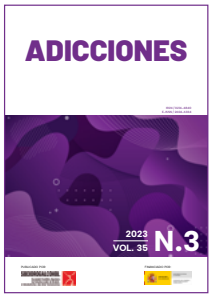

ORIGINAL

An approach to the evaluation of the potency of cannabis resin in Madrid: A health hazard?

Aproximación a la evaluación de la potencia de la resina de cannabis en Madrid: ¿Un riesgo para la salud?

Inmaculada Santos-Álvarez*; Pilar Pérez-Lloret*; Juncal González-Soriano*; Manuel Pérez-Moreno*.

* Departamento de Anatomía y Embriología, Sección Departamental en Facultad de Veterinaria. Universidad Complutense de Madrid, Madrid. España.

Abstract

The present study investigates the concentration of Delta (9)-tetrahidrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN) in 60 samples of cannabis resin acquired on the streets of Madrid region and its potential danger to consumers' health. Additionally, we study the possible correlation between the potency of samples and their organoleptic characteristics. The analysis of cannabinoids was carried out using a high performance liquid chromatography (RP-HPLC-UV). To classify samples, a strength scale based on THC content was established. THC content in 76.7% of the samples was higher than 15%. This potency allows these samples to be classified as Schedule I or drugs with "unacceptable risk" for human health. THC content in 36.7% of the samples was 28.8% on average, which means very high potency. The mean CBD content was 5%, while the correlation between the CBD/THC ratio and potency was negative. The mean content of CBN was 1.74% and the CBN/THC ratio also showed a negative correlation in respect to potency. When investigating the possible correlation between sample potency and organoleptic characteristics, those samples which simultaneously presented sticky texture, high elasticity and light brown colour had very high potency, with an average THC content of 28.7%. Our study shows that the THC content of most of the cannabis that can be purchased in Madrid region is over 15% and poses a health hazard. Additionally, we demonstrate for the first time that only those samples with very high potency can be directly associated with certain organoleptic characteristics.

Keywords: cannabis resin, cannabis potency, THC, CBD, CBN

Resumen

El presente estudio investiga la concentración de Delta(9)-tetrahidrocannabinol (THC), cannabidiol (CBD) y cannabinol (CBN) en 60 muestras de resina de cannabis adquiridas en las calles de Madrid y su potencial riesgo para la salud del consumidor. Adicionalmente, estudiamos la posible asociación entre la potencia de las muestras y sus características organolépticas. El análisis de cannabinoides se llevó a cabo mediante cromatografía líquida de alta resolución (RP-HPLC-UV). Atendiendo al contenido en THC se estableció una escala de potencia para clasificar las muestras. El 76,7% de las muestras tenía un contenido en THC superior al 15%, esta potencia las cataloga como drogas de Grado I con "riesgo inaceptable" para la salud. El 36,7% de las muestras presentaron un contenido medio en THC del 28,8% (potencia muy alta). El contenido medio en CBD fue del 5% y el de CBN 1,74%; ambas ratios, CBD/THC y CBN/THC, mostraron una correlación negativa con la potencia. Al investigar la posible asociación entra potencia y características organolépticas, se observó que las muestras que presentaban a la vez una textura pegajosa, una elasticidad alta y un color marrón claro, tenían una potencia muy alta, con un contenido medio en THC del 28,7%. Nuestro estudio muestra que el contenido en THC de la mayoría de la resina de cannabis que puede adquirirse en Madrid es superior al 15% y supone un elevado riesgo para la salud. Adicionalmente, demostramos por primera vez que solo aquellas muestras con una potencia muy alta pueden asociarse directamente con ciertas características organolépticas.

Palabras clave: resina de cannabis, potencia del cannabis, THC, CBD, CBN

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■ **Send correspondence to:**
Inmaculada Santos Álvarez. Departamento de Anatomía y Embriología, Sección Departamental en Facultad de Veterinaria. Universidad Complutense de Madrid. Avda. Puerta de Hierro s/n, 28040 - Madrid, España. Email: inmasant@ucm.es

The increase in adverse effects caused by cannabis use has generated growing concern in recent years. Although illegal in most countries, this drug is the most widely used drug of abuse in the world (United Nations Office on Drugs and Crime [UNODC], 2018). Indeed, in Spain, cannabis is the illicit substance which causes the highest number of first admissions for treatment in outpatient centres, representing 40.7% of these, according to statistics on admissions for psychoactive substance use (Delegación del Gobierno de España para el Plan Nacional sobre Drogas, 2019). Likewise, ER statistics on psychoactive substance use show that cannabis is linked to over 40.1% of such emergency cases (Delegación del Gobierno de España para el Plan Nacional sobre Drogas, 2019).

In 2017, the prevalence of cannabis use among young adults (aged 15 to 34 years) in Spain was 18.3%, with a prevalence among students aged 15-16 years of 27%, a value much higher than the European average of 16% for this age group (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2019). Among the 35 countries included in this study, Cyprus and Greece can be highlighted as having the lowest prevalences among 15- to 16-year-old students (7% and 9%, respectively), with 15% in Portugal, and the highest prevalences in Italy (27%) and France, at 31%.

Cannabis contains more than 500 different compounds, of which approximately 100 are cannabinoids. Of the latter, the most relevant, given both their great presence and the effects they produce on the individual, are Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN); for this reason, they are also the compounds whose content is usually analysed in most studies (Dujourdy & Besacier, 2017; Niesink, Rigter, Koeter & Brunt, 2015; Pijlman, Rigter, Hoek, Goldschmidt & Niesink, 2005; Potter, Hammond, Tuffnell, Walker & Di Forti, 2018; Zamengo, Frison, Bettin & Sciarrone, 2014).

The active components of cannabis mimic the effects of endogenous cannabinoids, activating specific cannabinoid receptors, in particular CB1, which is predominantly found in the central nervous system (Bridgeman & Abazia, 2017; Matsuda, Lolait, Brownstein, Young & Bonner, 1990), and CB2, located mainly in cells related to immune function (Abrams & Guzman, 2015). Both are protein-based membrane receptor and associated with the G protein (Matsuda et al., 1990; Ramos Atance & Fernandez Ruiz, 2000).

Being the most important active ingredient responsible for the psychoactive properties of the plant (Casajuana Köguel, López-Pelayo, Balcells-Olivero, Colom & Gual, 2018; Gaoni & Mechoulam, 1964; Waller, 1971), THC is also the main reason behind the recreational use of cannabis derivatives. The content of this substance is expressed as a percentage of product weight and determines the potency of cannabis (Niesink & van Laar, 2013). High THC content can increase anxiety, depression and psychotic symptoms (Di Forti et al., 2009; Hall & Degenhard, 2009). Likewise, recent research indicates that the occasional use of cannabis with high THC content impairs cognitive capacity, in particular memory and emotional processing (Colizzi & Bhattacharyya, 2017).

However, the effects of cannabis on humans depend not only on THC content, but also on the amount of other substances and the ratio between them. One of these compounds is CBD, with the CBD/THC ratio being very important (Casajuana et al., 2018; Colizzi et al., 2017; Lafaye, Karila, Blecha & Benyamina, 2017; Niesink et al., 2013). Previous studies have shown that there is a direct relationship between increasing potency (THC) and decreasing CBD concentration (ElSohly et al., 2016; Potter et al., 2018). Logically, this circumstance can have serious implications on the health of consumers. Although CBD lacks psychoactive effects, it is the second most important active ingredient in the composition of cannabis. It provides a sedative, relaxing, antiemetic and analgesic effect, which favours its therapeutic use (Lleonart, 2018). CBD is believed to counteract some of the harmful effects of THC, at least in part (Niesink et al., 2013), as it promotes relaxation and possibly even provides some antipsychotic effect. Some evidence, still limited, suggests that the administration of CBD can improve cognitive aspects in cannabis users, although not in individuals with neuropsychiatric disorders (Colizzi et al., 2017). Consequently, lower CBD concentrations reduce the protective effect generated by this active ingredient, in contrast to the damage induced by THC in emotional processing and memory (Colizzi et al., 2017).

For its part, CBN is a compound derived from the oxidation of THC, as a result of the passage of time or inadequate storage conditions. Since CBN is not present in the fresh product (Ross & ElSohly, 1997), it is considered a primary product of THC degradation, with a psychoactive effect up to ten times lower. These characteristics mean that the relationship between CBN and THC concentrations (the CBN/THC ratio) is used as an indicator of the freshness of the cannabis samples or their "age" (Ross et al., 1997).

In Spain, cannabis resin (or hashish) is an illegal drug of abuse which can be acquired mainly through small-scale street sales. This type of product is clearly not subject to any quality control, nor is its potency monitored routinely. It must also be taken into account that hashish consumers consider some of external characteristics, such as texture, elasticity and colour, as quality indicators in identifying products with greater potency (i.e. with higher THC content). Thus, in the opinion of users, brown samples, with great elasticity and a sticky texture, would theoretically be of the best quality.

The street sale of cannabis in the Madrid region has been the subject of a previous study, which analysed the degree of adulteration and contamination of samples (Pérez-Moreno, Pérez-Lloret, González-Soriano & Santos-Álvarez, 2019). However, neither the potency of this type of sample nor the possible relationship between potency and some of the organoleptic characteristics valued by consumers, such as texture, elasticity and colour, was determined. This study therefore extends our previous work, investigating the concentration of the three main active ingredients, that is, THC, CBD and CBN of the cannabis resin sold on the streets in the Madrid area and its potential danger to the health of users. We also study the possible association between the potency of the samples and their organoleptic characteristics.

Materials and methods

Samples

A total of 60 samples of cannabis resin acquired on the street were analysed. The sampling, at a rate of 5 samples per month over the 12 months of the year, was designed on the one hand to minimize possible seasonal variation and, on the other, to try to guarantee that samples came from different consignments. The samples were collected in different localities of the Community of Madrid (Madrid capital (n = 17), northern zone of the region (n = 10), southern zone (n = 15), eastern zone (n = 10) and western zone (n = 8)) to achieve as representative a population as possible. Although the number of samples may appear somewhat small, it can serve as a first approximation in the study; the difficulty of obtaining samples whose sale is not legal should also be taken into account. After purchase, the samples were stored in sterile bags and stored frozen at -40ºC until subsequent analysis, carried out in a period not exceeding 15 days after acquisition. The first step consisted in assessing the organoleptic characteristics of interest in this study in each case, that is, colour, elasticity and texture, and subsequently to analyse cannabinoid content: Delta (9) -tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN). Content was expressed as a percentage of cannabis resin weight. The mean weight of the samples was 6.9 g (range: 4.9 - 9.9 g). Prices ranged from 20 to 40 euros. This is not a minor detail since it means that the purchase of cannabis in the Community of Madrid can be accessible to practically any group.

Organoleptic characteristics

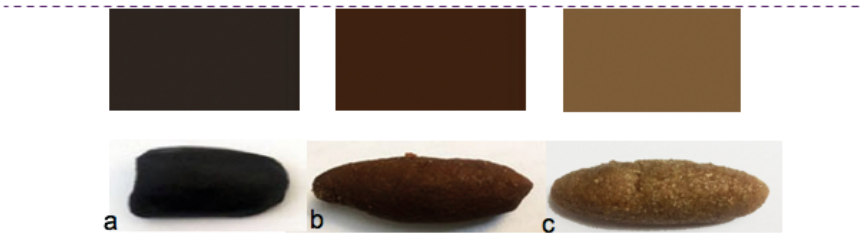
To define colour, three shades of brown were used: dark, medium and light. To minimize the degree of subjectivity in colour appreciation as far as possible, each sample was compared to the colour scale shown in Figure 1. Elasticity was also classified into three levels: zero, medium or high. Zero elasticity describes when the sample broke with minimum traction; average if, when bending the sample, it was possible to join both ends but then fractured when returning to its initial position; and high if, after bending it and joining both ends, it was possible to return it to the initial position without breaking. Texture was considered sticky if, after slight pressure, the sample adhered to the glove fingers or dry if the sample did not adhere at all.

Cannabinoid analysis by RP-HPLC-UV

The active components of the samples (THC, CBN, CBD), as well as their acidic or inactive forms (THC-A and CBD-A), were analysed according to the method recommended by the American Herbal Pharmacopeia (ElSohly & Chandra, 2013). The method consists of three steps: 1) extraction of the compounds with methanol, 2) quality control of the method, and 3) identification and quantification of the compounds using chromatographic techniques.

1. To extract the compounds, 5 ml of methanol (99% LC methanol, Sigma-Aldrich) was added to 50 mg from each sample, previously ground with an electric grinder for 20 seconds at 3500 rpm. This mixture was sonicated in an ultrasound bath for 15 minutes before sieving with a 0.45 µm pore diameter filter. The extract was analysed by chromatography at this initial concentration and at the following dilutions: a) 200 µl

Figure 1
Colour scale used to classify cannabis resin samples: a) dark brown; b) medium brown; c) light brown



of the initial solution diluted to 1 ml with methanol; and b) 16 µl of the starting solution diluted to 1 ml with methanol.

The standard samples of active ingredients, or reference standard cannabinoids (purity = 99%, Lipomed AG) for calibration were: Δ9-THC (1 mg/ml in ethanol and 50 mg/ml in ethanol), CBN, CBD, THC-A and CBD-A (1 mg/ml in ethanol).

2. For quality control of the method, several parameters were used: to check the linearity of the chromatographic response (r2 ≥ 0.99), the correlation coefficient of each extract and its dilutions were assessed; limit of quantification (LOQ) for the compounds was 0.1 µg/ml; daily relative standard deviation (intra- and inter-day) (% RSD) for retention times and areas under peaks was ≤ 5%; finally, sample recovery was ≥ 95%.
3. Cannabinoid analysis by RP-HPLC-UV: analysis of THC, CBD and CBN was carried out using a high performance liquid chromatography system with a column oven (Jasco Co-2060 Plus Intelligent Column Thermostat), a quaternary low pressure gradient pump (Jasco pump PU 2089 Plus Intelligent) and an automatic sample injection system (Jasco AS-2057 Plus Intelligent Sampler), coupled with an ultraviolet-visible detector (Jasco UV-2075 Plus Intelligent UV/Vis Detector). The chromatographic separation of the compounds was carried out using a C18 Agilent column (150 x 46 mm, 5 µm). For each sample, 10 µl of the extract at the initial concentration, as well as of the two dilutions, were injected into the system. Throughout the test, elution from the column was achieved by a linear elution gradient (total time 20 minutes) using a mixture of water (LC grade, Panreac) and acetonitil (LC grade, Sigma-Aldrich) in a 90% proportion: 10% to a final mixture in the ratio 10%: 90%. The column oven temperature was kept at 35°C.

The total concentration of THC and CBD was the sum of their acidic forms plus their decarboxylated forms. CBN, as a product obtained by the degradation of THC, was generated in a neutral fashion (Fig. 2).

Assessment of sample potency

The THC richness scale published by the Instituto Nacional de Toxicología y Ciencias Forenses [INTCF] (2013) was used to assess the potency of the samples. The cannabis resin was classified as: very high potency (THC > 25%); high potency (20% < THC ≤ 25%); medium potency (15% < THC ≤ 20%); low potency (10% < THC ≤ 15%); and very low potency (5% < THC ≤ 10%).

Statistical analysis

All data were registered in a database using the Excel program. Statistical analysis was performed with the SAS 9.4 program.

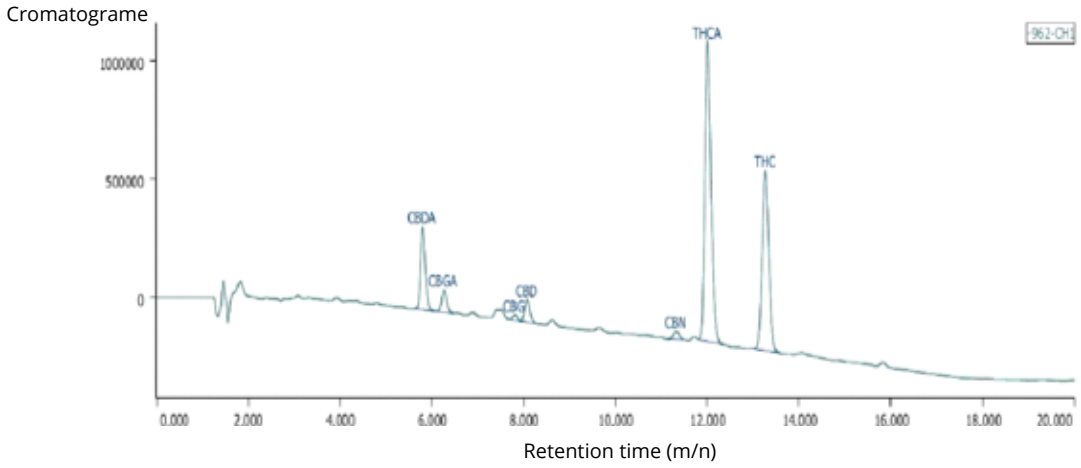
Qualitative variables (colour, elasticity and texture) are shown in distribution tables with frequencies and percentages. For quantitative variables (concentration of THC, CBD and CBN), the number of cases (n), the mean, the standard deviation (SD) and the minimum and maximum values were recorded.

Qualitative variables were compared using Pearson's chi square (comparison of percentages) or Fisher's exact test (when frequencies were too low for any category).

The relationship between dichotomous qualitative variables (texture: dry or sticky) and ordinal variables (e.g., elasticity: zero = 0, medium = 1, high = 2; potency scale) was assessed using the Wilcoxon rank sum test.

The relationship between qualitative variables with more than two levels (e.g.: colour) and ordinal variables was assessed using the non-parametric Kruskal-Wallis test. If significant, a nonparametric multiple comparisons test was used.

Figure 2
Chromatogram of a real sample analysed



Given the significant lack of fit to the normal distribution produced by the numerical variables studied, the relationship between qualitative and numerical variables was assessed with the same tests as for the ordinal ones (Wilcoxon and Kruskal-Wallis).

Finally, to determine the relationship between quantitative and ordinal variables (e.g.: power scale), the Spearman rank correlation coefficient was calculated.

A 95% confidence level was established in all analyses, i.e., statistical significance was found at $p < 0.05$.

Results

The distribution of the cannabis resin samples on the potency scale, as well as their average THC, CBD and CBN content and respective CBD/THC and CBN/THC ratios, are shown in Table 1. As can be seen, the average THC content of 76.7% of the samples was higher than 15%, distributed as follows: 36.7% of the samples had very high potency (n = 22), 20% (n = 12) were potent, while another 20% (n = 12) were considered of medium strength. Regarding CBD content, it is interesting to note that those samples with very high potency were also those that had the most CBD, up to an average of 6.1%; conversely, those samples with very low potency were those containing the least CBD, with an average value of 3.1%. However, the CBD/THC ratio had a negative correlation with respect to potency. Regarding CBN content, the most potent samples were those with a lower average value, specifically 0.68%, while the highest amount, up to 4%, was directly related to the least potent. The CBN/THC ratio, which refers to the freshness of the sample, was also negatively correlated with respect to sample strength, with a range from 0.024 (in very high potency samples) to 0.490 (in very low potency samples) (Table 1).

Table 2 relates sample strength with each of the organoleptic characteristics of interest in this study: texture, elasticity and colour. Most of the samples with a sticky texture (56.7%), high elasticity (94.4%) and light brown colour (81.2%) were found to be highly potent. Furthermore, no samples with high elasticity and light brown colour had very low potency; in the case of texture, we did find a sample with a sticky texture and very low potency. However, in Table 2 it is also striking that a high percentage of samples with dry texture, zero or medium elasticity and dark or medium brown colour presented high or medium potency. On the other hand, when analysing the average THC content of the samples based on their organoleptic characteristics (Table 3), it was observed that the samples with the three characteristics, sticky texture, high elasticity and light brown colour, had a medium THC content of 23.1%, 28.1% and 27%, respectively, higher than that detected in the rest of the samples with other characteristics. As can be seen, the average CBD content of the samples with these three characteristics was also higher than that found in the rest of the samples with other organoleptic characteristics (except for texture). Another interesting fact is that in the CBD/THC ratio, when the three organoleptic characteristics of interest are considered, no statistically significant differences are observed. However, when the CBN/THC ratio is calculated, only in the case of texture does the value turn out to be not significant.

Those samples that simultaneously met the three characteristics (sticky texture, high elasticity and light brown colour, n = 11) had higher THC content (28.7%) and lower CBN content (0.89%) than the rest of samples (n = 49; THC 19.2% and CBN 1.93%), differences which were statistically significant (Table 4).

Table 1
Average content (%) of THC, CBD, CBN, and CBD/THC and CBN/THC ratios of the cannabis resin samples as a function of the potency scale

Potency nº (%)	THC (%)		CBD (%)		CBN (%)		ratio CBD/ THC		ratio CBN/ THC	
	Mean ± DE	Range	Mean ± DE	Range	Mean ± DE	Range	Mean ± DE	Range	Mean ± DE	Range
Very high 22 (36.7)	28.8 ± 2.2	25.3 – 33.0	6.1 ± 1.0	4.2 – 8.8	0.68 ± 0.6	0.2 – 3.2	0.21 ± 0.0	0.2 – 0.3	0.024 ± 0.02	0.006 – 0.107
High 12 (20)	22.8 ± 1.9	20.0 – 25.0	5.2 ± 1.6	3.0 – 8.0	1.51 ± 0.7	0.2 – 2.3	0.23 ± 0.1	0.2 – 0.4	0.069 ± 0.04	0.008 – 0.115
Medium 12 (20)	18.3 ± 1.1	15.0 – 19.2	4.6 ± 1.3	3.0 – 7.0	2.32 ±1.0	0.7 – 3.8	0.25 ± 0.1	0.2 – 0.4	0.129 ± 0.06	0.037 – 0.211
Low 10 (16.7)	11.7 ± 1.0	10.2 – 14.0	3.7 ± 0.9	2.3 – 5.0	2.73 ± 0.8	1.8 – 4.3	0.32 ± 0.1	0.2 – 0.5	0.235 ± 0.07	0.167 – 0.391
Very low 4 (6.7)	8.4 ±1.4	6.6 – 9.5	3.1 ± 1.4	1.7 – 4.6	.00 ± 0.6	3.5 – 4.5	0.36 ± 0.2	0.2 – 0.5	0.490 ± 0.14	0.368 – 0.682
Average	21.3 ± 7.3	6.6 – 33.0	5.0 ± 1.5	1.7 – 8.8	1.74 ± 1.2	0.2 – 4.5	0.25 ± 0.1	0.2 – 0.5	0.120 ± 0.14	0.006 – 0.682

Nota. THC: Δ9-tetrahydrocannabinol; CBD: cannabidiol; CBN: cannabinol. Potency scale: very high potency: THC > 25%; high potency: 20%> THC ≤ 25%; medium potency: 15%> THC ≤ 20%; low potency 10% > THC ≤ 15%; very low potency: 5% > THC ≤ 10%.

Discussion

In this study, we analysed the potency of cannabis resin available on the streets in the Madrid region. The collection of cannabis resin samples was spread across a whole year and across all areas of the region to ensure that the samples did not come from the same consignment or the same vendor. We consider that this sampling can provide a fairly good idea of the potency of cannabis resin consumed in the Madrid region. It should be noted that this is the first study of its kind carried out in the Autonomous Community of Madrid.

To this end, the quality scale published by the INTCF (2013) was used as a yardstick. However, rather than the term "THC concentration", for this study the term

Table 2
Distribution of samples (number and percentage) of cannabis resin on the potency scale according to their organoleptic characteristics

Organoleptic characteristics (n)	Potency n (%)					P value
	very high	high	medium	low	very low	
Texture						
dry (30)	5 (16.7)	9 (30)	10 (33.3)	3 (10)	3 (10)	<0.05
sticky (30)	17 (56.7)	3 (10)	2 (6.7)	7 (23.3)	1 (3.3)	
Elasticity						
zero (22)	2 (9.1)	6 (27.3)	8 (36.4)	3 (13.6)	3 (13.6)	
medium (20)	3 (15)	6 (30)	4 (20)	6 (30)	1 (5)	<0.0001
high (18)	17 (94.4)	0	0	1 (5.6)	0	
Colour						
dark brown (26)	4 (15.4)	6 (23.1)	6 (23.1)	6 (23.1)	4 (15.4)	
medium brown (18)	5 (27.8)	5 (27.8)	4 (22.2)	4 (22.2)	0	<0.0005
light brown (16)	13 (81.2)	1 (6.2)	2 (12.5)	0	0	

Note. THC: Δ9-tetrahydrocannabinol. Very high potency: THC > 25%; high potency: 20% > THC ≤ 25%; medium potency: 15% > THC ≤ 20%; low potency 10% > THC ≤ 15%; very low potency: 5% > THC ≤ 10%.

Table 3
Comparison of the mean content (%) of THC, CBD, CBN and ratios CBD/THC and CBN/THC of the cannabis resin samples according to their organoleptic characteristics

Characteristics organoleptic (n)	THC (%)		CBD (%)		CBN (%)		ratio CBD/ THC			
	Mean ± DE	p	Mean ± DE	p	Mean ± DE	p	Mean ± DE	p	Mean ± DE	p
Texture										
dry (30) sticky (30)	19.5 ± 6.1 23.1 ± 8.0	<0.05	4.80 ± 1.46 5.29 ± 1.62	NS	1.84 ± 1.14 1.64 ± 1.34	NS	0.26 ± 0.09 0.25 ± 0.08	NS	0.13 ± 0.14 0.11 ± 0.13	NS
Elasticity										
null (22) medium (20) high (18)	18.1 ± 6.2 18.6 ± 6.2 28.1 ± 4.8	<0.0001a <0.0001b	4.42 ± 1.31 4.84 ± 1.67 6.02 ± 1.22	<0.005[a] <0.05[b]	2.26 ± 1.15 1.93 ± 1.24 0.89 ± 0.90	<0.0005a <0.01b	0.26 ± 0.07 0.28 ± 0.11 0.22 ± 0.05	NS	0.17 ± 0.16 0.14 ± 0.13 0.04 ± 0.07	<0.0005a <0.005b
Colour										
dark brown (26) medium brown (18) light brown(16)	18.0 ± 7.5 20.9 ± 6.5 27.0 ±3.9	<0.0005c <0.01d	4.26 ± 1.30 5.47 ± 1.54 5.83 ± 1.41	<0.005[c]	2.42 ± 1.30 1.53 ± 0.93 0.86 ± 0.75	<0.0001c	0.26 ± 0.09 0.28 ± 0.09 0.22 ± 0.05	NS	0.19 ± 0.17 0.09 ± 0.07 0.03 ± 0.03	<0.00005c

Note. THC: Δ9-tetrahydrocannabinol; CBD: cannabidiol; CBN: cannabinol. a: High elasticity versus zero elasticity; b: high elasticity versus medium elasticity; c: dark brown colour versus light brown colour; d: medium brown colour versus light brown colour.

Table 4
Comparison of the average content (%) of THC, CBD, CBN and ratios CBD/THC and CBN/THC between the groups of cannabis resin samples

Groups nº (%)	THC (%)		CBD (%)		CBN (%)		CBD/THC ratio		CBN/THC ratio	
	Mean ± DE	ratio	Mean ± DE	ratio	Mean ± DE	ratio	Mean ± DE	ratio	Mean ± DE	ratio
Group 1 11 (18.3)	28.7 ± 2.2[a]	25.5 – 33.0	6.0 ± 1.1[b]	4.2 – 8.0	0.89 ± 0.86b	0.30 – 3.20	0.210 ± 0.047	0.150 – 0.308	0.031 ± 0.029[c]	0.009 – 0.107
Group 2 49 (81.7)	19.6 ± 7.0	6.6 – 33.0	4.8 ± 1.6	1.7 – 8.8	1.93 ± 1.24	0.20 – 4.50	0.262 ± 0.088	0.150 – 0.500	0.140 ± 0.141	0.006 – 0.682

Note. Group 1: samples with simultaneously sticky texture, high elasticity and light brown colour. Group 2: other samples. THC: Δ9-tetrahydrocannabinol; CBD: cannabidiol; CBN: cannabinol. a: $p < 0.0005$; b: $p < 0.05$; c: $p < 0.005$.

"potency" was preferred, which in our opinion better expresses the strength, despite the negative connotations in this case, of a sample high in THC. The samples were classified according to their content of this compound as having very high, high, medium, low and very low potency.

When analysing the concentrations of THC, CBD and CBN, it is very important to take into account the type of cannabis derivative under analysis (marijuana, seedless, cannabis resin, imported cannabis, national cultivation, etc.) (INTCF, 2013; Niesink et al. al., 2015; Pijlman et al., 2005; Potter et al., 2018; Zamengo et al., 2014). Given the increase in the THC content of cannabis and the greater knowledge of the risks it poses for the health of users, especially young people, it has been suggested that the forms of potent cannabis (containing over 15% THC) be reclassified as Grade I drugs, that is, drugs "with unacceptable risk" to health, thereby equating them to heroin and cocaine (Niesink et al., 2015; Van Laar, Nan der Pol & Niesink, 2016). Our study shows that the cannabis resin (or hashish) acquired on the streets of Madrid has high average THC content. It should be noted that this is not an isolated value, but rather reflects very similar figures found in previous studies carried out in other regions of Spain (Asociación Vasca de Personas Usuarias de Drogas para la Reducción de Riesgos [Ai Laket], 2016; Energy Control, 2016) or in France (Dujourdy et al., 2017), which support our results. One of our study's findings of particular relevance is that three quarters of the samples contained over 15% THC, which would put them within Group I, i.e. drugs with an "unacceptable risk" to health. Furthermore, over a third of these samples were very potent (with a THC content above 25%). These data are much higher than those found in other European countries such as Italy and the Netherlands, where the average THC content of the cannabis resin samples are reported to be 8.9% and 16.5%, respectively (Niesink et al., 2015; Zamengo et al., 2014). In other words, the cannabis that can be purchased and consumed in the Madrid area would be more harmful to consumers than that available for purchase in other countries of the European Community. However, in recent years there has been a general increase in the potency of cannabis samples (Dujourdy et al., 2017; ElSohly et al., 2016; Potter et al., 2018), and the different years in which the various studies were carried out could thus explain, at least in part, the higher THC content of the cannabis resin samples analysed in this study compared to that found in other European countries.

The adverse psychological effects induced by THC can be partially offset by the CBD content of cannabis samples (Casajuana et al., 2018; Colizzi et al., 2017; Lafaye et al., 2017; Niesink et al. 2013). When estimating the risk of psychotic effects from cannabis, it is therefore important to determine the CBD/THC ratio. It might be thought that cannabis resins with a CBD/THC ratio close to unity would be less harmful to the consumer than those with lower values. Our results indicate that the more potent a sample is, the lower its CBD/THC ratio and even samples with medium potency have a ratio far below unity. These data, added to the high THC content of the samples, suggest that the cannabis available in different parts of the Madrid area would have a very significant negative impact on the health of the regular user. We have not found studies that analyze the THC, CBD and CBN content of the cannabis resin consumed in the Madrid region, but there have been earlier studies in Spain (Ai Laket, 2016; Energy Control, 2016) that collected some similar values for hashish sold in other autonomous communities, which would confirm the high potency of cannabis sold in the country and the potential danger that this poses for Spanish users.

If the sustained use of cannabis can have very harmful effects on the health of regular users, this problem increases as the age of users decreases. Niesink et al. (2013) drew attention to the permanent psychological disorders that the recreational use of cannabis can cause in adolescents. In the case of Spain, as already described in the introduction, the prevalence of cannabis use among Spanish students aged 15 to 16 years is higher than the European average (EMCDDA, 2019). Indeed, the Spanish government's report (Delegación del Gobierno de España para el Plan Nacional sobre Drogas, 2019), based on the national system of drug addiction indicators (Sistema Estatal de Indicadores sobre Toxicomanías), found that among those aged under 18 years, cannabis was the drug responsible for almost all admissions to treatment for psychoactive substance use in outpatient centres, representing 96.6% of such admissions. Moreover, attenuated psychotic experiences have been analysed in adolescents in relation to cannabis use, with the finding that its consumption increased the risk of comorbid psychopathology (Fonseca-Pedrero, Lucas-Molina, Pérez-Albéniz, Inchausti & Ortuño-Sierra, 2020). Similar studies, also carried out in adolescents, have observed that symptoms such as depression or anxiety partially mediate between cannabis use and psychotic experiences (Bourque, Afzali, O'Leary-Barrett & Conrod, 2017; Reeves et al., 2014). However, attempts to establish an association between cannabis use and cognitive impairment in schizophrenia and first psychotic episodes have been hampered by the great disparity observed in the published results, thus preventing relevant conclusions from being reached in this regard (García Álvarez, Gomar, García-Portilla & Bobes, 2019). In short, the results of our study support the opinion of health officials that cannabis is not a harmless drug of abuse, but rather a highly dangerous substance with aggravating effects on certain groups.

CBN is a product of THC degradation. Therefore, its content in fresh cannabis is minimal. In fact, it is possible to estimate the freshness or "age" of cannabis products based on the relative concentration of CBN to THC (Ross et al.,

1997). Thus, cannabis samples with a CBN/THC ratio below 0.013 would be less than six months old, and those with a ratio between 0.04 and 0.08 would be between one and two years old (Ross et al., 1997). By this criterion, only samples with very high potency could be considered fresh in our analysis, with an estimated age of between six months and one year. High potency samples would be between one and two years old and the rest of our samples (with medium, low or very low strength) would be at least two years old. Especially significant is the fact that the samples with high and medium potency, although they could not be considered fresh, presented THC values above 15%. These data corroborate the high potency of the cannabis samples that can be obtained in the Madrid region.

Certain organoleptic characteristics of cannabis such as its colour, elasticity and texture are commonly used by consumers to make a subjective estimate of the quality (strength) of the samples, with those samples with a sticky, elastic and dark-coloured texture considered to be of best quality. However, there have not been any previous studies analysing the possible relationship between the potency of the samples and their organoleptic characteristics objectively. Our results indicate that only in the case of very highly potent samples is there an association with a sticky texture and high elasticity. Interestingly, and contrary to the general belief among consumers (*Hachís: cómo reconocer su buena calidad* [Hashish: how to recognize good quality], 2017), it is the light brown samples and not the dark coloured samples that have the highest strength. In fact, the samples that simultaneously met the three characteristics (sticky texture, high elasticity and light brown colour) had significantly higher THC content than the other samples. However, it should be noted that there was a high percentages of samples with high potency which also presented dry texture, zero elasticity and dark brown colour. Therefore, with the exception of those samples with very high potency, we cannot conclude that texture, elasticity and colour are useful characteristics to use as criteria on which to base an estimate of the quality/strength of cannabis resin.

Conclusions

The present study shows that most of the cannabis resin that can be bought in the Autonomous Community of Madrid contains over 15% THC. This finding, together with the low values of the CBD/THC ratio, shows that cannabis is not a harmless substance, and its use, both regular and occasional, represents a high health risk, especially in the case of Spanish adolescents, who use it at higher rates than in the rest of Europe. For this reason, the Spanish authorities should consider establishing systematic programs to monitor the strength of the cannabis made available to consumers and assess the negative consequences of high-potency cannabis use. Likewise, the sticky texture, high elasticity and light brown colour characteristics of the samples would only be useful for estimating the quality/strength of the cannabis resin when all three concur simultaneously.

Contributions

Inmaculada Santos-Álvarez, Pilar Pérez-Lloret, Juncal González-Soriano and Manuel Pérez Moreno designed the study. Manuel Pérez Moreno acquired and analysed the samples. Inmaculada Santos-Álvarez, Manuel Pérez-Moreno and Pilar Pérez-Lloret wrote the first draft of the manuscript. Inmaculada Santos-Álvarez and Juncal González-Soriano analysed and interpreted the data and carried out the editing and critical review of the article. All authors approved the final document.

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Conflicts of interest

The authors declare that they have no conflict of interest.

References

Abrams, D. I. & Guzman, M. (2015). Cannabis in cancer care. *Clinical Pharmacology and Therapeutics, 97*, 575-586. doi:10.1002/cpt.108.

Asociación Vasca de Personas Usuarias de Drogas para la Reducción de Riesgos (Ai Laket). (2016). *Informe de composición de drogas ilícitas 2015*. http://www.ailaket.com/?page_id=19/informes.

Bourque, J., Afzali, M. H., O'Leary-Barrett, M. & Conrod, P. (2017). Cannabis use and psychotic-like experiences trajectories during early adolescence: the coevolution and potential mediators. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 58*, 1360-1369. doi:10.1111/jcpp.12765.

Bridgeman, M. B. & Abazia, D. T. (2017). Medicinal cannabis: History, pharmacology, and implications for the acute care setting. *Pharmacy and Therapeutics, 42*, 180-188.

Casajuana Köguel, C., López-Pelayo, H., Balcells-Olivero, M. M., Colom, J. & Gual, A. (2018). Psychoactive constituents of cannabis and their clinical implications: a

systematic review. *Adicciones, 30*, 140-151. doi:10.20882/adicciones.858.

Colizzi, M. & Bhattacharyya, S. (2017). Does cannabis composition matter? Differential effects of delta-9-tetrahydrocannabinol and cannabidiol on human cognition. *Current Addiction Reports, 4*, 62-74. doi:10.1007/s40429-017-0142-2.

Delegación del Gobierno de España para el Plan Nacional sobre Drogas. (2019). *Memoria del Plan Nacional sobre Drogas 2017. Ministerio de Sanidad, Consumo y Bienestar Social*, Secretaría de Estado de Servicios Sociales. http://www.pnsd.mscbs.gob.es/pnsd/memorias/docs/2019_MEMORIA_2017.pdf.

Di Forti, M., Morgan, C., Dazzan, P., Pariante, C., Mondelli, V., Marques, T. R.,… Murray, R. M. (2009). High-potency cannabis and the risk of psychosis. *The British Journal of Psychiatry, 195*, 488-491. doi:10.1192/bjp.bp.109.064220.

Dujourdy, L. & Besacier, F. (2017). A study of cannabis potency in France over a 25 year period (1996-2016). *Forensic Science International, 272*, 72-80. doi:10.1016/j.forsciint.2017.01.007.

ElSohly, M. & Chandra, S. (Eds.) (2013). *Analytical HPLC*. Scotts Valley, CA: American Herbal Pharmacopoeia.

ElSohly, M. A., Mehmedic, Z., Foster, S., Gon, C., Chandra, S. & Church, J.C. (2016). Changes in cannabis potency over the last 2 decades (1995-2014): Analysis of current data in the United States. *Biological Psychiatry, 79*, 613-619. doi:10.1016/j.biopsych.2016.01.004.

Energy Control. (2016). *Informe 2015*. ONG Asociación Bienestar y Desarrollo: Servicio de Análisis de Sustancias. https://energycontrol.org/mediateca/.

European Monitoring Center for Drugs and Drug Addiction (EMCDDA). (2019). *European School Survey Project on Alcohol and Other Drugs: Spain, country drug report.* Lisboa, Portugal: EMCDDA. http://www.emcdda.europa.eu/countries/drug-reports/2019/spain/key-statistics_en.

Fonseca-Pedrero, E., Lucas-Molina, B., Pérez-Albéniz, A., Inchausti, F. & Ortuño-Sierra, J. (2020). Psychotic-like experiences and cannabis use in adolescents from the general population. *Adicciones, 32*, 41-51. doi:10.20882/adicciones.1149.

Gaoni, Y. & Mechoulam, H. R. (1964). Isolation, structure, and partial synthesis of an active constituent of hashish. *Journal of the American Chemical Society, 86*, 1646-1647. doi:10.1021/ja01062a046.

García Álvarez, L., Gomar, J. J., García-Portilla, M. P. & Bobes, J. (2019). Cannabis use and cognitive impairment in schizophrenia and first-episode psychosis. *Adicciones, 31*, 89-94. doi:10.20882/adicciones.1328.

Hachís: cómo reconocer su bhttps://www.canamo.cl/2019/01/11/.

Hall, W. & Degenhard, L. (2009). Adverse health effects of non-medical cannabis use. *Lancet, 374*, 1383-1391. doi:10.1016/S0140-6736(09)61037-0.

Instituto Nacional de Toxicología y Ciencias Forenses (INTCT). (2013). *Escala de calidad de la resina de Cannabis. Informe anual*. Madrid: Ministerio de Justicia. https://www.mjusticia.gob.es/cs/Satellite/Portal/1292430763728?blobheader=application%2Fpdf&blobheadername1=Content-Disposition&blobheadername2=Grupo&blobheadervalue1=attachment%3B+filename%3DMemoria_INTCF_2013.PDF&blobheadervalue2=INTCF.

Lafaye, G., Karila, L., Blecha, L. & Benyamina, A. (2017). Cannabis, cannabinoids, and health. *Dialogues in Clinical Neuroscience, 19*, 309-316.

Lleonart, E. (2018). ¿Cuál es la diferencia entre índica y sativa? *El Salto* [Blog]. https://www.elsaltodiario.com/nekwo-blog/cual-es-la-diferencia-entre-indica-y-sativa.

Matsuda, L. A., Lolait, S. J., Brownstein, M. J., Young, A. C. & Bonner, T. I. (1990). Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature, 346*, 561-564. doi:10.1038/346561a0.

Niesink, R. J., Rigter, S., Koeter, M. W. & Brunt, T. M. (2015). Potency trends of Δ9-tetrahydrocannabinol, cannabidiol and cannabinol in cannabis in the Netherlands: 2005-15. *Addiction, 110*, 1941-1950. doi:10.1111/add.13082.

Niesink, R. J. & van Laar, M. W. (2013). Does cannabidiol protect against adverse psychological effects of THC? *Frontiers in Psychiatry, 4*, 130. doi:10.3389/fpsyt.2013.00130.

Oficina de las Naciones Unidas Contra la Droga y el Delito (UNODC). (2018). *Informe mundial sobre las Drogas 2018*. UNODC Research. https://www.unodc.org/wdr2018/prelaunch/WDR18_ExSum_Spanish.pdf

Pérez-Moreno, M., Pérez-Lloret, P., González-Soriano, J. & Santos-Álvarez, I. (2019). Cannabis resin in the region of Madrid: Adulteration and contamination. *Forensic Science International, 298*, 34-38. doi:10.1016/j.forsciint.2019.02.049.

Pijlman, F. T., Rigter, S. M., Hoek, J., Goldschmidt, H. M. & Niesink, R. J. (2005). Strong increase in total delta-THC in cannabis preparations sold in Dutch coffee shops. *Addiction Biology, 10*, 171-180. doi:10.1080/13556210500123217.

Potter, D. J., Hammond, K., Tuffnell, S., Walker, C. & Di Forti, M. (2018). Potency of Δ9 -tetrahydrocannabinol and other cannabinoids in cannabis in England in 2016: Implications for public health and pharmacology. *Drug Testing and Analysis, 10*, 628-635. doi:10.1002/dta.2368.

Ramos Atance, J. A. & Fernandez Ruiz, J. J. (2000). Sistema cannabinoide endógeno: Ligandos y receptors acoplados a mecanismos de transducción de señales. *Adicciones, 12* (Supl. 2), 59-81. doi:10.20882/adicciones.672.

Reeves, L. E., Anglin, D. M., Heimberg, R. G., Gibson, L. E., Fineberg, A. M., Maxwell, S. D.,… Ellman, L. M. (2014). Anxiety mediates the association between cannabis use and attenuated positive psychotic symptoms. *Psychiatry Research, 218*, 180-186. doi:10.1016/j.psychres.2014.03.040.

Ross, S. & ElSohly, M. A. (1997). CBN and D9-THC concentration ratio as an indicator of the age of stored marijuana samples. *Bulletin on Narcotics, 49*, 139-147.

Van Laar, M., Nan der Pol, P. & Niesink, R. (2016). Limitations to the Duch cannabis toleration policy. Assumptions underlying the reclassification of cannabis above 15% THC. *International Journal of Drug Policy, 34*, 58-64. doi:10.1016/j.drugpo.2016.02.011.

Waller, C. W. (1971). Chemistry of marihuana. *Pharmacological Reviews, 23*, 265-271.

Zamengo, L., Frison, G., Bettin, C. & Sciarrone, R. (2014). Variability of cannabis potency in the Venice area (Italy): A survey over the period 2010-2012. *Drug Testing and Analysis, 6*, 46-51. doi:10.1002/dta.1515.

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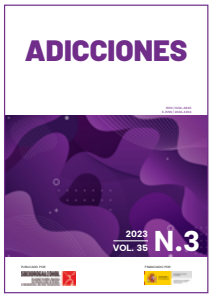

ORIGINAL

Impact of lockdown on the addictive behavior of university students in La Rioja

Impacto del confinamiento en la conducta adictiva de los universitarios riojanos

Alicia Pérez-Albéniz*,**; Cristina Nuez***; Beatriz Lucas-Molina**,****; Margarita Ezquerra*; Eduardo Fonseca-Pedrero*,**.

* Universidad de La Rioja.
** Programa Riojano de Investigación en Salud Mental (PRISMA), España.
*** Gobierno de La Rioja.
**** Universitat de València.

Abstract

One of the consequences of the COVID-19 health crisis was the general lockdown. Research shows that lockdown situations may cause changes in addictive behaviors. The objective of the present study was to analyze the impact of lockdown on the addiction pattern of university students in order to design interventions adjusted to the students' needs. The study was conducted through a non-probabilistic sample of 540 students, with a mean age of 22.3 years and a proportion of women of 69.3%. The results indicated a significant decrease in the consumption of tobacco, alcohol, and psychotropic drugs during the participants' lockdown, both in the number of users and in the amounts consumed. Regarding behaviors related to behavioral addictions, participants showed a significant increase in problematic Internet use and use of video games and eSports, although the level of gambling decreased. Despite the fact that consumption patterns were reduced due to changes in the leisure and free time patterns of this population subgroup, it was possible to identify some indicators that deserve attention due to their increase, such as relapses in smoking, an increase in the number of participants who drank alcohol on a daily basis and an increase in the level of discomfort related to the use of technology. The implications of the results are analyzed and possible actions demanded by the students are examined.

Keywords: COVID-19, substance use, behavioral addictions, university students, lockdown

Resumen

Una de las implicaciones de la crisis sanitaria de la COVID-19 ha sido el confinamiento de la población. La investigación previa muestra que las situaciones de confinamiento provocan cambios en las conductas adictivas. El objetivo del presente estudio fue conocer el impacto del confinamiento en el patrón de las adicciones de los y las estudiantes universitarios con la intención de diseñar intervenciones ajustadas a las necesidades de esta población. La muestra no probabilística estuvo compuesta por 540 estudiantes de la Universidad de La Rioja, con una media de edad de 22,3 años y una proporción de mujeres del 69,3%. Los resultados indicaron un descenso significativo en el consumo de tabaco, alcohol y psicofármacos durante el confinamiento de los y las participantes tanto en el número de consumidores como en las cantidades consumidas. Respecto a las conductas relacionadas con las adicciones comportamentales, los y las participantes indicaron un aumento significativo del uso problemático de Internet y de videojuegos y eSports, aunque descendió el nivel de juego de apuestas. A pesar de que los patrones de consumo se vieron reducidos por el impacto que el confinamiento tuvo en los patrones de ocio y tiempo libre de este subgrupo poblacional, se identificaron algunos indicadores merecedores de atención por su aumento, como recaídas en el consumo de tabaco, aumento del número de participantes que consumen alcohol a diario y aumento en el nivel de malestar relacionado con el uso de Internet. Se analizan las implicaciones de los resultados y se examinan posibles acciones demandadas por el estudiantado.

Palabras clave: COVID-19, consumo de sustancias, adicciones comportamentales, estudiantes universitarios, confinamiento

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■ **Send correspondence to:**
Beatriz Lucas Molina. Universidad de Valencia, Departamento de Psicología Evolutiva y de la Educación. Avda. Blasco Ibáñez, 21. 46010, Valencia.
Email: beatriz.lucas@uv.es

On March 11, 2020, the World Health Organization (WHO) declared the outbreak of the COVID-19 coronavirus to be a pandemic. As a consequence, and given the rapid spread of the virus, a state of emergency was declared in Spain on March 14 (RD 463/2020). With the different lockdown measures adopted by the government, decreed by Order SND/380/2020 and RD 537/2020, the Spanish population spent 10 weeks in lockdown or with one hour a day outside. Although these demanding measures of social isolation served at the time to reduce the spread of the virus, they may have had important consequences from psychological, socio-health and financial points of view. In this sense, social distancing, emotional isolation, the adoption of a sedentary lifestyle (teleworking, limitation in carrying out sports and leisure activities, etc.) and the financial difficulties resulting from the interruption of work activity were able to have some negative effects on the well-being and mental health of the population (Pfefferbaum & North, 2020).

Previous research has shown that the lockdown during the coronavirus pandemic may have caused some difficulties such as depression, anxiety, emotional problems or sleep disorders (Brooks et al., 2020; Lima et al., 2020; Wang et al., 2020). For example, in China the study by Qiu et al. (2020) showed that 35% of participants presented moderate to severe levels of psychological distress after the quarantine situation. In Spain, a study carried out during lockdown with a large sample of the general population (García-Álvarez et al., 2020) found that the most frequent emotional responses were associated with depressive symptomatology (46.7%) and avoidant coping styles (44.3%). Other studies show that lockdown can generate feelings of frustration, boredom, fear and confusion, aggressive behaviour, post-traumatic stress symptoms (Mazza, Marano, Lai, Janiri & Sani, 2020; Rossi et al., 2020) and an increase in the risk of suicidal behaviour (Reger, Stanley & Joiner, 2020). The psychological effects of lockdown seem to increase in certain vulnerable groups of the population, such as those with a previous mental disorder (Brooks et al., 2020; Rossi et al., 2020). Likewise, those people with substance use problems could be groups at risk of other mental health related problems (Brooks et al., 2020; Pfefferbaum & North, 2020), including suicidal behaviour (Espandian et al., 2021). In addition, it is important to highlight the need to understand and prevent possible increases in tobacco smoking, given that this substance has been considered a risk factor for infection and complications associated with COVID-19 (Volkow, 2020).

Furthermore, the negative impact of lockdown on the psychological well-being of the population could lead to the abuse of alcohol and/or other psychoactive substances, as well as a greater tendency to engage in pathological behaviours (e.g., gambling and Internet addiction) (Martinotti et al., 2020). It has therefore been proposed that the use of alcohol, tobacco and other substances, as well as the problematic use of the Internet and gambling, could increase not only as a consequence of the stress, anxiety or depressive symptoms experienced by the population, but also as a form of distraction or behavioural avoidance strategy in the face of this health emergency situation (García-Álvarez et al., 2020; Rojas-Jara, 2020). A study carried out along these lines with a large sample of participants over 18 years of age in the United States (Czeisler et al., 2020) revealed that 13.3% of the sample started or increased substance use in order to deal with the stress and emotions generated by the COVID-19 pandemic.

On the other hand, at European and national levels, studies have been carried out that indicate a general trend towards stabilization and decrease in substance use. For example, to analyze the use of psychoactive substances, the European Observatory on Drugs and Addictions (EMCDDA, 2020) conducted a substance use survey in the context of the COVID-19 pandemic (Mini-EWSD-COVID-19). The results derived from the sample of Spanish participants indicated that, during the period of lockdown, the majority of those surveyed who declared themselves users of illicit psychoactive substances claimed to have ceased or reduced the frequency or quantity consumed (71.9%). In 16.3% of the cases there were no changes. However, consistent with what happened in the United States (Czeisler et al., 2020), the study showed a not insignificant group of people (11.9%) who increased the frequency or amount of illicit psychoactive drug use during the COVID-19 lockdown.

The general pattern of reduced consumption is also seen for alcohol (Kilian et al., 2020; Villanueva et al., 2021), tobacco and exposure to environmental tobacco smoke (Ministerio de Sanidad, 2020). However, for cannabis, the results are contradictory. While Villanueva et al. (2021) observed a decrease in use, the Mini-EWSD-COVID-19 study of the European Observatory on Drugs and Addictions (2020) showed that there was a greater percentage of people who did not change their use or even increased it. This fact may be linked to the greater availability of this substance.

The outlook is more negative in terms of behaviours at risk of addiction. For example, a Chinese study with a sample of 6,416 adults on the risk of Internet addiction conducted by Sun et al. (2020) revealed a 23% increase in the prevalence of participants with a severe level of Internet addiction as a result of lockdown. In Spain, the data offered by the Spanish Observatory of Drugs and Addictions (2020) showed a significant increase in the use of video games and the Internet for recreational purposes. Gambling behaviour, however, decreased during lockdown (Observatorio Español de las Drogas y las Adicciones, 2020; Villanueva et al., 2021). Nevertheless, the results presented to date contrast with those from studies in the

university population, which, although few in number, indicate a negative impact of COVID-19 on smoking, alcohol and cannabis use during lockdown (Lechner et al., 2020; Yehudai et al., 2020). In Spain, a recent study with 310 university students showed that during quarantine, 9% presented obsessive behaviour regarding social networks, 27.7% showed a lack of personal control in the use of social networks and 47.1% an excessive use of social networks (Gómez-Galán, Martínez-López, Lázaro-Pérez & Sarasola, 2020). Therefore, it is possible that situations of stress due to isolation or lockdown can generate a series of psychological consequences that increase the risk of substance use and Internet addiction as coping strategies (Brooks et al., 2020; Czeisler et al., 2020; Rojas-Jara, 2020; Sun et al., 2020). This risk may be even greater among young people, who are more vulnerable to developing behavioural addictions (e.g., tobacco, alcohol, psychoactive substances, Internet) (Kar et al., 2020).

The scarcity of studies carried out in a university context makes a needs analysis of this population necessary to understand the impact of the crisis on their substance use and behaviours at risk of addiction that guide the university's strategy in the field of addiction prevention. Specifically, the University of La Rioja has been a member of the Spanish Network of Healthy Universities since 2008 with a commitment to develop a work project that incorporates the concept of health promotion in university culture, in its institutional policies, structure, processes and study plans and to include the identification of the needs of the university community, areas of work and intervention strategies. This study responds to the need to measure the impact of the health crisis on students and to make available to them the necessary resources to mitigate the potential damage it may cause.

Within this research context, the aim of our study was to analyze the prevalence of substance use and behaviours at risk of addiction. The following specific objectives were derived from this general aim: a) to analyze the prevalence of smoking, cannabis, alcohol and tranquilizer use and to find out how consumption changed during lockdown; b) to study the prevalence of behaviours at risk of addiction such as gambling, problematic Internet use (PIU) and gaming (video games and eSports) and the impact of lockdown on these prevalences; and c) to analyze other changes in participant consumption, lifestyles and well-being. Based on the literature review, a general decrease in use was expected. However, the existence of some indicators of changes in use and distress associated with the increased use of technologies (i.e., the Internet) was also expected. Finding out about this reality based on a needs analysis will allow training, information, awareness and prevention activities to be proposed, as well as the subsequent move towards relevant and contextualized interventions in the university environment on which they are based.

Method

Participants

The non-probabilistic sample comprised 540 participants from the total population of 5,700 students enrolled at the University of La Rioja in the 2019-2020 academic year. To calculate the minimum number of participants needed, a formula combining population (5,700), confidence level (95%) and margin of error (5%) was applied, resulting in a minimum size of 360 responses, which was therefore widely exceeded by number of participating students.

The participants were students of 32 different university degrees (Bachelors, Masters and Doctorates) and had been at university for different lengths of time: 25.7%, 14.8%, 17.8% and 18.3% were in their first, second, third and fourth years, respectively. Those who had been enrolled for more than four years made up 18.05% of the sample, and 5.4% had been enrolled for over four years with discontinuity in enrolment.

A total of 32 participants were removed from the sample since they claimed to be over 36 years old and were considered outliers. Mean age was 22.29 years (SD = 3.30 years; range = 18 to 35 years), and 69.3% were women (n = 374).

Instruments

Smoking and other forms of tobacco consumption. Questions from the survey "Tobacco, Other Forms of Consumption and Lockdown" (Ministry of Health, 2020) were used. The original questionnaire had 18 items assessing the impact of lockdown on the use of tobacco and other related products. The items regarding age of onset (tobacco and cannabis), frequency of use before and during lockdown, type of use before and during lockdown, perception of change in use during lockdown, intention to quit, and exposure to environmental tobacco smoke were used.

Alcohol use. Items from both the EDADES and ESTUDES surveys of the Government Delegation for the National Plan on Drugs (2018, 2019) and the study on smoking (Ministry of Health, 2020) adapted to alcohol consumption were used. The items on age of onset of consumption, frequency of use, and type of use were applied, and an additional item on the use of energy drinks was introduced. These questions were adapted to examine consumption before and during lockdown. Additionally, two of the three items from the brief version of the *Alcohol Use Disorders Identification Test* (AUDIT-C) (Contel, Gual & Farran, 1999) were introduced to assess risky alcohol use: number of drinks consumed before and after lockdown and frequency of binge drinking (consumption of 6 or more drinks in a single day).

Use of psychotropic drugs with and without prescription. Items from both the EDADES and ESTUDES surveys of the Government Delegation for the National Plan on Drugs (2018, 2019) and the study on smoking (Ministry of

Health, 2020) adapted to the consumption of prescription and non-prescription psychoactive drugs were used. Items on age of onset were used, as were those referring to frequency and quantity of use adapted to examine such use before and during lockdown.

Gambling. Items from the ESTUDES survey of the Government Delegation for the National Plan on Drugs (2019) were used. The starting age for face-to-face and online gambling and the frequency of gambling before and during lockdown were assessed.

Compulsive Internet Use Scale (CIUS) (Meerkerk Van Den Eijnden, Vermulst & Garretsen, 2009). The CIUS is one of the most widely used scales to assess problematic Internet use (PIU). The scale was developed under the premise that this behaviour shared some of the diagnostic criteria included in substance dependence (seven criteria) and pathological gambling (ten criteria) of the DSM-IV (1994), behavioural addictions (Griffiths, 1999; Meerkerk et al., 2009) and obsessive-compulsive disorder (López-Fernández et al., 2019). López-Fernández et al. (2019) carried out a study analyzing the psychometric properties of different versions (CIUS-14, CIUS-9, CIUS-7, CIUS-5) developed in eight languages (German, French, English, Finnish, Spanish, Italian, Polish and Hungarian) and endorsed its use as valid and especially useful for its brevity. A recent study by Fonseca-Pedrero, Ortuño-Sierra, Pérez and Pérez-Albéniz (2020) showed that the 14-item scale in Spanish had adequate psychometric properties and a unidimensional structure. For the present study, the ESTUDES (2019) version was used, but the items were presented in a dichotomous response format (Yes/No) in which the participants had to answer whether or not they had experienced each of the indicators (e.g., difficulties to stop using the Internet, sleeping less due to being connected to the Internet, neglecting obligations) before and during lockdown. The scores of the Spanish version of this scale (Fonseca-Pedrero et al., 2020) have shown adequate levels of reliability (McDonald's Omega = 0.91).

Gaming participation. Items from the ESTUDES survey of the Government Delegation for the National Plan on Drugs (2019) were used. The frequency of playing video games, eSports and eSports spectatorship before and during lockdown was assessed.

Other substances used, behavioural changes and perceived needs. Finally, three qualitative questions were introduced with the aim of analyzing possible substance use not contemplated in the previous questions (*During these weeks of lockdown, have you used any other type of substance that we have not asked you about and that you have observed that you have used more frequently?*), changes in perceived behaviour (*Do you want to highlight any other changes in your behaviour that have taken place during these weeks of lockdown?*) and proposals for action by the participants for the prevention services in the university that they would like to apply for or consider to be of interest (*What type of activities would you like to see carried out by the university to address the prevention of these uses and addictions?*).

Procedure

The research was approved by the Ethics Committee of the University of La Rioja (Resolution of 4/8/2020 of the University Board of Directors). The administration of the questionnaires was carried out online and the study was reported through email messages to the student body sent from the University's Occupational Risk Prevention Service.

Confidentiality of responses was ensured at all times, as well as the voluntary nature of participation, and no reward was given for collaboration in the study.

Data analysis

First, descriptive statistics for the items were calculated. Second, the possible existence of statistically significant differences in the two time points (before and during lockdown) of the different consumption indicators was analysed through tests of repeated measures. For continuous variables, the t-test for related samples was used. For categorical data, in the case of dichotomous data, the McNemar test was used and for those variables with different categories, the marginal homogeneity test was used. The latter is an extension of McNemar's test from binary to multinomial response. It tests response changes using the chi-square distribution and is useful for detecting response changes in before-after designs. To analyze the individual changes, i.e., the number of participants who modified their use in the referenced quantities of some substances, a recoding of the variables was carried out. Data analysis was performed using SPSS 26.0.

Results

Substance use

Use of tobacco, cigarettes, cigars, cannabis and other forms of consumption. The mean age at which the participants reported starting smoking tobacco and cannabis was 15.59 years (SD = 2.60) and 16.59 years (SD = 2.33), respectively. Regarding the use of tobacco and other substances before and during lockdown, the results indicate a change in consumption habits. As can be seen in Table 1 and based on the results of the marginal homogeneity test to contrast the proportions between the categories, use decreases in a statistically significant way (*standard MH* = 5.39; $p < .001$). although the number of former smokers who return to smoking is also significant.

The results regarding the type of use (the type of tobacco and other substances consumed) can be seen in Table 2.

Regarding the participants' perception of change in the level of consumption, the results revealed that 2.4% of the students reported starting to smoke or relapsing, 8% stated

that they smoked more and 14.8% claimed to have smoked less during lockdown than before. Regarding the proposals to quit smoking during the weeks of lockdown, although 59 participants (57.3%) stated that they had not considered it, 44 (42.7%) had done so. Of these, 20 (45.45%) succeeded, 13 (29.5%) were trying at the time of data collection, and 11 (25%) failed.

Regarding passive smoking or exposure to environmental tobacco smoke (ETS), Table 1 shows the results of the McNemar test for dichotomous variables revealing that exposure had decreased in a statistically significant way (x^2 = 64, 03, $p < .05$). The participant analysis showed that 17.4% who had been exposed before lockdown stopped being exposed during it.

Alcohol consumption. The mean age at which the participants claim to have started drinking alcohol was 14.99 (*SD* = 2.19).

Regarding drinking before and during lockdown, results indicated a decrease. As can be seen in Table 1, the marginal homogeneity test showed that drinking decreased significantly (*standard MH* =10.90; $p < .001$). It is observed that sporadic and weekend drinking was much lower, as expected given the decrease in social leisure opportunities during lockdown, although the test also indicated that the number of participants drinking daily increased significantly.

Regarding the type of alcohol and energy drinks (mixed with alcohol or consumed alone) that were consumed

Table 1
Frequency of use of different substances before and during lockdown

	Before lockdown ***n*** **(%)**	**During lockdown** ***n*** **(%)**
Smoking		
Daily	69 (12.8)	66 (12.2)
Smoker, but not daily	60 (11.1)	41 (7.6)
Ex-smoker	73 (13.5)	47 (8.7)
Never	330 (61.1)	383 (70.9)
Exposure to environmental tobacco smoke (ETS)		
Yes	229 (42.4)	147 (27.2)
No	308 (57.0)	393 (72.8)
Alcohol		
Daily drinking	18 (3.3)	30 (5.6)
Every weekend	89 (16.5)	43 (8.0)
Sporadic drinking	379 (70.2)	247 (45.7)
Never	53 (9.8)	220 (40.7)
Binge drinking (6 or more drinks on the same occasion)		
Daily or almost daily	3 (0.6)	6 (1.4)
Weekly	49 (9.9)	21 (5.0)
Monthly	72 (14.5)	17 (4.0)
Less than once a month	160 (32.3)	28 (6.7)
Never	211 (42.6)	349 (82.9)
Prescription psychoactive drugs		
Daily	30 (5.6)	26 (4.8)
At least once a week	5 (0.9)	6 (1.1)
Sporadic use	28 (5.2)	10 (1.9)
Never	477 (88.3)	498 (92.2)
Non-prescription psychoactive drugs		
Daily	4 (0.7)	6 (1.1)
At least once a week	2 (0.4)	9 (1.7)
Sporadic use	40 (7.4)	24 (4.4)
Never	494 (91.5)	501 (92.8)

Table 2
Type of substances used before and during lockdown

	Before lockdown ***n*** **(%)**	**During lockdown** ***n*** **(%)**
Tobacco and other substances		
Cigarettes	139 (25.7)	72 (13.3)
Hand-rolling tobacco	115 (21.3)	58 (10.7)
Cannabis	97 (17.9)	45(8.3)
Waterpipe	52 (9.6)	5 (.9)
Cigars or cigarillos	19 (3.5)	10 (1.8)
Electronic cigarettes	16 (2.9)	14 (2.6)
Herbs for smoking	7 (1.3)	4 (.7)
Heated tobacco products	3 (.5)	3 (.5)
Other	13 (2.4)	6 (1.1)
Alcohol and energy drinks		
Beer	383 (70.9)	286 (52.9)
Wine	332 (61.5)	191 (35.4)
Mixed drinks (spirit-based)	384 (71.1)	91 (16.8)
Fruit liqueurs, unmixed	141 (26.1)	30 (5.5)
Strong liquors, unmixed	125 (23.1)	32 (5.9)
Other	61 (11.3)	19 (3.5)
Energy drinks	175 (32.4)	87 (16.1)
Energy drinks and alcohol	124 (22.9)	26 (4.8)

Note. For each substance, the sum of the percentages exceeds 100% (because of the simultaneous use of substances).

Table 3
Amount of alcohol drunk before and during lockdown

	Before lockdown ***n*** **(%)**	**During lockdown** ***n*** **(%)**
1 or 2 units	90 (26.4)	123 (69.9)
3 or 4 units	144 (42.2)	24 (13.6)
5 or 6 units	58 (17.0)	15 (8.5)
From 7 to 9 units	28 (8.2)	11 (6.3)
10 or more units	21 (6.2)	3 (1.7)

before and during lockdown (see Table 2), results showed that the most frequently consumed drinks were beer, wine and spirit-based mixed drinks, in that order and at both moments in time. Consumption of all types of beverages decreased.

With reference to the amount of alcohol consumed (see Table 3) in each drink, participants stated that they drank significantly less alcohol (*standard MH* = 13.58; $p < .001$).

To analyze the individual changes, that is, the number of participants who had modified their use of the referenced quantities, a recoding of the variables was carried out. The frequencies indicated that 318 participants (58.9%) claimed to have drunk less during lockdown, 196 (36.35%) maintained their drinking pattern, but 26 participants (4.8%) increased the number of alcoholic drinks when they drank.

In terms of binge drinking (6 or more drinks on the same occasion) (see Table 3), the results indicated a general reduction in frequency. As with the amount of alcohol drunk, the variables were also recoded to reveal individual changes in this type of consumption. The frequencies indicated that 175 participants (42.0%) claimed to have participated in binge drinking fewer times during lockdown, 228 (54.7%) did so with a similar frequency, and 14 (3.4%) increased the number of binge drinking episodes.

Consumption of psychotropic drugs with and without a prescription. The mean age at which the participants stated that they started using psychoactive drugs with and without

a prescription was 19.41 years (*SD* = 5.88) and 18.66 years (*SD* = 4.33), respectively.

Regarding the frequency of psychotropic drug use with and without a prescription, before and during lockdown (Table 1), the results indicated a fall in consumption. However, the decrease was only significant for prescription psychoactive drugs (*standard MH* = 2.36, p = .018). The fall in the use of non-prescription psychotropic drugs did not reach statistical significance (*standard MH* = -.442; p > .05) in the marginal homogeneity test.

Regarding the number of types of psychoactive drugs, the participants stated means of .34 (*SD* = .69) and .21 (*SD* = .69) before and during, respectively, for prescription psychoactive drugs, and .19 (*SD* = .47) and .15 (*SD* = .42) before and during, respectively, for non-prescription psychoactive drugs. The decrease in the variability of psychotropic drugs used in both types (with and without prescription) was statistically significant [(t (539) = 6.13, p < .001) and [(t (539) = 3.20, p < .01), respectively].

Prescribed psychotropic drugs were therefore used less during lockdown, and the students who used them consumed fewer types. However, for psychotropic drugs used without a prescription, there was no decrease in quantity but rather in variety.

In reference to the type of psychotropic drug (see Table 4), the results indicated a differential pattern with and without a prescription. For prescription drugs, the results showed a fall in all drugs studied (antidepressants, sleeping pills and tranquilizers). However, for over-the-counter psychoactive drugs, a significant drop (p < .05) was only observed in sleeping pills.

Behaviours at risk of behavioural or non-substance addictions

Gambling. The mean age at which participants reported starting face-to-face and online gambling was 18.64 (*SD* = 3.47) and 18.93 (*SD* = 3.99), respectively.

Since face-to-face gambling was not possible during lockdown, data on gambling frequency was collected without distinguishing between types. As can be seen in Table 5, the frequency of gambling behaviour decreased significantly during lockdown (*standard MH* = 7.82; p < .001).

Problematic Internet use. The results showed statistically significant differences (t (539) = -6.32, p < .001) when comparing the total CIUS scale scores at the two time points: before (*M* = 2.52, *SD* = 2 .28) and during (*M* = 3.03, *SD* = 2.51) lockdown, indicating greater distress associated with Internet use.

Use of video games, eSports and spectator in eSports or electronic sports. As shown in Table 5, the frequency of use of video games, eSports and spectator in eSports or electronic sports was highly prevalent during lockdown. In fact, the data shows a significant increase for the three categories (*standard MH* = -7.839; p < .001) for video games, (*standard MH* = -3.101; p < .01) for eSports, and (*standard MH* = -3.113; p < .01) for spectator in eSports or electronic sports.

Other types of consumption, changes in behaviour and need for intervention

In the first place, in reference to the possibility that they made some other type of consumption, the students indicated (see Table 6) changes in the pattern of use of

Table 4
Consumption of prescription and non-prescription psychoactive drugs, before and during lockdown, according to type (antidepressants, sleeping pills and tranquilizers)

	Prescription			
	Before *n* (%)	During *n* (%)	*MH*	*P*
Antidepressants	41 (7.6)	23 (4.2)	-3.67	<.001
Sleeping pills	48 (8.8)	29 (5.4)	-3.96	<.001
Tranquilizers/sedatives	49 (9.1)	17 (42.5)	-5.48	<.001
Other	48 (8.9)	46 (8.5)	-.63	.527
	Non-prescription			
	Before *n* (%)	During *n* (%)		
Antidepressants	5 (0.9)	3 (0.5)	-1.41	.157
Sleeping pills	45 (8.3)	31 (5.7)	-2.64	.008
Tranquilizers/sedatives	21 (3.9)	16 (2.9)	-1.29	.197
Other	35 (6.5)	34 (6.3)	-1.00	.317

Table 5
Frequency of gambling, video games, eSports and spectator in eSports or electronic sports before and during lockdown

	Before lockdown ***n*** **(%)**	**During lockdown** ***n*** **(%)**
Gambling		
6 or more days a week	4 (0.7)	2 (0.4)
4-5 days a week	3 (0.6)	1 (0.2)
2-3 days a week	2 (0.4)	2 (0.4)
2-4 days a month	10 (1.9)	3 (0.6)
One day a month or less	99 (18.3)	20 (3.7)
Never	422 (78.1)	512 (94.8)
Video games		
Daily	40 (7.4)	80 (14.8)
Several days a week	40 (7.4)	64 (11.9)
Some day a week	36 (6.7)	49 (9.1)
Sporadically	168 (31.1)	97 (18.0)
Never	256 (47.4)	250 (46.3)
eSports		
Daily	23 (4.3)	36 (6.7)
Several days a week	17 (3.1)	18 (3.3)
Some day a week	23 (4.3)	23 (4.3)
Sporadically	46 (8.5)	37 (6.9)
Never	431(79.8)	426 (78.9)
Spectator		
Daily	17 (3.1)	26 (4.8)
Several days a week	14 (2.6)	16 (3.0)
Some day a week	19 (3.5)	22 (4.1)
Sporadically	46 (8.5)	40 (7.4)
Never	444 (82.2)	436 (80.7)

Table 6
Other types of consumption during lockdown that the participants wanted to point out

Type of consumption	*n*	**%**
Food	23	4.3
Sweets, sugar, chocolate	15	2.8
Coffee	10	1.9
ICT, TV, series	15	2.8
Pornography	4	0.7
Other psychoactive substances: cocaine, amphetamines, etc.	2	0.4
Others (example: melatonin, sports, internet shopping)	7	1.3

Table 7
Changes in behaviour during lockdown reported by student

	***N* (%)**	**Description reported by the student body (examples)**
Negative aspects		
Higher levels of anxiety, stress	52 (9.6)	Feelings of anxiety, stress or being overwhelmed.
Negative emotions	51 (9.4)	Sadness, depression, lack of motivation, tiredness, irritability and even suicidal thoughts.
Negative changes in physical activity performed	7 (1.3)	Increased sedentary lifestyle and lack of activity.
Negative changes in diet	2 (0.4)	Increased food intake.
Changes in sleep and rest	24 (4.4)	Presence of episodes of insomnia, difficulty falling asleep, lower number of hours of rest.
Concerns related to the academic sphere	33 (6.1)	Increased level of stress due to the demands of tasks, jobs and type of work. Difficulty concentrating and performing work with the same level of quality and effort.
Social difficulties	10 (1.9)	Problems living with the family, difficulties restarting social life after lockdown, loss of interest or isolation.
Claustrophobia	5 (0.9)	Difficulties related to the feeling of lockdown and lack of space.
ICT	6 (1.1)	Perception of the negative impact due to the increase in technology consumption.
Physical symptoms	5 (0.9)	Increased intensity and frequency of migraines, dizziness and pain of various kinds.
Others	4 (0.7)	For example, increased consumption of pornography, coffee.
Positive aspects		
Positive changes in physical activity performed	16 (3.0)	Starting new activities or increasing regular physical activity.
Positive changes in diet	6 (1.1)	Greater variety and quality in food.
Others	16 (3.0)	Changes in healthy habits, perception of better time management and development of new skills, etc.

some foods and fundamentally the use of information and communication technologies.

Secondly, regarding the changes in behaviour during the weeks of lockdown indicated by participants (see Table 7), it is worth noting the presence of symptoms related to anxiety, the presence of negative emotions and changes in their lifestyle (physical activity, food and rest). Concerns related to academic tasks and social difficulties were also prevalent. Similarly, it should be highlighted that some participants also indicated positive aspects derived from the lockdown situation (also shown in Table 7) related to lifestyle improvements. Some even pointed to a positive impact of lockdown on their ability to manage time, in the carrying out activities or in the development of critical thinking and problem-solving skills.

Finally, the responses of the participants to the question about the activities that they would like university services to offer in order to address addiction prevention resulted in the following categorization (in order of frequency): a) workshops, in general or for the prevention of alcohol, drugs, gambling and mental illness, as well as awareness-raising activities or talks, b) financially affordable sports and extracurricular activities for the development of healthy leisure, c) activities and days of health education and promotion of health and healthy lifestyles.

Discussion

The overall aim of the study was to analyze the prevalence of behaviours at risk of addiction in a non-probabilistic sample of students from the University of La Rioja during COVID-19. Three specific objectives were derived from this general aim, comprising the analysis of substance use prevalence in the university population and finding out the changes in said consumption during lockdown, the study of the prevalence of behaviours at risk of behavioural addiction during lockdown and, finally, the analysis of other changes in the consumption, lifestyles and well-being of the participants.

Firstly, for all substances and gambling, the age at which consumption began was explored as a possible indicator of the level of risk in this population. The data showed that the age of onset for the use of tobacco, cannabis, alcohol, prescription and non-prescription psychoactive drugs, and face-to-face and online gambling was 15.59 years, 16.59 years, 14.99 years, 19.41 years, 18.66 years, 18.64 years

and 18.93 years, respectively. The comparison of these data with other studies of a similar nature, in this case the national surveys ESTUDES (National Plan on Drugs, 2019) and EDADES (National Plan on Drugs, 2018) and, specifically, with the most recent ESTUDES due to the proximity of the profile (ESTUDES 2018-19), indicated that consumption for all categories analyzed started late. In fact, for tobacco, cannabis and alcohol use, the difference in onset age was greater than one year. The differences are even greater for the use of psychotropic drugs, with or without prescription, and with face-to-face and online gambling. These data could indicate that early initiation of use is not a risk factor in this population.

In terms of the change in smoking pattern, the data reveal a decrease during lockdown. This result is consistent with that found in the study by the Ministry of Health (2020), which also indicated that the highest rates of decrease are found in students (when occupation is taken into account) and those under 24 years of age (when age is analyzed). Conversely, Yehudai et al. (2020) found an increase in smoking by university students, and a study by the Ministry of Health (2020), through the Smoking Unit of the General Directorate of Public Health, found that 73.5% of smokers maintained the same frequency of use in the both periods, and that 15.7% of the participants reduced the frequency with which they smoked. However, the results showed that 10.8% of the sample increased their smoking (5.5% changed from occasional to daily use), 0.9% of smokers started smoking and 4.5% had relapsed into smoking during lockdown. Regarding the quantities used, a significant increase in smoking was detected during lockdown in general and for all types of products analyzed. Regarding the possibility of quitting this habit, the study showed potential target groups of people who tried without success and who did not even consider it (more than 50%). In line with the above and in relation to the present study, besides the effects of the pandemic, there are relevant issues to take into account in the face of possible intervention. It is important to highlight that the use of tobacco in its various types is very frequent, as is cannabis use.

The results also showed people starting to smoke and relapsing (2.4% of the sample) during lockdown. This data is in line with that provided by the study by the Ministry of Health (2020), which reaches 7.8%. These data are certainly worthy of attention.

The decrease observed in this study in cannabis use is consistent with that found by Villanueva et al. (2021), but contrasts with the data found by Yehudai et al. (2020) in university students and by the MINI-EWSD-COVID-19 survey of the European Observatory on Drugs and Addictions (2020), which showed that cannabis was the illicit drug of which a lower percentage of people changed their use. The study attributes this result to the greater availability of this substance compared to other illicit substances.

Regarding ETS, the data show fewer passive smokers. This result is consistent with the study carried out by the Ministry of Health (2020), in which 60.7% (compared to 17.4% in our study) of those who reported being exposed to tobacco smoke and/or cigarette emissions before lockdown had ceased to be so during lockdown, and among non-smokers there was a significant drop from 25.6% to 11.7%. On the other hand, this result was to be expected both because home lockdown reduces exposure contexts and because of the lower consumption observed.

It is also important to highlight the existence of a significant group of smokers who are at the stage of thinking about quitting (more than 40% of the participating smokers in this study, and more than 50% in the Ministry study, stated that they had considered trying to quit).

The results in relation to alcohol use also showed a significant decrease, especially in sporadic drinking and at weekends. This data was expected, as was the reduction in binge drinking, given the lockdown situation and the link between alcohol use and leisure time with young people. Likewise, the personal situation of university students could affect drinking patterns since it is possible that many live with their families, which means a greater level of control in lockdown situation. However, an increase in daily use was also observed in terms of frequency, although not of the amount drunk daily. A European study focusing on changes in alcohol use during the health crisis (Kilian et al., 2020) also showed a trend towards a decrease or stabilization. Similar results were found in the MINI-EWSD-COVID-19 survey and in the study by Villanueva et al. (2021), who point out that drinking decreased during lockdown compared to pre-pandemic levels, and specify that it occurred especially among the youngest (18-29 years). However, these data contrast with those provided by Lechner et al. (2020) and Yehudai et al. (2020), who observed an increase in drinking as time passed during lockdown. However, the study by Lechner et al. (2020) also found a relationship between drinking and symptoms of depression and anxiety. As a hypothesis, the results of this study in relation to the increase in people drinking daily could be interpreted in this sense.

In relation to psychotropic drugs, the results of the present study show that participants used fewer prescribed psychotropic drugs in general. When the analysis was carried out by substance, consumption was significantly lower for all those studied. In addition, fewer types of substances were used. Regarding non-prescription psychoactive drugs, participants used the same amount in general but fewer sleeping pills. Also, fewer types of substances were used. To our knowledge, the only study carried out in similar context to ours and in a university population is that of Corujo, Díaz, García and Saavedra (2020) at the University of La Laguna. Among its results, a decrease in alcohol use stands out, consistent with our study, but an increase in sedative-hypnotics was also found.

Outside the university environment, it seems that there is a change in consumption patterns regarding psychotropic drugs, although there are currently not many studies. For example, a global study (Winstock et al., 2020) with a non-probabilistic sample of more than 40,000 people reported increased use of cannabis and benzodiazepine products due to the general feeling of stress caused by the pandemic and the associated restrictions, while a decrease in the demand for stimulants was observed due to the inaccessibility of the usual recreational environments.

Regarding other behaviours at risk of addiction, the picture is more complex. On the one hand, in relation to gambling, the results of this study showed a significant decrease in gambling behaviour with money. These data are consistent with those provided by the study by Villanueva et al. (2021) and by the Spanish Observatory of Drugs and Addictions survey (2020) on the Internet, video games and gambling during the COVID-19 pandemic (IVJ-COVID-19), which revealed a decrease in the frequency of gambling. On the other hand, the results showed a significant increase in the frequency of use of video games, eSports and spectator in eSports or electronic sports, data which are consistent with those provided by the IVJ-COVID-19 survey, which revealed a significant rise in the use of video games (especially among students).

The present study, however, did not include an examination of the frequency of Internet use. Nevertheless, it did introduce an assessment of distress derived from its use and specifically from the problematic use of the Internet through the CIUS scale. The results revealed that this distress increased in a statistically significant way, indicating the need to take it into consideration as it is in line with other studies of the same nature. For example, research conducted in China by Sun et al. (2020) with a sample of 6,416 adults revealed a 23% rise in the prevalence of participants with a severe level of dependence on the Internet as a result of lockdown. In Spain, the report derived from the IVJ-COVID-19 survey also presented a general increase in the use of the Internet (specifically, a rise of 68.9% was established) and the problematic use of the Internet (with a rate of participants representing possibly problematic use of 11.2% according to the CIUS scale), especially prevalent among participants aged between 14 and 17 years. Villanueva et al. (2021) also noted in their research that two out of ten young adults showed indicators of problematic Internet use. The data unequivocally highlights the urgent need to address problematic Internet use.

Some groups within the student body also reported some other type of non-habitual consumption in lockdown, such as an increase or change in the pattern of eating unhealthy foods or technology use. Others reported changes in mood, in their lifestyles or concerns related to academic tasks and social relationships.

Taken together, these results lead us to believe that Spanish university students may have experienced a change in the pattern of substance use and behaviours at risk of addiction as a consequence of emotional responses or as an avoidance strategy during lockdown and the pandemic. Despite the significant decrease in substance use and gambling behaviour, it is also important to point out a series of risky behaviours by some groups derived from the analysis of the results, such as the increase in frequency of alcohol use (i.e., daily drinking), starting to use a substance or relapsing (i.e., smoking) or the increase in the use of others substances (i.e., cannabis) collected in other studies. Similarly, the increase in distress associated with the use of video games and the Internet needs to be addressed, even though this behaviour is in principle recreational. In summary, various indicators of initiation, relapse or increase in use are observed that may represent inadequate coping strategies. As pointed out by Czeisler et al. (2020), some groups of students started or increased substance use in order to deal with the stress and negative emotions generated by the COVID-19 pandemic. This involves the challenge of generating positive and alternative psychosocial conditions that allow the population in general and university students in particular to face forced contexts of isolation and stress through different sources of adaptation (routines, habits, exercises, contact, communication, etc.) that weaken the use of substances as the exclusive method of mitigation and facilitate the return to normative behavioural patterns (García-Álvarez et al., 2020; Rojas-Jara, 2020).

It is also interesting to note that part of the student body also reported positive changes in various aspects related to lifestyle, and that some even pointed out the positive impact of lockdown on relevant aspects of their lives. In addition, a significant number of participants made very sound specific proposals on possible actions that could be developed by the university for the prevention of substance use and behavioural addictions. These results may indicate that the student body perceives the training and actions that the university can offer in a very positive way. In fact, the university should be considered as a context of holistic education, as the Delors report (1996) argues, involving the development not only of knowledge per se and know-how skills, but also attitudes and behaviours for knowing how to be and how to live.

As previously mentioned, the University of La Rioja is a member of the Spanish Network of Healthy Universities. This network, which is committed to promoting health in the university culture, has among its aims the identification of intervention needs. This study provides an assessment of the impact of the health crisis situation on the student body and is a first step in designing the necessary resources to cushion its effects in coordinated work between the professionals responsible for La Rioja University's

Occupational Risk Prevention Service and the Drug and Other Addictions Service of the La Rioja Government. Together with the identification of global needs, it should be noted that the detection and identification and possible diagnoses must be accompanied by empirically supported psychological treatments (Fonseca-Pedrero et al., 2021).

The present study is not without limitations. In the first place, as it is an online survey with a self-selected sample, its results do not allow generalization to the population at large; nevertheless, they can provide a first approximation to the changes that the COVID-19 pandemic has brought about in the university population. In addition, the data belong to a single autonomous community, so caution is required when generalizing the results to other populations of interest. Second, it is a study based on self-reports and the usual limitations must be considered. Third, inclusion and exclusion criteria have not been explicitly considered, as well as important covariates (IQ, socio-economic level, etc.) that could affect the results found in this research. Fourth, the cross-sectional nature of the study does not allow causal relationships to be established, and the study would have benefited from assessments throughout the pandemic to determine the medium- and long-term effects on the student body.

Notwithstanding these limitations, the results offered, which are based on contextualized assessment and located in a moment of unprecedented pandemic, allow the design of actions that respond to the interests and needs of the student body.

Conflict of interests

The authors declare no conflict of interest.

References

Brooks, S. K., Webster, R. K., Smith, L. E., Woodland, L., Wessely, S., Greenberg, N. & Rubin, G. J. (2020). The psychological impact of quarantine and how to reduce it: Rapid review of the evidence. *Lancet, 395*, 912-920. doi:10.1016/S0140-6736(20)30460-8.

Contel, M., Gual, A. & Farran, J. (1999). Test para la identificación de trastornos por uso del alcohol (AUDIT). Traducción y validación del AUDIT al catalán y al castellano. *Adicciones, 11*, 337-347. doi:10.20882/adicciones.613.

Corujo, Z., Díaz, L., García, J. D. & Saavedra, M. L. (2020). *Incidencia del estado de alarma por COVID-19 en el consumo de alcohol y psicofármacos en alumnado de la Universidad de La Laguna*. Unpublished document. Facultad de Ciencias Sociales y de la Comunicación: Universidad de La Laguna.

Czeisler, M. É., Lane, R. I., Petrosky, E., Wiley, J. F., Christensen, A., Njai, R.,... Czeisler, C. A. (2020). Mental health, substance use, and suicidal ideation during the COVID-19 pandemic—United States, June 24–30, 2020. *Morbidity and Mortality Weekly Report, 69*, 1049. doi:10.15585/mmwr.mm6932a1.

Delors, J. (1996). *La educación encierra un tesoro*. Madrid: Santillana.

Espandian, A., Flórez, G., Peleteiro, L., Tajes, M., Sáiz, P., Villa, R. & Bobes, J. (2021). Estrategias de intervención en la prevención de comportamiento suicida en pacientes con trastorno por consumo de sustancias en tiempos de COVID-19. *Adicciones, 33*, 185-192. doi:10.20882/adicciones.1717.

Fonseca-Pedrero, E., Ortuño-Sierra, J., Pérez, J. & Pérez-Albéniz, A. (2020). *Propiedades psicométricas de la Escala de Uso Problemático de Internet (CIUS) en su versión en castellano.* Manuscript submitted for publication.

Fonseca-Pedrero, E., Pérez-Álvarez, M., Al-Halabí, S., Inchausti, F., Muñiz, J., López-Navarro, E.,... Montoya, I. (2021). Tratamientos psicológicos empíricamente apoyados para adultos: Una revisión selectiva. *Psicothema, 33*, 188-197. doi:10.7334/psicothema2020.426.

García-Álvarez, L., de la Fuente-Tomás, L., García-Portilla, M. P., Sáiz, P. A., Moya-Lacasa, C., dal Santo, F.,… Bobes, J. (2020). Early psychological impact of the 2019 coronavirus disease (COVID-19) pandemic and lockdown in a large Spanish sample. *Journal of Global Health, 10*, 020505. doi:10.7189/jogh.10.020505.

Gómez-Galán, J., Martínez-López, J. Á., Lázaro-Pérez, C. & Sarasola Sánchez-Serrano, J. L. (2020). Social networks consumption and addiction in college students during the COVID-19 pandemic: Educational approach to responsible use. *Sustainability, 12*, 7737. doi:10.3390/su12187737.

Griffiths, M. D. (1999). Internet addiction: Fact or fiction? *Psychologist, 12*, 46–50.

Kar, S. K., Arafat, S. Y., Sharma, P., Dixit, A., Marthoenis, M. & Kabir, R. (2020). COVID-19 pandemic and addiction: Current problems and future concerns. *Asian Journal of Psychiatry, 51*, 102064. doi:10.1016/j.ajp.2020.102064.

Kilian, C., Manthey, J., Braddick, F., Matrai, S., Gual, A. & Rehm, J., con el Grupo de estudio europeo sobre el consumo de alcohol y COVID-19. (2020). *Cambios en el consumo de alcohol desde el brote de la pandemia de SARS-CoV-2 en Europa: Un protocolo de estudio.* https://www.deep-seas.eu/standard-eu-alcohol-survey/.

Lechner, W. V., Laurene, K. R., Patel, S., Anderson, M., Grega, C. & Kenne, D. R. (2020). Changes in alcohol use as a function of psychological distress and social support following COVID-19 related University closings. *Addictive Behaviors, 110*, 106527. doi:10.1016/j.addbeh.2020.106527.

Lima, C. K. T., Carvalho, P. M. M., Lima, I., Nunes, J., Saraiva, J. S., de Souza, R. I.,… Neto, M. L. R. (2020).

The emotional impact of Coronavirus 2019-nCoV (new Coronavirus disease). *Psychiatry Research, 287,* 112915. doi:10.1016/j.psychres.2020.112915.

López-Fernández, O., Griffiths, M. D., Kuss, D. J., Dawes, C., Pontes, H. M., Justice, L.,… Billieux, J. (2019). Cross-cultural validation of the compulsive Internet use scale in four forms and eight languages. *Cyberpsychology, Behavior, and Social Networking, 22*, 451–464. doi:10.1089/cyber.2018.0731.

Martinotti, G., Alessi, M. C., Di Natale, C., Sociali, A., Ceci, F., Lucidi, L.,... Fiori, F. (2020). Psychopathological burden and quality of life in substance users during the COVID-19 lockdown period in Italy. *Frontiers in Psychiatry, 11*, 896. doi:10.3389/fpsyt.2020.572245.

Mazza, M., Marano, G., Lai, C., Janiri, L. & Sani, G. (2020). Danger in danger: Interpersonal violence during COVID-19 quarantine. *Psychiatry Research, 289,* 113046. doi:10.1016/j.psychres.2020.1130463.

Meerkerk, G. J., Van Den Eijnden, R. J. J. M., Vermulst, A. A. & Garretsen, H. F. L. (2009). The Compulsive Internet Use Scale (CIUS): Some psychometric properties. *Cyberpsychology and Behavior, 12*, 1–6. doi:10.1089/cpb.2008.0181.

Ministerio de Sanidad (Unidad de Tabaquismo de la Dirección General de Salud Pública). (2020). *Tabaco, otras formas de consumo y confinamiento.* https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov/documentos/Informe_de_los_resultados_de_la_encuesta.pdf.

Observatorio Español de las Drogas y las Adicciones (2020). *Breve encuesta online sobre internet, videojuegos y juego con dinero online durante la pandemia por Covid-19.* https://pnsd.sanidad.gob.es/noticiasEventos/actualidad/2020_Coronavirus/pdf/20200715_Informe_IMPACTO_COVID-19_OEDA_final.pdf.

Observatorio Europeo de las Drogas y las Adicciones. (2020). *Encuesta europea sobre consumo de drogas en el contexto de la pandemia por COVID-19 (Mini-EWSD-COVID-19*). https://pnsd.sanidad.gob.es/noticiasEventos/actualidad/2020_Coronavirus/pdf/20200715_Informe_IMPACTO_COVID-19_OEDA_final.pdf.

Plan Nacional sobre Drogas (2018). *Encuesta sobre alcohol y drogas en España (EDADES) 2017-2018.* https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2019_Informe_EDADES.pdf.

Plan Nacional sobre Drogas (2019). *Encuesta sobre el uso de drogas en enseñanzas secundarias en España (ESTUDES) 2018-2019.* https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/ESTUDES_2018-19_Informe.pdf.

Pfefferbaum, B. & North, C. S. (2020). Mental health and the Covid-19 pandemic. *The New England Journal of Medicine, 383*, 510-512. doi:10.1056/NEJMp2008017.

Qiu, J., Shen, B., Zhao, M., Wang, Z., Xie, B. & Xu, Y. (2020). A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: Implications and policy recommendations. *General Psychiatry, 33*, e100213. doi:10.1136%2Fgpsych-2020-100213.

Orden SND/380/2020, de 30 de abril, sobre las condiciones en las que se puede realizar actividad física no profesional al aire libre durante la situación de crisis sanitaria ocasionada por el COVID-19. *Boletín Oficial del Estado, 121.* https://www.boe.es/eli/es/o/2020/04/30/snd380/con.

Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por el COVID-19. *Boletín Oficial del Estado, 67,* 25390-25399. https://www.boe.es/boe/dias/2020/03/14/pdfs/BOE-A-2020-3692.pdf.

Real Decreto 537/2020, de 22 de mayo, por el que se prorroga el estado de alarma declarado por el Real Decreto 463/2020, de 14 de marzo, por el que se declara el estado de alarma para la gestión de la situación de crisis sanitaria ocasionada por el COVID-19. *Boletín Oficial del Estado, 145*, 34001-34011. https://www.boe.es/boe/dias/2020/04/25/pdfs/BOE-A-2020-4652.pdf.

Reger, M. A., Stanley, I. H. & Joiner, T. E. (2020). Suicide mortality and coronavirus disease 2019-A perfect storm? *JAMA Psychiatry, 77*, 1093-1094. doi:10.1001/jamapsychiatry.2020.1060.

Rojas-Jara, C. (2020). Cuarentena, aislamiento forzado y uso de drogas. *Cuadernos de Neuropsicología/Panamerican Journal of Neuropsychology, 14*, 24-28. doi:10.7714/CNPS/14.1.203.

Rossi, R., Socci, V., Talevi, D., Mensi, S., Niolu, C., Pacitti, F.,... Di Lorenzo, G. (2020). COVID-19 pandemic and lockdown measures impact on mental health among the general population in Italy. *Frontiers in Psychiatry, 11,* 790. doi:10.1101/2020.04.09.20057802.

Sun, Y., Li, Y., Bao, Y., Meng, S., Sun, Y., Schumann, G.,... Shi, J. (2020). Brief report: Increased addictive Internet and substance use behavior during the COVID-19 pandemic in China. *The American Journal on Addictions, 29*, 268-270. doi:10.1111/ajad.13066.

Villanueva, V. J., Motos, P., Isorna, M., Villanueva, V., Blay, P. J. & Vázquez, A. (2021). *Impacto de las medidas de confinamiento en la* pandemia de covid-19 en el consumo de riesgo de alcohol. *Revista Española de Salud Pública, 20, e202101015.*

Volkow, N. D. (2020). Collision of the COVID-19 and addiction epidemics. *Annals of Internal Medicine, 173*, 61–62. doi:10.7326/M20-1212.

Wang, C., Pan, R., Wan, X., Tan, Y., Xu, L., Ho, C. S. & Ho, R. C. (2020). Immediate psychological responses and associated factors during the initial stage of the

2019 coronavirus disease (COVID-19) epidemic among the general population in China. *International Journal of Environmental Research and Public Health, 17*, 1729. doi:10.3390/ijerph17051729.

Winstock, A. R., Davies, E. L., Gilchrist, G., Zhuparris, A., Ferris, J. A., Maier, L. J. & Barratt, M. J. (2020). *GDS Global Drug Survey on COVID-19*. https://www.globaldrugsurvey.com/wp-content/themes/globaldrugsurvey/assets/GDS_COVID-19-GLOBAL_Interim_Report-2020.pdf.

Yehudai, M., Bender, S., Gritsenko, V., Konstantinov, V., Reznik, A. & Isralowitz, R. (2020). COVID-19 fear, mental health, and substance misuse conditions among university social work students in Israel and Russia. *International Journal of Mental Health and Addiction,* 1-8. doi:10.1007/s11469-020-00360-7.

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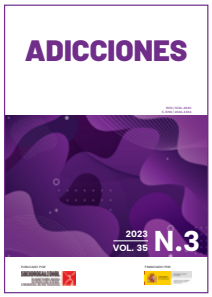

ORIGINAL

A 35-year follow-up study of patients admitted to methadone treatment between 1982-1984 in Asturias, Spain

Estudio de seguimiento de 35 años de pacientes admitidos a tratamiento con metadona entre 1982-1984 en Asturias, España

Luis Jiménez-Treviño *,**,***,****,*****; Clara Martínez-Cao*,***,*****; Fernando Sánchez-Lasheras******; Celso Iglesias*,**,***,****,*****; María Jesús Antuña****; Leonor Riera*****; Pilar Alejandra Sáiz*,**,***,****,*****; Julio Bobes*,**,***,****,*****.

* Área de Psiquiatría, Universidad de Oviedo, Oviedo, España.
** Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, España.
*** Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, España.
**** Servicio de Salud del Principado de Asturias (SESPA), Oviedo, España.
***** Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, España.
****** Research Department, Tecniproject S.L., Oviedo, España.

Abstract

The objective was to evaluate outcomes in a heroin-dependent population 35 years after first enrolment in methadone maintenance treatment (MMT). An ad hoc protocol was used to assess drug misuse, treatment, and drug-related morbidity in the survivor sample. The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated. A total of 214 heroin-dependent patients entered MMT between 1982 and 1984 in the Asturias Public Health Service. Information was received on 195 subjects, of whom 146 were deceased. Men accounted for 77.5% of the study cohort. Over the 35-year follow-up period, the SMR was 11.75 (95% CI = 9.95 - 13.77). In the survivor sample, 5.7% were still enrolled in MMT; human immunodeficiency virus (HIV) was diagnosed in 38.77% and hepatitis B/C in 73.46%. No sex differences were found for mortality or HIV and hepatitis B/C status. None of the female survivors were using heroin at the 35-year follow-up, compared with 5.26% of males. In conclusion, our study confirms the high long-term mortality rate of heroin addicts, even after enrollment in MMT.

Keywords: mortality, heroin addiction, methadone maintenance therapy, follow-up

Resumen

El objetivo fue evaluar el estado de una población dependiente a la heroína 35 años después de su primera inscripción en un tratamiento de mantenimiento con metadona (TMM). Se utilizó un protocolo ad hoc para evaluar morbilidad, consumo y tratamiento de la adicción en la muestra de supervivientes. Se calculó la razón de mortalidad estandarizada (RME) con un intervalo de confianza (IC) del 95%. Un total de 214 pacientes ingresaron en TMM entre 1982 y 1984 en el Servicio de Salud Pública de Asturias. Se recibió información sobre 195 sujetos, de los cuales 146 habían fallecido. Los hombres representaron el 77,5% de la cohorte del estudio. Durante el período de seguimiento de 35 años, la RME fue de 11,75 (IC 95% = 9,95 – 13,77). En la muestra de supervivientes, el 5,7% todavía estaba inscrito en TMM; el virus de inmunodeficiencia humana (VIH) se diagnosticó en un 38,77% y la hepatitis B/C en un 73,46%; el consumo actual de heroína se informó en un 4,1%. No hubo diferencias de género en la mortalidad o la condición de VIH y hepatitis B/C. Ninguna de las mujeres consumía heroína en el seguimiento de 35 años en comparación con el 5,26% de los hombres. En conclusión, nuestro estudio confirma la alta tasa de mortalidad a largo plazo, incluso después de la inscripción en TMM.

Palabras clave: mortalidad, adicción a la heroína, tratamiento de mantenimiento con metadona, seguimiento

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■ **Send correspondence to:**
Pilar Alejandra Sáiz. Dpto. de Psiquiatría – CIBERSAM. Facultad de Medicina, Univ. de Oviedo. Julián Clavería, s/n, Oviedo, 33006, España.
Email: frank@uniovi.es

Heroin addiction is a chronic, relapsing disease that causes medical, social, and economic problems. There are three types of factors that contribute to the development of heroin dependence: environmental, drug-induced, and genetic (Hser, Hoffman, Grella & Anglin, 2001; Randesi et al., 2016). The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimates the prevalence of opiate use in Europe at 0.4%, the equivalent of 1.3 million adults. However, these data suggest that in the European Union, prevalence rates of use have decreased in recent years (EMCDDA, 2019).

One of the main treatments for heroin dependence in many countries is methadone maintenance treatment (MMT) (Hall, Lynskey & Degenhardt, 2002). This treatment was started as a research project in 1964 (Dole, Nyswander & Kreek, 1966; Dole, 2008) and has subsequently been replicated in programs throughout the world (Novick et al., 1993).

The greater retention of patients in MMT, compared with other treatments, indicates the effectiveness of this intervention in different population (Mattick, Breen, Kimber & Davoli, 2009; Maremmani et al., 2018; Sutlovic et al., 2018). There are diverse factors associated with this retention, including the prescribed dose and presence of infectious diseases (Adelson et al., 2013). Studies have also shown the positive effects of MMT, including reduced illicit opioid use, risk of human immunodeficiency virus (HIV) infection, and illegal activities, and improved overall functioning and mental and physical health (Holland et al., 2013; Kleber, 2008; Mattick et al., 2009; Soyka, Strehle, Rehm, Bühringer & Wittchen, 2017; Ward, Hall & Mattick, 1999; Wang et al., 2014). In addition, stabilizing patients in MMT programs gives them a better chance of finding and holding a suitable job and improves their family and social relationships, as well as their quality of life (Lin, Wu & Detels, 2011).

Mortality among opioid-dependent users varies across countries and populations, but drug overdose is the leading cause of death (Degenhardt et al., 2011; Evans et al., 2015; Russolillo, Moniruzzaman & Somers, 2018; Sutlovic et al., 2018), while medical comorbidities, such as HIV infection, were also associated with an increased mortality rate (Nosyk et al., 2015). MMT is clearly protective against mortality, even in non-randomized observational studies (Clausen, Anchersen & Waal, 2008; Degenhardt et al., 2011; Esteban et al., 2003; Marotta & McCullagh, 2017; Nosyk et al., 2015; Sordo et al., 2017). In the last decade, follow-up studies show that patients in MMT have a 1-year mortality rate between 1% and 1.63% (Cousins et al., 2016; Russolillo et al., 2018; Soyka et al., 2017), while the annual death rate in young adult opiate abusers is around 2% to 6% per year (Darke, Mills, Ross & Teesson, 2011; Degenhardt et al., 2011).

Despite this, the induction phase of methadone treatment and the time immediately after leaving treatment are periods of particularly high mortality risk (Cousins et al., 2016; Evans et al., 2015; Sordo et al., 2017). Furthermore, high rates of mental illness, cocaine and benzodiazepine abuse, sleep disorders, and disruptive behavior are problems that persist in many MMT programs (Dunn, Finan, Tompkins & Strain, 2018; Maremmani et al., 2018; Nordmann et al., 2016; Motta-Ochoa, Bertrand, Arruda, Jutras-Aswad & Roy, 2017; Potik, Abramsohn, Schreiber, Adelson & Peles, 2020).

Relatively little is currently known about long-term recovery processes among addicts who do achieve and maintain abstinence, their needs, and the impact and suitability of MMT, as there are few long-term follow-up studies on this type of patient (Evans et al., 2015; Hser, Evans, Grella, Ling & Anglin, 2015; Jimenez et al., 2000; Jimenez et al., 2011). This may be related to low patient retention in treatment, making longitudinal research very difficult (Hser et al., 2015; Zhou & Zhuang, 2014). Therefore, the aim of our work was to evaluate outcome in a heroin-dependent population 35 years after their first enrollment in MMT. More specifically, we assessed mortality, current drug use, treatment, drug-related morbidity, socioeconomic level, and legal disability in survivors.

Method

Design and sample

This was an observational 35-year follow-up study in a sample of 214 heroin-dependent patients who entered MMT in the Asturias Public Health Service between 1982 and 1984. They were the first patients to be enrolled in MMT in Asturias. Inclusion criteria for enrollment in MMT were (1) severely ill patients with a poor prognosis; (2) patients older than 18 years of age; and (3) patients with two therapeutic failures.

The MMT program in Asturias is a universal program, integrated into the public assistance network, which is easily accessed through Primary Care and Mental Health Services. It is a medium-demand program, as there is no waiting list, time limitation of treatment, or methadone dosage limit. The reasons for expulsion are verbal or physical violence, and drug trafficking or consumption within the center.

The first interview took place at the time of enrollment in MMT. The data were collected by means of an ad hoc protocol on drug dependence, including sociodemographic, clinical, family, job, and legal data. All subjects who presented for treatment were included in the sample, even if they left treatment prematurely.

Follow-up procedure

At the 15- and 25-year follow-up, patients were contacted by telephone. Data were collected via telephone interviews

and/or review of medical records. The main findings from the 15- and 25-year follow-up are reported elsewhere (Jimenez et al., 2000; Jimenez et al., 2011).

The 35-year follow-up is the main subject of the present work. Before the assessment, we made an extensive effort to find the patients. Patients were invited to participate in the study via telephone interview conducted by members of the research team.

A trained research psychologist assessed the interviews. Additional data was obtained from medical records and from the Spanish Population and Health Resources Information System (SIPRES) that collects sociodemographic information (date of birth, personal address, employment status and living situation). A total of 19 subjects (8.8%) could not be located. Information was therefore obtained on 195 subjects (91.1%), of whom 3 (1.5%) refused an interview and 146 (74.8%) had died. In all, 46 (23.5%) subjects were interviewed.

Number of deaths

We received information about the number of deaths from the Spanish Ministry of Health death register and from the SIPRES. Information on cause of death was collected via direct personal interviews of relatives or by a review of medical records, resulting in incomplete data.

Measures

An ad hoc protocol was used to collect data on the use of addiction treatment resources. Actual drug misuse was assessed via personal interview. Information concerning patient HIV and HBV/HCV status was obtained via personal interview and from medical records.

Statistical Analyses

Our aim was to determine whether the study sample of heroin-dependent patients had a survival rate comparable to the demographically matched general population, according to the 2018 results provided by Spain's National Statistics Institute (Instituto Nacional de Estadística, 2018). The standardized mortality ratio (SMR) and 95% confidence interval (CI) were calculated using the expected number of deaths in the sample, according to demographic statistics for the overall population. The null hypothesis was tested using a one-sample log-rank test. Additionally, Kaplan-Meier curves were constructed, which showed the expected and observed results. In order to assess the annual death rate for each year of age during follow-up, we used the convention proposed by Finkelstein, Muzikansky & Schoenfeld (2003) that both diagnosis and end of follow-up occurred on a patient's birthday. All calculations were performed using R statistical software, version 3.6.1 (R Core Team, 2019). Mean comparisons between two groups were performed using the t-test for normally distributed independent samples. Nonparametric tests were used as necessary. When comparing categorical data, chi-square (χ^2) tests were used. Finally, a logistic regression model (forward stepwise selection) was estimated to determine the independent factors associated with dying in the last 20 years. The level of statistical significance was set at $\alpha = 0.05$ (two-tailed).

Ethics

The study was conducted in compliance with Spanish national legislation. It was approved by the Clinical Research Ethics Committee of Hospital Universitario Central de Asturias, Oviedo, Spain (ref. no. 52/19) and was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (World Medical Association, 1989).

Results

Baseline versus follow-up samples

Demographic and clinical characteristics of survivors (n=49) compared with previous data are shown in Table 1, Table 2, and Fig. 1. Men accounted for 76.2% (n=163)

Table 1
Clinical characteristics of survivors at follow-up

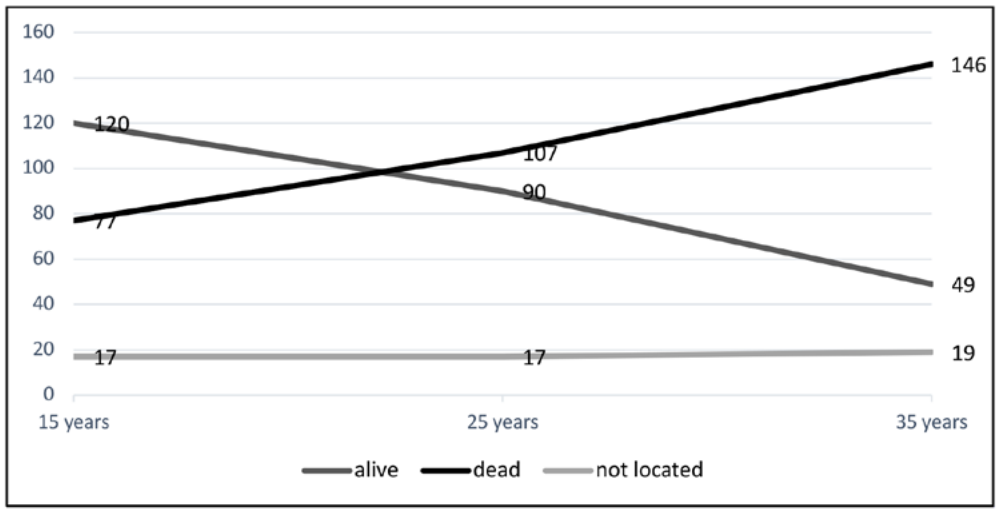
	Baseline (N=214)		15 years (N=120)		25 years (N=90)		35 years (N=49)	
Sex	Men 78.1%	Women 21.9%	Men 77.5%	Women 22.5%	Men 77.8%	Women 22.2%	Men 77.60%	Women 22.40%
Age (SD)	26.05 (8.57)	25.29 (4.30)	40.16 (7.58)	38.81 (3.27)	50.13 (7.19)	49.05 (3.67)	61.61 (9.22)	59.27 (3.85)
HIV+	No data	No data	45.6%	47.1%	37.1%	35.0%	42.1%	27.3%
HBV/HCV	No data	No data	68.2%	70.0%	65.7%	60.0%	76.3%	63.6%
Current heroin	100%	100%	51.1%*	20.0%*	32.5%*	0%*	5.26%	0%
Current MMT	100%	100%	72.5%	84.6%	50.0%	37.5%	5.7%	0%

Note. *Men vs. women difference $p<0.05$. MMT=methadone maintenance treatment; Fisher's exact test: Heroin: $p = 1$, MMT: $p = 1$; Chi-square: HBV/HCV: $\chi^2 = 1.977$, $p = 0.372$; HIV: $\chi^2 = 0.808$, $p = 0.668$.

Table 2
Sociodemographic characteristics of survivors at follow-up

	15 years (N = 120)			35 years (N = 49)		
Sex	Men (n = 93)	Women (n = 27)	Total (N = 120)	Men (n = 38)	Women (n = 11)	Total (N = 49)
Education level [n (%)]						
Primary	17 (56.7)	3 (30.0)	20 (50.0)	9 (52.9)	1 (25.0)	10 (47.6)
Secondary	11 (36.7)	6 (60.0)	17 (47.2)	6 (35.3)	3 (75.0)	9 (42.9)
University	2 (6.7)	1 (10.0)	3 (7.5)	2 (11.8)	--	2 (9.5)
Work status [n (%)]						
Working	17 (50.0)	4 (40.0)	21 (47.7)	11 (34.4)	3 (30.0)	14 (33.3)
Unemployed	7 (20.6)	3 (11.1)	10 (22.7)	3 (9.4)	1 (10.0)	4 (9.5)
Retired	10 (29.4)	2 (7.4)	12 (27.3)	18 (56.2)	6 (10.0)	24 (57.1)
Student	--	1 (3.7)	1 (2.3)	--	--	--
Legal disability [n (%)]						
Yes	14 (16.1)	3 (11.1)	17 (14.9)	12 (33.3)	2 (18.2)	24 (29.8)
No	12 (13.8)	5 (18.5)	17 (14.9)	5 (13.9)	2 (18.2)	7 (14.9)
Unknown	61 (70.1)	19 (70.4)	80 (70.2)	19 (52.8)	7 (63.6)	26 (55.3)
Marital status [n (%)]						
Married	22 (61.1)	7 (58.3)	29 (61.7)	4 (36.4)	1 (33.3)	5 (35.7)
Never married	9 (25.0)	–	9 (19.1)	3 (27.3)	--	3 (21.4)
Separated/Divorced	3 (8.4)	3 (27.3)	6 (12.8)	3 (27.3)	1 (33.3)	4 (28.6)
Widowed	2 (5.6)	1 (9.1)	3 (6.4)	1 (9.1)	1 (33.3)	2 (14.3)

Figure 1
35-year follow-up



of the study cohort and had a mean age of 26.05 years (SD=8.57) at their first interview. Women accounted for 23.8% (n=38) of the study cohort and had a mean age of 25.29 years (SD=4.31). There was no difference in mean age between men and women (Kruskal-Wallis test, p=0.594).

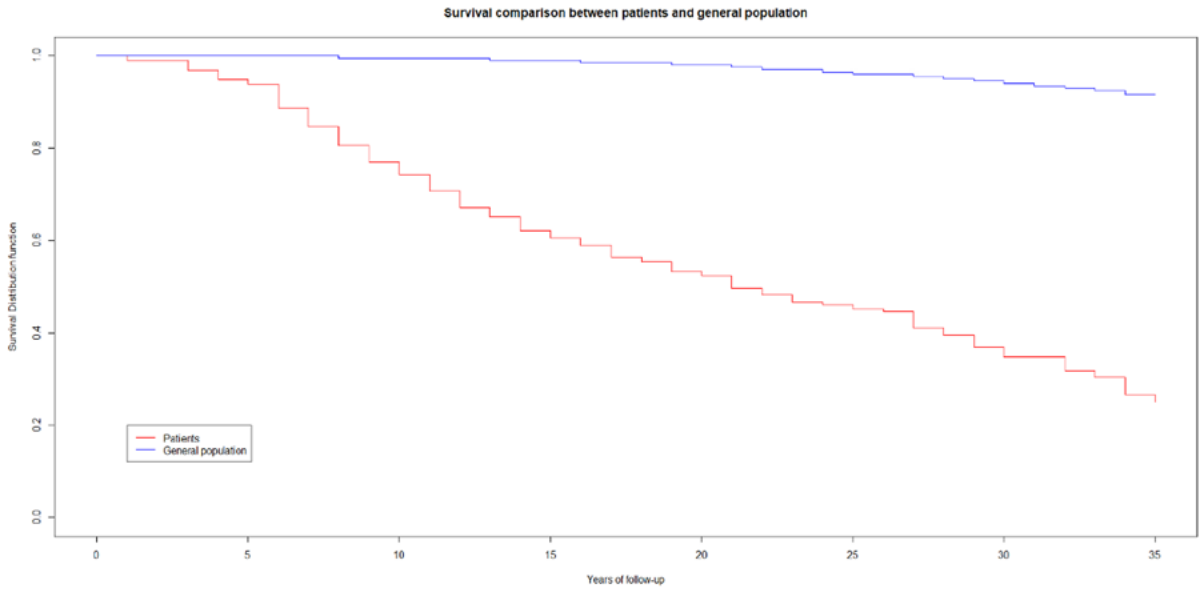
Men accounted for 77.6% (n=38) of the survivor cohort and 88.4% (n=129) of the deceased cohort. Women accounted for 22.4% (n=11) of the survivor cohort and 24.7% (n=36) of the deceased cohort. There was no difference in sex distribution of the survivors and deceased cohorts (χ^2=0.0321, p=0.8578).

HIV/Hepatitis B status

Overall, 38.77% (n=19) of the survivors had an HIV diagnosis at the 35-year follow-up, while the percentage was 36.66% (n=33) at the 25-year follow-up and 28.33% (n=34) at the 15-year follow-up.

Hepatitis B or C was diagnosed in 73.46% (n=36) at the 35-year follow-up, while it was present in the 64.44% (n=58) at the 25-year follow-up and 49.16% (n=59) at the 15-year follow-up. There were no sex differences in either HIV (χ^2=0.808, p=0.668) or hepatitis B/C (χ^2=1.977, p=0.372) status at the 35-year follow-up.

Figure 2
Kaplan-Meier curve estimated for the heroin-dependent sample of patients against the curve that would be expected if the sample had been chosen randomly from the total Spanish population



Observed deaths (n)	Expected deaths (n)	Standardized mortality ratio	Upper 95% SMR-CI	Lower 95% SMR-CI	Log-rank test *p* value
146	12.43	11.75	9.95	13.77	$2 \cdot 10^{-16}$

Past and current use of heroin

The entire sample was using heroin at the start of the study. At the 25-year follow-up, the mean age of first heroin use was 18.39 (SD=2.995). Women started using heroin 1.77 years later than men (t-test=−2.008, p=0.049). There was no difference in mean age of first heroin use between the survivor and deceased samples (t-test=−1.185, p=0.241). Therefore, for the present study, we did not estimate the differences; the mean age of first use of heroin was the same as at the 25-year follow-up.

At the 35-year follow-up, 4.1% of survivors reported current heroin use, while 22.6% were using heroin at the 25-year follow-up and 39.7% at the 15-year follow-up. None of the female survivors were using heroin at the 35-year follow-up or at the 25-year follow-up compared with 5.3% of male survivors.

Current methadone maintenance therapy

The entire sample started MMT at the beginning of the study. At the 15-year follow-up, 60.4% of the survivors were still enrolled in MMT, whereas 39.6% were still enrolled at the 25-year follow-up, and 5.7% at the 35-year follow-up. There were no sex differences in current MMT enrollment in the survivor sample (Fisher's exact test, p=1), but it should be noted that only two of the survivors are currently enrolled in MMT.

Mortality

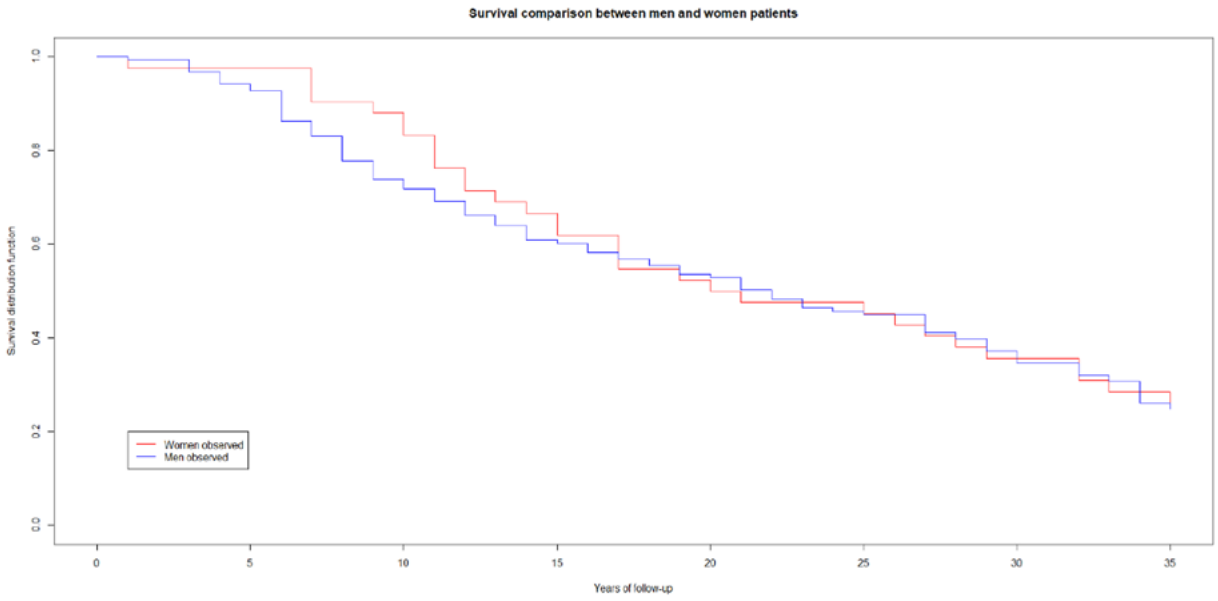
A total of 146 individuals (115 men, 31 women) had died by December 31, 2019. The first SMR calculations were performed using this sample size. The mean age of deceased patients was 42.68 years (SD=12.52); the youngest person died at the age of 22 and the oldest at the age of 93 years. There was no sex difference in mean age of death (t-test=0.530, p=0.601).

The expected death rate for the general population in the follow-up period analyzed was 12.43 in comparison with 146 deaths observed in the heroin-dependent population. Over the 35-year follow-up period, the SMR in the deceased group (n=146) was 11.75 (95% CI=9.95 – 13.77) (Fig. 2).

After repeating the analysis by sex, the results were as follows: 115 deaths were observed in the male heroin-dependent population in comparison to the expected death toll of 13.20 for the general population. Over the 35-year follow-up period, the SMR in the deceased group (n=115) was 8.71 (95% CI=7.22–10.44).

Thirty-one deaths were observed in the female heroin-dependent population in comparison to the expected death toll of 1.83 for the general population. Over the 35-year follow-up period, the SMR in the deceased group (n=31) was 16.94 (95% CI=11.71 – 23.75). There were no sex differences in Kaplan-Meier curves (p=0.070) (Fig. 3).

Figure 3
Kaplan-Meier curve estimated for the heroin-dependent sample of patients against the curve that would be expected if the sample had been chosen randomly from the total Spanish population



	Observed deaths (n)	Expected deaths (n)	Standardized mortality ratio	Upper 95% SMR-CI	Lower 95% SMR-CI	Log-rank test *p* value
Women	31	1.83	16.94	11.71	23.75	0.070
Men	115	13.2	8.71	7.22	10.42	

Table 3
Causes of death by sex since 15-year endpoint

	Men (n = 61)	Women (n = 16)	Total (N = 77)
Age (SD)	34.58 (8.43)	35.25 (4.69)	34.72 (7.77)
Cause of death [n (%)]			
HIV/AIDS	18 (29.5)	4 (25.0)	22 (28.6)
HCV/HBV/Cirrhosis	–	–	–
Overdose	6 (9.8)	–	6 (7.8)
Diseases*	1 (1.6)	–	1 (1.3)
Suicide	–	–	–
Accident	–	1 (6.3)	1 (1.3)
Homicide	1 (1.6)	–	1 (1.3)
Unknown	35 (57.4)	11 (68.8)	46 (59.7)

Note. *Diseases: Cancer, cerebrovascular event, respiratory disease.

Detailed information concerning cause of death was obtained for only 55 (37.67%) of these subjects using medical records and information provided by direct interview of relatives. Causes of death by sex are shown in Table 3 and Table 4. At the 15-year follow-up, the leading cause of death was HIV (28.6%), however, in the last 20 years, the leading causes of death were different diseases such as cancer, cerebrovascular events, or respiratory diseases (17.4%). However, statistical tests were not applied due to lack of data and excessive missing/unknown causes.

Risk factors associated with dying in the last 20 years

Logistic regression models were developed in order to identify risk factors associated with dying in the last 20 years (see Table 5 and Table 6). Excessive missing data made it difficult to identify these factors; therefore, we used only

Table 4
Causes of death by sex in the last 20 years

	Men (n = 54)	Women (n = 15)	Total (N = 69)
Age (SD)	50.84 (10.58)	49.53 (6.85)	50.55 (9.8)
Cause of death [n (%)]			
HIV/AIDS	3 (5.6)	1 (6.7)	4 (5.8)
HCV/HBV/Cirrhosis	3 (5.6)	–	3 (4.3)
Overdose	3 (5.6)	–	3 (4.3)
Diseases*	8 (14.8)	4 (26.7)	12 (17.4)
Suicide	1 (1.9)	–	1 (1.4)
Accident	–	–	–
Homicide	1 (1.9)	–	1 (1.4)
Unknown	35 (64.8)	10 (66.7)	45 (65.2)

*Note.**Diseases: Cancer, cerebrovascular event, respiratory disease.

Table 5
Deaths in the last 20 years and survivors

	Deaths (N = 69)	Survivors (N = 49)	Statistical test, *p*
Sex, male [n (%)]	54 (78.26)	38 (77.60)	.008[a], .927
HBV/HCV [n (%)]	35 (79.5)	36 (83.7)	8.771[a], .012
HIV+ [n (%)]	30 (71.4)	19 (46.3)	12.700[a], .002

Note. [a] Chi-square test.

Table 6
Variables associated with dying in the last 20 years

	β	SE	Wald	df	*p*	O.R.	95% CI
Death, Yes							
Intersection	-.134	.544	.060	1	.806	.875	
HIV+	1.089	.490	4.491	1	.026	2.972	1.138-7.765
HBV/HCV	-.687	.604	1.297	1	.255	.503	.154-1.642
Cox and Snell R2	.069						
Nagelkerke R2	.091						
Correct predictions	61.3%						

Table 7
Mortality in heroin-dependent population in follow-up studies

Study (year)	Country	Follow-up (years)	Deaths (%)	Sample size and derivation
Hser et al. (2001)	USA	33	48,9	581 white men admitted to the California Civil Addict Program
Nehkant et al. (2005)	UK	33	22	86 heroin dependents seen for therapeutic intervention
Jiménez-Treviño et al. (present study)	Spain	35	68,2	214 heroin dependents entering MMT for the first time
Stenbacka et al. (2010)	Sweden	37	50,4	1705 substance abusers identified through medical records
Fridell et al. (2019)	Sweden	42	42,3	1405 patients admitted to the unit for detoxification from narcotics

Note. MMT=methadone maintenance treatment.

clinical data such HIV+ and HBV/HCV infection. Our results show that HIV+ was associated with an increased risk of death in the last 20 years [OR = 2.972 (95% CI = 1.138-7.765)]. However, HBV/HCV infection was not significant in predicting these deaths.

Discussion

We present the third wave of the follow-up on a sample of 214 heroin-dependent patients consecutively enrolled in MMT between 1982 and 1984 in the Asturias Public Health Service, 35 years after first entering MMT. Previous reports by our group show data at the 15- and 25-year endpoints (Jimenez et al., 2000; Jimenez et al., 2011).

To our knowledge, including ours, there are only 5 published studies of heroin-dependent patients with more than 30 years' follow-up, all in Western countries (see Table 7).

In this third wave, we were able to locate 91.1% of the original sample. This attrition rate of under 10% is similar to the other long-term follow-up studies (Fridell et al., 2019; Hser et al., 2001; Nehkant, Rathod, Addenbrooke & Rosenbach, 2005) and constitutes an improvement compared to our attrition rates at 15 years (63.6%) and 25 years (25.7%). The main reason for the increase in our location rate is the progressive transition to electronic health and death records in Spain. Electronic health records (EHRs) have emerged largely as a mean to improve health-care quality and to capture billing data, but they may potentially be used to facilitate data collection or conduct entirely EHR-based observational studies (Cowie et al., 2017).

Our study confirms the high long-term mortality of heroin addicts, even after enrollment in MMT. Our death rate of 68.2% after 35 years is the highest among the long-term follow-up studies but agrees with a number of studies in non-MMT patients with an annual death rate of around 2% per year in young adult drug abusers (Haastrup & Jepsen, 1988; Oppenheimer, Tobutt, Taylor & Andrew, 1994; Ravndal & Vaglum, 1998; Segest, Mygind & Bay, 1990), suggesting a failure of long-term death prevention in MMT programs. It should be noted that it is difficult to compare these types of studies: there are differences in MMT programs (access, duration, inclusion criteria, etc.) between countries and within the same country, they use different study groups, methods, and calculations as well as different sample sizes, countries of origin, and length of follow-up periods.

We have used the SMR as a more accurate way to compare death figures. After a mean follow-up period of 35 years, the SMR of 11.75 (8.71 men vs. 16.94 women) in our cohort was higher than the 6.68 men vs. 4.98 women found by Fridell et al. (2019) and the 3.3 men vs. 3.5 women found by Stenbacka, Leifman & Romelsjö (2010), but there is a significant decrease compared with the 22.51 SMR we found at the 25-year endpoint (Jimenez et al., 2011).

The reason for this drop in the SMR may be found in the low rates of opiate use in our sample for the last 10 years (only 5% of the males and none of the females reported current heroin use at the 35-year endpoint), as well as the universal availability of an effective HCV treatment in Spain in the past decade (Berenguer, 2018). In fact, despite a near 70% prevalence of HBV/HCV infection in our sample, it is not one of the variables associated with dying in the last 20 years. Cirrhosis of the liver remained among the top 5 causes of death in the 37-year follow-up study by Stenbacka et al. (2010). Nehkant et al. (2005) also reported that liver disease was frequently mentioned on the death certificates in their study, highlighting the need for regular liver function screening for early detection and treatment. Unfortunately, our lack of data on causes of death in our sample prevents us from confirming this statement. Based on Spanish population studies, elimination of HCV infection would have decreased HCV-related deaths by 20% (Buti et al., 2017). The impact of HCV on mortality has been already highlighted in studies on the HIV population: having an HCV co-infection with AIDS yielded an SMR of 20.8 (16.5-26.1) in HIV+ subjects followed-up for the period from 1997 - 2008 in the Cohorts of Spanish Network on HIV/AIDS (Hernando et al., 2012).

While numerous studies have demonstrated the effectiveness of MMT for reducing morbidity, risk of HIV infection, and mortality (Kleber, 2008), our HBV/HCV and HIV rates of 70% and 45% respectively, as well as our mortality rate of 68.2% in MMT patients, seem to reflect poor effectiveness. Unfortunately, we do not have a control sample of non-MMT heroin addicts for comparison, but our rates of HIV and HBV/HCV are higher than those published in previous long-term follow-up studies: 30.7% of HIV infection rate in Bauer et al. (2008) 10-year sample or 41.7% and 48% of HBV/HCV infection rate in Hser et al. (2001) and Fridell et al. (2019) studies. It is important to point out that most of the HCB/HCV and HIV cases were diagnosed in the first 15 years of follow-up. Only 18% of the HBV/HCV and 29% of the HIV cases were diagnosed in the last 20 years of follow-up.

On the other hand, the rate of current heroin use in our survivor sample (5.26% men/0% women) is lower than previous reports in long-term follow-up studies of heroin addicts such as the ones by Hser et al. (2001) (20.7% after 33 years), Nehkant et al. (2005) (20% after 33 years), and Nyhlén, Fridell, Bäckström, Hesse & Krantz (2011) (27% after 37 years). It is encouraging that trend studies find that the proportion of patients still addicted is declining, despite the pessimistic views expressed two decades ago by Hser et al. (2001). However, there is no way of knowing whether the proportion of drug-related deaths reflects selection bias. The 35-year follow-up survivors may represent the patients in the initial sample with the least severe dependency and thus more likely to stop using heroin.

Taken together these results, they may explain our higher mortality rate and lower current heroin use, as previous follow-up studies in Spanish, Swiss and Scandinavian populations have showed that HIV-related deaths are the most prevalent in MMT patient cohorts (Davstad, Stenbacka, Leifman, & Romelsjö, 2009; Rehm et al., 2005; Sánchez-Carbonell & Seus, 2000; Stenbacka et al., 2010). Even after the implementation of antiretroviral treatments, HIV infection is still associated with increased mortality among heroin users as heroin dependence also compromise effective HIV treatment by influencing both access and adherence to antiretroviral therapy. Exposure to addictive substances may also have direct immunosuppressive effects independent of their impact on access and adherence to treatment (Sammet, Walley & Bridden, 2007).

Moreover, Hepatitis B and HIV increased infection rates are also associated with severity of the addiction and duration of injecting drug use (Levine et al., 1995; Sammet, Walley & Bridden, 2007) and this may be the cause of our low rates of actual heroin use in our sample, as most of the heavy users would have died due to a higher risk of death, not only by overdose but also because of the greater prevalence of these medical conditions.

As a brief conclusion to these results, we may safely say that, 35 years after seeking methadone treatment for heroin dependence, either you have quit or you are dead.

Limitations of the study have already been covered in the Discussion. The main limitations of the study include the large amount of missing data on causes of death as well as the lack of an untreated control sample. Other limitations include the lack of data on HIV and HBV status at the start of the follow-up period and the lack of standardization of the ad hoc protocol that was used.

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Conflict of interests

The authors declare that there is no conflict of interest. The funding sources had no involvement in this study.

References

Adelson, M., Wilson, H. W., Celeste, V. Y. M., Linzy, S., Kreek, M. J. & Peles, E. (2013). Methadone maintenance treatment experience in Macao–prospective follow-up for initial 4.5 years. *Journal of Psychoactive Drugs*, *45*, 313-321. doi:10.1080/02791072.2013.825032.

Bauer, S. M., Loipl, R., Jagsch, R., Gruber, D., Risser, D., Thau, K.,… Fischer, G. (2008). Mortality in opioid-maintained patients after release from an addiction clinic. *European Addiction Research, 14*, 82–91. doi:10.1159/000113722.

Berenguer, J. (2018). Elimination of Hepatitis C Virus in Spain: A pending challenge. *Enfermedades Infecciosas y Microbiología Clínica, 36*, 323-324. doi:10.1016/j.eimc.2018.03.001.

Buti, M., Calleja, J. L., García-Samaniego, J., Serra, M. Á., Crespo, J., Romero, M.,… Razavi, H. (2017). Elimination of hepatitis C in Spain: Adaptation of a mathematical model based on the public health strategic plan for addressing hepatitis C in the National Health System. *Medicina Clínica, 148,* 277–282. doi:10.1016/j.medcli.2016.12.018.

Clausen, T., Anchersen, K. & Waal, H. (2008). Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study. *Drug and Alcohol Dependence, 94,* 151-157. doi:10.1016/j.drugalcdep.2007.11.003.

Cousins, G., Boland, F., Courtney, B., Barry, J., Lyons, S. & Fahey, T. (2016). Risk of mortality on and off methadone substitution treatment in primary care: A national cohort study. *Addiction, 111,* 73-82. doi:10.1111/add.13087.

Cowie, M. R., Blomster, J. I., Curtis, L. H., Duclaux, S., Ford, I., Fritz, F.,… Zalewski, A. (2017). Electronic health records to facilitate clinical research. *Clinical Research in Cardiology: Official Journal of the German Cardiac Society, 106,* 1–9. doi:10.1007/s00392-016-1025-6.

Darke, S., Mills, K. L., Ross, J. & Teesson, M. (2011). Rates and correlates of mortality amongst heroin users: Findings from the Australian treatment outcome study (ATOS), 2001–2009. *Drug and Alcohol Dependence, 115,* 190-195. doi:10.1016/j.drugalcdep.2010.10.021.

Davstad, I., Stenbacka, M., Leifman, A. & Romelsjö, A. (2009). An 18-year follow-up of patients admitted to methadone treatment for the first time. *Journal of Addictive Diseases,* 28, 39–52. doi:10.1080/10550880802544997.

Degenhardt, L., Bucello, C., Mathers, B., Briegleb, C., Ali, H., Hickman, M. & McLaren, J. (2011). Mortality among regular or dependent users of heroin and other opioids: A systematic review and meta-analysis of cohort

studies. *Addiction, 106,* 32-51. doi:10.1111/j.1360-0443.2010.03140.x.

Dole, V.P. (2008). Implications of methadone maintenance for theories of narcotic addiction. *Journal of the American Medical Association, 260*, 3025-3029.

Dole, V.P., Nyswander, M.E. & Kreek, M.J. (1966). Narcotic blockade. *Archives of Internal Medicine, 118,* 304-309.

Dunn, K.E., Finan, P.H., Tompkins, D. A. & Strain, E.C. (2018). Frequency and correlates of sleep disturbance in methadone and buprenorphine-maintained patients. *Addictive Behaviors, 76,* 8-14. doi:10.1016/j.addbeh.2017.07.016.

European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2019). *EMCDDA—Information on drugs and drug addiction in Europe.* http://www.emcdda.europa.eu/.

Esteban, J., Gimeno, C., Barril, J., Aragonés, A., Climent, J. M. & de la Cruz Pellín, M. (2003). Survival study of opioid addicts in relation to its adherence to methadone maintenance treatment. *Drug and Alcohol Dependence, 70,* 193-200. doi:10.1016/s0376-8716(03)00002-4.

Evans, E., Li, L., Min, J., Huang, D., Urada, D., Liu, L.,… Nosyk, B. (2015). Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–10. *Addiction, 110,* 996-1005. doi:10.1111/add.12863.

Finkelstein, D. M., Muzikansky, A. & Schoenfeld, D. A. (2003). Comparing survival of a sample to that of a standard population. *Journal of the National Cancer Institute, 95,* 1434–1439. doi:10.1093/jnci/djg052.

Fridell, M., Bäckström, M., Hesse, M., Krantz, P., Perrin, S. & Nyhlén, A. (2019). Prediction of psychiatric comorbidity on premature death in a cohort of patients with substance use disorders: A 42-year follow-up. *BMC Psychiatry, 19,* 150. doi:10.1186/s12888-019-2098-3.

Haastrup, S. & Jepsen, P.W. (1988). Eleven-year follow-up of 300 young opioid addicts. *Acta Psychiatrica Scandinavica, 77,* 22-26. doi:10.1111/j.1600-0447.1988.tb05071.x.

Hall, W., Lynskey, M. & Degenhardt, L. (2002). Trends in opiate-related deaths in the United Kingdom and Australia, 1985–1995. *Drug and Alcohol Dependence, 57,* 247–254. doi:10.1016/s0376-8716(99)00057-5.

Hernando, V., Perez-Cachafeiro, S., Lewden, C., Gonzalez, J., Segura, F., Oteo, J. A.,… CoRIS. (2012). All-cause and liver-related mortality in HIV positive subjects compared to the general population: Differences by HCV co-infection. *Journal of Hepatology, 57,* 743–751. doi:10.1016/j.jhep.2012.06.010.

Holland, R., Maskrey, V., Swift, L., Notley, C., Robinson, A., Nagar, J.,… Kouimtsidis. (2013). Treatment retention, drug use and social functioning outcomes in those receiving 3 months versus 1 month of supervised opioid maintenance treatment. Results from the super C randomized controlled trial. *Addiction, 109,* 596-607. doi:10.1111/add.12439.

Hser, Y. I., Evans, E., Grella, C., Ling, W. & Anglin, D. (2015). Long-term course of opioid addiction. *Harvard Review of Psychiatry, 23,* 76-89. doi:10.1097/HRP.0000000000000052.

Hser, Y.I., Hoffman, V., Grella, C.E. & Anglin, M.D. (2001). A 33-year follow-up of narcotics addicts. *Archives of General Psychiatry, 58,* 503–508. doi:10.1001/archpsyc.58.5.503.

Instituto Nacional de Estadística. (2018). *Defunciones según causa de muerte. Año 2018.* https://www.ine.es/dyngs/INEbase/es/operacion.htm?c= Estadistica_C&cid=1254736176780&menu=ultiDatos&idp=1254735573175.

Jimenez, L., Saiz, P. A., Gutierrez, E., Bascaran, M. T., Carreño, E. & González-Quiros, M. (2000). Valoración transversal tras quince años en una muestra de adictos a opiáceos en Asturias. *Adicciones, 12,* 507–513.

Jimenez-Treviño, L., Saiz, P. A., García-Portilla, M. P., Díaz-Mesa, E. M., Sánchez-Lasheras, F., Burón, P.,… Bobes, J. (2011). A 25-year follow-up of patients admitted to methadone treatment for the first time: Mortality and gender differences. *Addictive Behaviors, 36,* 1184-1190. doi:10.1016/j.addbeh.2011.07.019.

Kleber, H. D. (2008). Methadone maintenance 4 decades later: Thousands of lives saved but still controversial. *Journal of the American Medical Association, 300,* 2303–2305. doi:10.1001/jama.2008.648.

Levine, O.S., Vlahov, O., Koehler, J., Cohn, S., Spronk, A.M. & Nelson, K.E. (1995). Seroepidemiology of hepatitis B virus in a population of injecting drug users. Association with drug injection patterns. *American Journal of Epidemiology, 142,* 331-341. doi:10.1093/oxfordjournals.aje.a117639.

Lin, C., Wu, Z. & Detels, R. (2011). Opiate users' perceived barriers against attending methadone maintenance therapy: A qualitative study in china. *Substance Use and Misuse, 46,* 1190–1198. doi:10.3109/10826084.2011.561905.

Maremmani, A. G., Pallucchini, A., Rovai, L., Bacciardi, S., Spera, V., Maiello, M.,... Maremmani, I. (2018). The long-term outcome of patients with heroin use disorder/dual disorder (chronic psychosis) after admission to enhanced methadone maintenance. *Annals of General Psychiatry, 17,* 14. doi:10.1186/s12991-018-0185-3.

Marotta, P. L. & McCullagh, C. A. (2017). A cross-national analysis of the association between years of implementation of opioid substitution treatments and drug-related deaths in Europe from 1995 to 2013. *European Journal of Epidemiology, 33,* 679-688. doi:10.1007/s10654-017-0342-z.

Mattick, R.P., Breen, C., Kimber, J. & Davoli, M. (2009). Methadone maintenance therapy versus no

opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews, 3,* 1-32. doi:10.1002/14651858.CD002209.pub2.

Motta-Ochoa, R., Bertrand, K., Arruda, N., Jutras-Aswad, D. & Roy, E. (2017). "I love having benzos after my coke shot": The use of psychotropic medication among cocaine users in downtown Montreal. *International Journal of Drug Policy, 49,* 15–23. doi:10.1016/j.drugpo.2017.07.012.

Nehkant, H., Rathod, W., Addenbrooke, M. & Rosenbach, A.F. (2005). Heroin dependence in an English town: 33-year follow-up. *British Journal of Psychiatry, 18,* 421-425. doi:10.1192/bjp.187.5.421.

Nordmann, S., Lions, C., Vilotitch, A., Michel, L., Mora, M., Spire, B.,… ANRS Methaville study group. (2016). A prospective, longitudinal study of sleep disturbance and comorbidity in opiate dependence (the ANRS Methaville study). *Psychopharmacology, 233*, 1203-1213. doi:10.1007/s00213-016-4202-4.

Nosyk, B., Min, J. E., Evans, E., Li, L., Liu, L., Lima, V. D.,… Montaner, J.S.G. (2015). The effects of opioid substitution treatment and highly active antiretroviral therapy on the cause-specific risk of mortality among HIV-positive people who inject drugs. *Clinical Infectious Diseases, 61*, 1157-1165. doi:10.1093/cid/civ476.

Novick, D. M., Richman, B. L., Friedman, J. M., Friedman, J. E., Fried, C., Wilson, J. P.,… Kreek, M.J. (1993). The medical status of methadone maintenance patients in treatment for 11–18 years. *Drug and Alcohol Dependence, 33,* 235-245. doi:10.1016/0376-8716(93)90110-c.

Nyhlén, A., Fridell, M., Bäckström, M., Hesse, M. & Krantz, P. (2011). Substance abuse and psychiatric co-morbidity as predictors of premature mortality in Swedish drug abusers: A prospective longitudinal study 1970-2006. *BMC Psychiatry, 11*, 122. doi:10.1186/1471-244X-11-122.

Oppenheimer, E., Tobutt, C., Taylor, C. & Andrew, T. (1994). Death and survival in a cohort of heroin addicts from London clinics: A 22-year follow-up study. *Addiction, 89,* 1299–1308. doi:10.1111/j.1360-0443.1994.tb03309.x.

Potik, D., Abramsohn, Y., Schreiber, S., Adelson, M. & Peles, E. (2020). Drug abuse and behavioral transgressions during methadone maintenance treatment (MMT) are related to high psychopathy levels. *Substance Use & Misuse, 55,* 460-468. doi:10.1080/10826084.2019.1685546.

R Core Team (2019). *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

Randesi, M., Van den Brink, W., Levran, O., Blanken, P., Butelman, E. R., Yuferov, V.,… Kreek, M.J. (2016). Variants of opioid system genes are associated with non-dependent opioid use and heroin dependence. *Drug and Alcohol Dependence, 168,* 164-169. doi:10.1016/j.drugalcdep.2016.08.634.

Ravndal, E. & Vaglum, P. (1998). Psychopathology, treatment completion and 5 years outcome. A prospective study of drug abusers. *Journal of Substance Abuse Treatment, 15,* 135–142.

Rehm, J., Frick, U., Hartwig, C., Gutzwiller, F., Gschwend, P. & Uchtenhagen, A. (2005). Mortality in heroin-assisted treatment in Switzerland 1994-2000. *Drug and Alcohol Dependence, 79,* 137–143. doi:10.1016/j.drugalcdep.2005.01.005.

Russolillo, A., Moniruzzaman, A. & Somers, J. M. (2018). Methadone maintenance treatment and mortality in people with criminal convictions: A population-based retrospective cohort study from Canada. *PLoS Medicine, 15*. doi:10.1371/journal.pmed.1002625.

Sammet, J.H., Walley, A.Y. & Bridden, C. (2007). Illicit drugs, alcohol, and addiction in human immunodeficiency virus. *Panminerva Medica, 49,* 67-77.

Sánchez-Carbonell, X. & Seus, L. (2000). Ten-year survival analysis of a cohort of heroin addicts in Catalonia: The EMETYST project. *Addiction, 95,* 941–948. doi:10.1046/j.1360-0443.2000.95694110.x.

Segest, E., Mygind, O. & Bay, H. (1990). The influence of prolonged stable methadone maintenance treatment on mortality and employment: An 8-year follow-up. *International Journal of the Addictions, 25,* 53–63.

Sordo, L., Barrio, G., Bravo, M. J., Indave, B. I., Degenhardt, L., Wiessing, L.,... Pastor-Barriuso, R. (2017). Mortality risk during and after opioid substitution treatment: Systematic review and meta-analysis of cohort studies. *British Medical Journal,* 357, 1550. doi:10.1136/bmj.j1550.

Soyka, M., Strehle, J., Rehm, J., Bühringer, G. & Wittchen, H. U. (2017). Six-year outcome of opioid maintenance treatment in heroin-dependent patients: Results from a naturalistic study in a nationally representative sample. *European Addiction Research, 23,* 97-105. doi:10.1159/000468518.

Stenbacka, M., Leifman, A. & Romelsjö, A. (2010). Mortality and cause of death among 1705 illicit drug users: A 37 year follow up. *Drug and Alcohol Review, 29,* 21-27. doi:10.1111/j.1465-3362.2009.00075.x.

Sutlovic, D., Kljucevic, Z., Sliskovic, L., Susnjar, H., Viskovic, I. & Definis-Gojanovic, M. (2018). Methadone maintenance treatment: A 15-year retrospective study in Split-Dalmatia County, Croatia. *Therapeutic Drug Monitoring, 40,* 486-494. doi:10.1097/FTD.0000000000000519.

Wang, K., Fu, H., Longfield, K., Modi, S., Mundy, G. & Firestone, R. (2014). Do community- based strategies reduce HIV risk among people who inject drugs in China? A quasi-experimental study in Yunnan and

Guangxi provinces. *Harm Reduction Journal, 6,* 11-15. doi:10.1186/1477-7517-11-15.

Ward, J., Hall, W. & Mattick, R.P. (1999). Role of maintenance treatment in opioid dependence. *Lancet, 353*, 221–226. doi:10.1016/S0140-6736(98)05356-2.

Zhou, K. & Zhuang, G. (2014). Retention in methadone maintenance treatment in mainland China, 2004–2012: A literature review. *Addictive Behaviors, 39,* 22-29. doi:10.1016/j.addbeh.2013.09.001.

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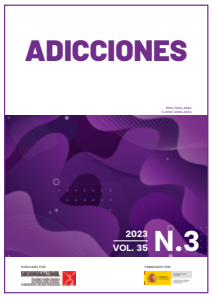

ORIGINAL

Characteristics of drug poisonings treated in eleven Spanish emergency departments: Differentiated analysis by sex

Características de las intoxicaciones por drogas atendidas en once servicios de urgencias españoles: Análisis diferenciado por sexo

Miguel Galicia*; Dima Ibrahim-Achi**; Òscar Miró*; August Supervía***; Jordi Puiguriguer****; María Ángeles Leciñena*****; Mª José Venegas de L'Hotellerie******; Beatriz Martín-Pérez*******; Ana Ferrer********; Guillermo Burillo-Putze*********; en representación de la Red de estudio de drogas en Urgencias Hospitalarias en España (REDUrHE).

* Área de Urgencias, Hospital Clínic, IDIBAPS, Universitat de Barcelona, Barcelona, España.
** Servicio de Urgencias, Hospital Universitario de Canarias, Tenerife, España.
*** Servicio de Urgencias y Unidad Funcional de Toxicología, Hospital del Mar, Barcelona, España.
**** Servicio de Urgencias y Unidad de Toxicología Clínica, Hospital Son Espases, Palma de Mallorca, España.
***** Servicio de Urgencias, Hospital Can Misses, Ibiza, España.
****** Servicio de Urgencias, Hospital Rey Juan Carlos, Móstoles, España.
******* Servicio de Urgencias, Hospital Río Hortega, Valladolid, España.
******** Unidad de Toxicología Clínica, Hospital Clínico Universitario Lozano Blesa, Zaragoza, España.
********* Departamento de Medicina Física y Farmacología, Universidad de La Laguna, Tenerife, España.

Abstract

In order to identify the sociodemographic, clinical, emergency management and severity differences of drug poisoning treated in Emergency Departments (ED) from a gender perspective, data on patients from 11 Spanish EDs were recorded over 24 months (August 2017-July 2019). The severity of intoxication was compared by sex and was based on the combined adverse event (orotracheal intubation, cardiorespiratory arrest, intensive care hospitalization, and death). We included 4,526 patients (men 75.5%), with a mean age of 33 years. The most frequent drugs were: cocaine (47.8%), cannabis (44.4%) and amphetamines (25.5%). Men consumed more GHB (5.6% vs. 1.9%, p < .001) and less benzodiazepines (8.0% vs. 11.1%, p = .002) and alcohol (57.2% vs. 61.2%, p = .028) than women, with no differences in other types of drugs. Men presented significantly more severe bradycardia (OR = 4.39, 95%CI = 1.03-18.7), chest pain (OR = 1.72, 95%CI = 1.27-2.35) and symptomatic hypertension (OR = 1.56, 95%CI = 1.06-2.30) and less anxiety (OR = 0.74, 95%CI = 0.61-0.89) and vomiting (OR = 0.64, CI95% = 0.51-0.80). Men had more combined adverse events (3.1% vs. 2.0%, p = .047) and a greater intubations (1.9% vs. 1.0%, p = .044), with no significant differences in the adjusted model (OR = 1.349, 95%CI = 0.827-2.202 and OR = 1.371, 95%CI = 0.700-2.685, respectively). Twelve patients died (0.3%), with no differences according to sex. Drug intoxications attended in the ED differ according to sex. GHB, benzodiazepines and alcohol are more frequently involved in men than women. Cardiovascular symptomatology is more prevalent in men, while anxiety and vomiting are more frequent in women, which cannot be explained by differences in sociodemographic characteristics or the drugs used. There were no differences in the severity of the intoxication episodes.
Keywords: intoxication, drugs, sex, severity, emergency department

Resumen

Con el objetivo de identificar, con perspectiva de género, las diferencias sociodemográficas, clínicas, manejo en urgencias y gravedad de las intoxicaciones por drogas atendidas en Servicios de Urgencias Hospitalarias (SUH), se registraron todos los pacientes atendidos en 11 SUH españoles durante 24 meses (agosto 2017-julio 2019). La gravedad de la intoxicación se basó en el evento adverso combinado (intubación orotraqueal, parada cardiorrespiratoria, hospitalización en intensivos, y muerte), comparándose según el sexo. Cuando se encontraron diferencias significativas en sintomatología o gravedad, los resultados se ajustaron por características sociodemográficas y drogas consumidas. Se incluyeron 4.526 pacientes (hombres 75,5%), con edad media de 33 años. Las drogas más frecuentes fueron cocaína (47,8%), cánnabis (44,4%) y anfetaminas (25,5%). Hubo más GHB en hombres (5,6% vs 1,9%, p < ,001) y más benzodiacepinas (8,0% vs 11,1%, p = ,002) y alcohol (57,2% vs 61,2%, p = ,028) en mujeres, sin diferencias en otras de drogas. Los hombres tuvieron significativamente más bradicardia grave (OR = 4,39, IC95% = 1,03-18,7), dolor torácico (OR = 1,72, IC95% = 1,27-2,35) e hipertensión sintomática (OR = 1,56, IC95% = 1,06-2,30) y menos ansiedad (OR = 0,74, IC95% = 0,61-0,89) y vómitos (OR = 0,64, IC95% = 0,51-0,80). Tuvieron también más eventos adversos combinados (3,1% vs 2,0%, p = ,047) y más intubaciones (1,9% vs 1,0%, p = ,044), pero sin diferencias significativas en el modelo ajustado (OR = 1,349, IC95% = 0,827-2,202 y OR = 1,371, IC95% = 0,700-2,685, respectivamente). Fallecieron 12 pacientes (0,3%), sin diferencias según sexo. Concluimos que existen diferencias según el sexo en las drogas que originan intoxicaciones atendidas en los SUH. Las diferencias en sintomatología cardiovascular (más en hombres) y ansiosa o digestiva (más en mujeres) no se explican por diferencias sociodemográficas o de drogas utilizadas. La gravedad de la intoxicación no se ve influida por el sexo.
Palabras clave: intoxicación, drogas, sexo, gravedad, urgencias hospitalarias

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■ **Send correspondence to:**
Dr. Guillermo Burillo-Putze. Departamento de Medicina Física y Farmacología. Facultad de Ciencias de la Salud. Carretera La Cuesta-Taco, s/n, La Laguna, 38320 Tenerife, España. Email: gburillo@telefonica.net

According to the national surveys carried out in Spain (Delegación del Gobierno para Plan Nacional sobre Drogas) in both the general population (EDADES survey, 2021) and specific groups (ESTUDES survey on drug use in secondary education, 2020), the prevalence of drug use is stable or rising. Between the ages of 15 and 64, 37.5% of the population has tried cannabis, 10.9% cocaine and 3.1% sedative-hypnotics at some time (in 2017 these percentages were 35.2%, 10% and 3%, respectively). Furthermore, 10.5% had used cannabis and 2.5% cocaine in the last 12 months, with men more often being users of cannabis and cocaine, and women more frequently taking sedative-hypnotics (Delegación del Gobierno para el Plan Nacional sobre Drogas, 2021).

The situation in the rest of Europe is similar. Of the 96 million European citizens aged between 15 and 64 years, 29% have used an illegal drug in their lifetime (cannabis 27%, amphetamines 8%, cocaine 5%) or in the last year (cannabis 7.6%, amphetamines 1.4%, cocaine 1.3%) (European Monitoring Centre for Drugs and Drug Addiction [EMCDDA], 2020), and among students aged 15-18 years, 18% have used cannabis at some point and 5% some other type of illegal drug (ESPAD Group, 2020). As is the case among the Spanish population, drug use among the general population is predominantly male (EMCDDA, 2020; ESPAD Group, 2020).

Adverse reactions after drug use are a frequent cause of admission to hospital emergency departments (EDs), in some cases comprising up to 1% of all visits (Fernández Egido, García Herrero, Romero García & Marquina Santos, 2008; Puiguriguer et al., 2013). The ED is often the only contact drug users have with the health system. For this reason, EDs provide an excellent opportunity to observe the drugs being used, new patterns of use, new clinical pictures derived from them, or the illicit use of some of these substances (Burillo-Putze, López-Hernández, Expósito-Rodríguez & Dueñas-Laita, 2013; Burillo-Putze & Matos Castro, 2018; Fernández Alonso, Óscar Quintela, Ayuso Tejedor, Santiago-Sáez & González Armengol, 2019; Hegazi et al., 2017; Perelló et al., 2018).

The creation of a network of EDs where incidences secondary to drug use can be collected makes it possible to increase knowledge regarding the clinical characteristics of these intoxications treated in Spanish EDs. The present study investigated sex differences in the characteristics of drug poisoning, based on a sample from 11 Spanish EDs, both in sociodemographic terms and with regard to the type of drug involved, symptoms presented by the patient, clinical management in the emergency department, and episode severity.

Method

This is a prospective, descriptive, observational study of patients treated for symptoms resulting from the consumption of drugs of abuse in the EDs of eleven Spanish hospitals spread across six autonomous communities, members of the REDUrHE group (research network on drugs in Spanish hospital emergency departments), over a 24-month period (August 2017-July 2019). Hospitals were chosen on a convenience basis to participate in the network, based on their previous history and interest in studying intoxicated patients during emergency care. The inclusion criteria for patients were being treated in ED for symptoms derived from the use of substances of abuse, and that this use was not for the purpose of suicide.

Sociodemographic variables collected were as follows: age, sex, mode of transport to the ED (ambulance or own means), location of the ED (area with a high incidence of recreational tourism -Palma de Mallorca, Tenerife, Ibiza-, large city -Barcelona and Móstoles- , or not mainly tourist city -Zaragoza, Valladolid, Burgos and Salamanca-), and day (work or holiday) and time (morning-early afternoon: 8:00-16:00; afternoon-evening: 16:00-24:00; night: 0:00-8:00) when the patient appeared in the ED. As clinical variables, the following were collected: vital signs (heart rate, blood pressure, respiratory rate and temperature) and symptoms (anxiety, vomiting, headache, hallucinations, agitation/aggressiveness, psychosis, seizures, cerebellar symptoms, palpitations, chest pain, arrhythmias). Decreased consciousness was defined as a score between 9 and 14 points on the Glasgow Coma Scale, with coma defined as ≤ 8. Finally, patient management details were noted (treatment received and destination at discharge from the ED).

Drug use was determined by clinical history or toxicological analysis by means of urine drug testing using enzyme immunoassay. This is the technique usually available in EDs and allows fast screening for various drugs (usually cannabis, cocaine, heroin, methadone, morphine, MDMA amphetamines and benzodiazepines), achieving an accurate diagnosis for these drugs. However, it should be borne in mind that certain groups of drugs, including gamma-hydroxybutyrate (GHB) and new psychoactive drugs, require more sophisticated techniques and that many EDs base the diagnosis of intoxication by them on the patient's clinical history and symptomatology. The drugs were grouped following a mixed criterion (chemical structure, pharmacodynamics and potential use in medicine). Patients who came to the ED purely with alcohol intoxication, having consumed no other drugs, were excluded.

Any combination of the following adverse events (AE) was considered the primary indicator of severity: need for orotracheal intubation, cardiorespiratory arrest, admission

to intensive care and death. Considered individually, each of these events was a secondary indicator of severity.

The following sociodemographic aspects were compared by sex: drug typology, symptoms, ED management and severity. In addition, regarding the type of drug involved, prevalence according to patient sex is also presented in detail by age group (< 20 years, 20-39 years, 40-59 years, ≥ 60 years). Quantitative variables were expressed as means (standard deviation (SD)) and groups were compared using Student's t or Mann-Whitney U tests, and qualitative variables as absolute numbers and percentages. Comparison between groups was by chi-square or Fisher's exact tests. The magnitude of association was calculated using logistic regression and expressed as an odds ratio (OR) with its 95% confidence interval (95% CI), first in crude form and, when statistical significance was present, adjusted for age, co-ingestion of ethanol and the drugs consumed. Statistical significance was considered when $p < .05$ or if the 95% CI estimations of OR excluded the value 1. The SPSS package version 25.0 for Windows was used for the statistical analysis. The study was approved by the Research Ethics Committee of the Hospital Universitario de Canarias (Tenerife), reference 2016_71.

Results

The study included 4,526 patients (men: 3,418, 75.5%; women: 1,108, 24.5%) with a mean age of 33 (11) years, the men being older (33 vs 31 years, $p < .001$). Cases by centre are detailed in Figure 1. Patients most frequently sought treatment during night hours (35.3%), although men attended the ED more in the morning-early afternoon hours (30.7% vs 27.2%) and women came more frequently at night (34.4% vs 38.2%; $p = .032$). Men were overrepresented in large cities (27.9%), while women predominated in the EDs in areas of greater leisure tourism (55.1%, $p < .001$), such as the Balearic and Canary Islands.

Patients consuming two or more drugs (mean 1.52 substances) comprised 39.4% (1,785), and 58.2% (2,282 cases) had also drunk alcohol, a fact that was more frequent in women (61.2% vs 57.2%, $p = .028$). The most commonly used drugs were cocaine (47.8%), cannabis (44.4%), amphetamines (25.5%), benzodiazepines (8.8%), opiates (7.3%), GHB (4.7%) and ketamine (3.8%). In 254 cases (5.6%) the substance involved could not be identified. Men consumed more GHB (5.6% vs 1.9%, $p < .001$) and women more benzodiazepines (8.0% vs 11.1%, $p = .002$), with no differences in other drugs. Other sociodemographic

Figure 1
Flowchart of patient inclusion

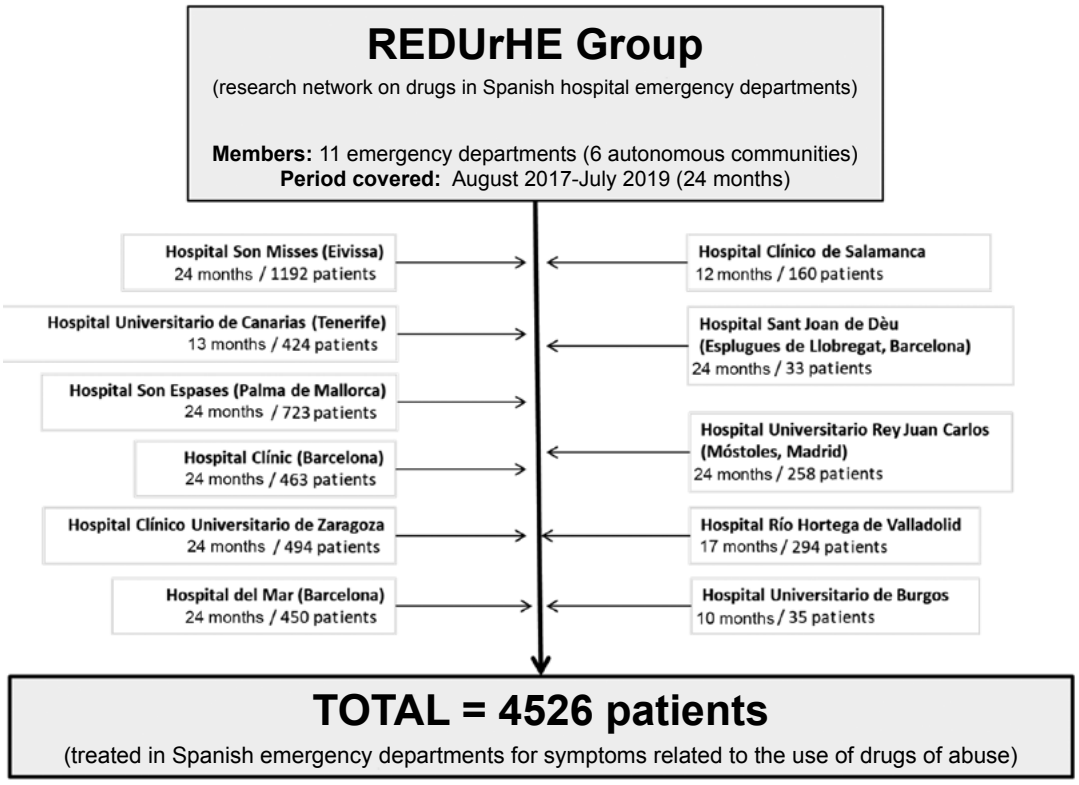
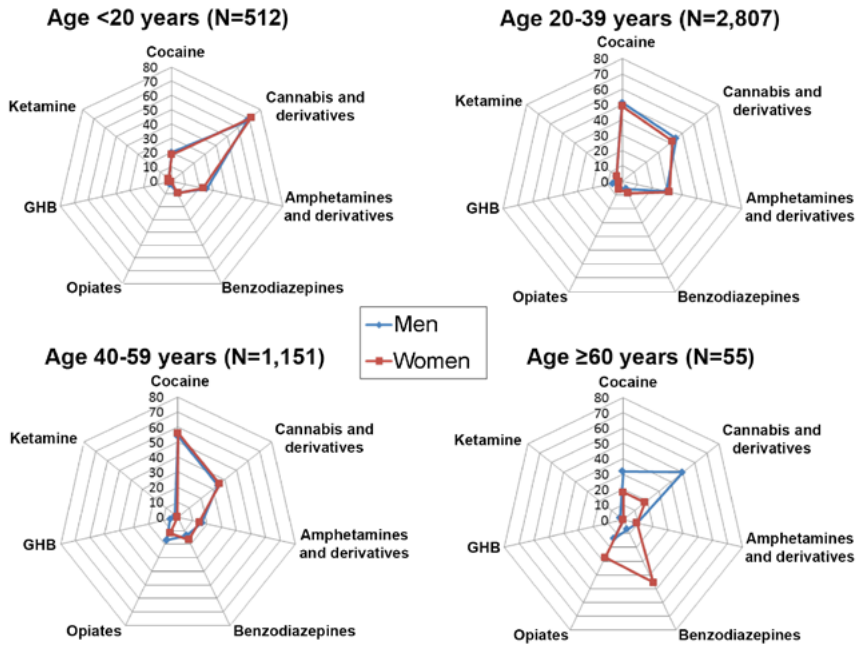


Table 1
Sociodemographic characteristics and drugs detected in the patients included in the present study and comparison by patient sex

	Total N=4526 n (%)	**Missing data** n (%)	**Men N=3418** n (%)	**Women N=1108** n (%)	***P***
Sociodemographic characteristics					
Age (years) (mean (SD))	32.6 (11.1)	5 (0.1)	33.1 (11.3)	31.1 (11.3)	**< .001**
Brought to ED by ambulance	2566 (58.9)	167 (3.7)	1952 (57.1)	614 (55.4)	.075
Location of ED		0			**< .001**
Area of leisure tourism	2339 (51.7)		1728 (50.6)	611 (55.1)	
Large city	1204 (26.6)		954 (27.9)	250 (22.6)	
Non-tourist city	983 (21.7)		736 (21.5)	247 (22.3)	
Attended ED on a holiday	2218 (49.0)	0	1675 (49.0)	543 (49.0)	.999
Time of attending ED		0			**.032**
Night (0:00-8:00)	1598 (35.3)		1175 (34.4)	423 (38.2)	
Morning - early afternoon (8:00-16:00)	1349 (29.8)		1048 (30.7)	301 (27.2)	
Late afternoon - evening(16:00-24:00)	1579 (34.9)		1195 (35.0)	384 (34.7)	
Substances identified					
Co-ingestion of alcohol	2282 (58.2)	606 (13.4)	1681 (57.2)	601 (61.2)	**.028**
Co-ingestion of multiple drugs	1785 (39.4)	0	1369 (40.1)	416 (37.5)	.138
Number of drugs consumed (mean (SD))	1.52 (0.73)	0	1.53 (0.73)	1.48 (0.71)	.06
Drugs involved					
Cocaine and derivatives	2164 (47.8)	0	1660 (48.6)	504 (45.5)	.075
Cannabis and derivatives	2011 (44.4)	0	1514 (44.3)	497 (44.9)	.744
Amphetamines and derivatives	1156 (25.5)	0	868 (25.4)	288 (26.0)	.692
Benzodiazepines	397 (8.8)	0	274 (8.0)	123 (11.1)	**.002**
Opiates	331 (7.3)	0	200 (7.6)	71 (6.4)	.183
Gamma-hydroxybutyrate and derivatives	212 (4.7)	0	191 (5.6)	21 (1.9)	**< .001**
Ketamine	174 (3.8)	0	135 (3.9)	39 (3.5)	.518
Psychotropic drugs (not included in other groups)	64 (1.4)	0	46 (1.3)	18 (1.6)	.495
LSD and other hallucinogenic substances	31 (0.7)	0	25 (0.7)	6 (0.5)	.505
New psychoactive drugs (not included in other groups)	14 (0.3)	0	11 (0.3)	3 (0.3)	.790
Other substances (not included in other groups)	57 (1.3)	0	48 (1.4)	9 (0.8)	.125
Unknown substance	254 (5.6)	0	192 (5.6)	62 (5.6)	.978

Note. SD: standard deviation. LSD: lysergic acid diethylamide.

Figure 2
Prevalence in men and women of the main drugs identified as a cause of intoxication, by age group (axes values indicate the percentage to which each drug was present)



characteristics and drugs present are detailed in Table 1. In addition, it was observed that while in the age groups below 60 years the prevalence of the main types of drugs is very similar in men and women, this diverges in patients aged 60 and over: here, cocaine and cannabis are more commonly used by men, while benzodiazepines and opiates are more frequent in women (Figure 2).

Among symptoms, psychomotor agitation (1,338 patients, 29.8%) and anxiety (1,152 patients, 25.6%) predominated, although as shown in Table 2, there was also a high percentage of patients with decreased consciousness or coma (816 cases -18.8%-, and 278 cases -6.4%-, respectively). When comparing the symptoms between sexes, a significant increase in chest pain, symptomatic hypertension, coma and severe bradycardia (< 50 bpm) was observed in men, and a greater presence of anxiety and vomiting in women. Systolic blood pressure and temperature on arrival were higher in men (Table 2). In the adjusted analysis, men were observed to have significantly more chest pain (OR = 1.72, 95% CI = 1.27-2.35), more symptomatic hypertension (OR = 1.56, 95% CI = 1.06 - 2.30) and more severe bradycardia (OR = 4.39, 95% CI = 1.03-18.7), and presented less anxiety (OR = 0.74, 95% CI = 0.61-0.89) and vomiting (OR = 0.64, 95% CI = 0.51-0.80), with no differences in the remaining variables analyzed (Figure 3).

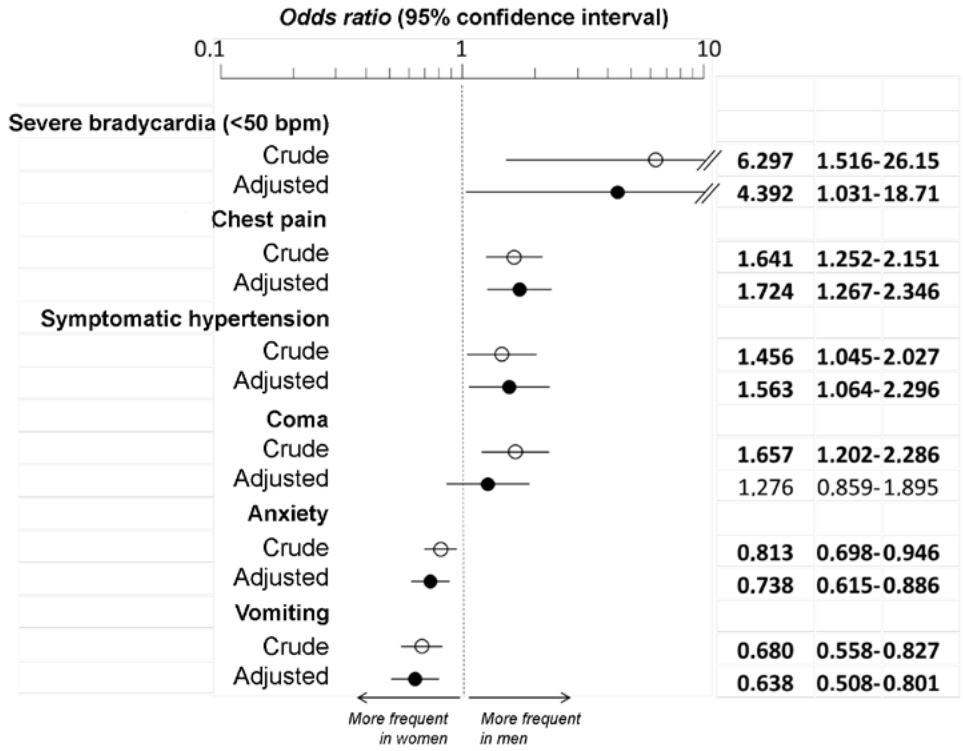
Treatment for intoxication was given to 76.1% of the patients received, in particular anxiolytics and sedatives, which were used more in men (34.6% vs 30.9%, p = .023).

Table 2
Characteristics of the emergency care episode of the patients included in the present study and comparison patient sex

	Total N=4526 n (%)	**Missing data** n (%)	**Men N=3418** n (%)	**Women N=1108** n (%)	***P***
Symptoms					
Agitation / Aggressive behaviour	1338 (29.8)	33 (0.7)	1028 (30.3)	310 (28.1)	.149
Anxiety	1152 (25.6)	33 (0.7)	835 (24.6)	317 (28.7)	**.008**
Decreased consciousness	816 (18.8)	183 (4.0)	622 (19.0)	194 (18.1)	.504
Palpitations	740 (16.5)	35 (0.8)	574 (17.0)	166 (15.0)	.133
Vomiting	536 (11.9)	33 (0.7)	368 (10.9)	168 (15.2)	**< .001**
Psychotic symptoms	429 (9.6)	34 (0.8)	340 (10.0)	89 (8.1)	.051
Chest pain	398 (9.0)	84 (1.9)	330 (9.8)	68 (6.2)	**< .001**
Hallucinations	352 (7.8)	36 (0.8)	272 (8.0)	80 (7.2)	.393
Seizures	243 (5.4)	34 (0.8)	192 (5.7)	51 (4.6)	.179
Symptomatic hypertension	242 (5.0)	116 (2.6)	197 (5.9)	45 (4.1)	.026
Headache	181 (4.0)	34 (0.8)	130 (3.8)	51 (4.6)	.251
Arrhythmias	123 (2.8)	164 (3.6)	91 (2.8)	32 (3.0)	.729
Symptomatic hypotension	93 (2.1)	119 (2.6)	72 (2.2)	21 (1.9)	.648
Coma	278 (6.4)	183 (4.0)	231 (7.1)	47 (4.4)	.002
Cerebellar symptomatology	9 (0.2)	51 (1.1)	6 (0.2)	3 (0.3)	.543
Vital signs in ED					
Systolic blood pressure (mmHg) (mean (SD))	126 (20)	558 (12.3)	128 (20)	122 (19)	**< .001**
Severe hypotension (< 80 mmHg)	22 (0.6)		19 (0.6)	3 (0.3)	.228
Severe hypertension (> 200 mmHg)	10 (0.3)		8 (0.3)	1 (0.2)	.730
Heart rate (bpm) (mean (SD))	94 (24)	529 (11.7)	94 (24)	95 (23)	.283
Severe bradycardia (< 50 bpm)	40 (1.0)		38 (1.3)	2 (0.2)	**.004**
Severe tachycardia (> 150 bpm)	66 (1.7)		50 (1.7)	16 (1.6)	.932
Respiratory rate (bpm) (mean (SD))	19 (6)	3684 (81.4)	19 (6)	18 (5)	.175
Severe tachypnea (> 30 bpm)	29 (3.4)		24 (3.6)	5 (2.8)	.611
Severe bradycardia (< 10 bpm)	13 (1.5)		11 (1.7)	2 (1.1)	.615
Temperature (ºC) (mean (SD))	36.2 (0.8)	1584 (35.0)	36.2 (0.8)	36.1 (0.8)	**.021**
Severe hypothermia (< 35 ºC)	100 (3.4)		74 (3.4)	26 (3.5)	.868
Severe hyperthermia (< 40 ° C)	5 (0.2)		4 (0.2)	1 (0.1)	1.000
ED management					
Administration of any kind of treatment (including fluid therapy)	3412 (76.1)	43 (1.0)	2579 (76.3)	833 (75.5)	.556
Administration of anxiolytics/sedatives	1511 (34.2)	43 (1.0)	1170 (34.6)	341 (30.9)	**.023**
Administration of antidotes	351 (7.8)	40 (0.9)	278 (8.2)	73 (6.6)	.084
Naloxone	243 (5.4)		199 (5.9)	44 (4.0)	**.015**
Flumazenil	229 (5.1)		174 (5.1)	55 (5.0)	.829
Determination of toxicological analysis	3473 (76.7)	0	2610 (76.4)	863 (77.9)	.296
Direct discharge from the ED without hospitalization	3908 (87.1)	33 (0.7)	2943 (87.0)	441 (13.0)	.704
Time spent in the emergency room until discharge (in hours) (median (IQR))	5.2 (3.1-9.5)	140 (3.1)	5.3 (3.1-9.7)	5.1 (2.9-8.9)	.124

Note. SD: standard deviation. IQR: interquartile range.

Figure 3
Crude and adjusted analyses of the differential symptoms between men and women consulting EDs for intoxication by drugs of abuse



Note. Values in bold are statistically significant (p < 0.05). As covariates in the adjusted model, all statistically significant symptoms in the crude analysis were forced-entry, as were age, ethanol co-ingestion, and each of the drugs analyzed in the present study.

Table 3
Markers of severity of the episode of care of patients attended for drug intoxication in the Emergency Department and comparison according to the sex of the patient

	Total N=4526 n (%)	**Missing data** n (%)	**Men N=3418** n (%)	**Women N=1108** n (%)	***p***	**Crude OR in men (95% CI)**	**Adjusted OR in men (95% CI)**
Primary marker of severity							
Combined adverse events	128 (2.9)	50 (1.1)	106 (3.1)	22 (2.0)	**.047**	**1.595 (1.002-2.537)**	1.349 (0.827-2.202)
Secondary marker of severity							
Initial cardiorespiratory arrest	11 (0.2)	0	8 (0.2)	3 (0.3)	.829	0.864 (0.229-3.264)	0.702 (0.177-2.777)
Need for intubation	75 (1.7)	39 (0.9)	64 (1.9)	11 (1.0)	**.044**	**1.917 (1.007-3.647)**	1.371 (0.700-2.685)
Admission to intensive care	90 (2.0)	33 (0.7)	73 (2.2)	17 (1.5)	.204	1.410 (0.828-2.400)	1.298 (0.740-2.275)
Death	12 (0.3)	0	10 (0.3)	2 (0.2)	.528	1.623 (0.355-7.419)	1.084 (0.230-5.099)

Note. OR: odds ratio. CI: confidence interval.

Antidotes were used in 351 patients (7.8%), with more naloxone being used in men (5.9% vs 4%, p = .015) and with no differences in the use of flumazenil. Toxins were detected in 3,473 cases (76.7%), with the toxins involved in the remaining cases being taken from the anamnesis data of the patient or their companions with a clinical picture (except in 254 cases in which a specific type of drug could not be determined given that no analytical toxicological history was made or no clinical history pointing to a particular source was available). There were no differences in terms of the percentage of men and women in whom toxicological confirmation was obtained. After their stay in the ED, (mean stay 5.4 hours), 87.1% of the patients (3,945) were discharged home (Table 2).

Combined adverse events were observed in 128 patients (2.9%), more frequently in men (3.1% vs 2.0%, p = .047) (Table 3). Among the AE considered individually, the need for intubation was the only difference by sex, being higher in men (1.9% vs 1.0%, p = .044). In the adjusted analysis, statistical significance disappeared in both cases (OR = 1.349, 95% CI = 0.827-2.202, and OR = 1.371, 95% CI = 0.700-2.685, respectively). Twelve patients (0.3%) died,

without sex differences (0.3% vs 0.2%, p = .528). Among the 12 deceased patients, cocaine was present in 8 cases (67%), amphetamine derivatives in 3 (25%), cannabis or derivatives in 3 (25%), GHB in 1 (8%) and new psychoactive drugs (cathinone) at 1 (8%). In 6 cases (50%), co-ingestion of ethanol was also present.

Discussion

Several absolute epidemiological data worthy of comment were found in the present study. First, in line with other published research on drug poisoning treated in EDs (Dines et al., 2015; Galicia et al., 2012; Miró et al., 2021), this phenomenon was more frequently observed in men than in women (with a 3:1 ratio in the present series). In addition, the relationship between drug use and recreational activity was also confirmed, being more frequent in tourist areas, on holidays and at night. Finally, it is noteworthy that the proportion of sexes among those treated varies depending on whether the ED was located in more touristy areas (in which women are overrepresented in relation to the expected proportion) or in large metropolises (where men are overrepresented). Drug use patterns are related to local, socioeconomic or cultural characteristics, which make it possible to identify differences between countries or regions. Thus, previous studies have shown that Spaniards, for example, consume more cocaine and fewer opiates and NPS (novel psychoactive substances) than citizens of the British Isles or regions of central and northern Europe (Miró et al., 2018).

Regarding the drugs involved in ED care, men used more cocaine, opiates, GHB and ketamine, and women more benzodiazepines, although the differences were only significant for GHB (more in men) and benzodiazepines (more in women). In relation to this last finding, we must consider the possibility that the greater prevalence of benzodiazepines in women is due to an increase in cases of use with suicidal ideation (and not exclusively to recreational purpose use), or that it is more easily within reach as the proportion of women receiving treatment with benzodiazepines prescribed by a doctor is higher. Although the principal investigators of each centre were advised that cases in which it was clear that substance users had a clear suicidal purpose were to be excluded, this possibility could not be consistently ruled out given the way in which the information was recorded as the etiology of intoxication was not prospectively collected. The fact that a higher prevalence was observed in patients aged 60 or over could suggest this bias, although the number of patients corresponding to this age group was minimal (55 of the total of 4,526) and its influence on the global comparison was therefore very small. Finally, it is striking that ethanol co-intake was clearly higher among women (61.2% vs 57.2%, p = .028). We have not found similar references in the literature in this regard, nor indeed was such a difference between the sexes found in a European study that included more than 17,000 patients (Miró et al., 2021).

Regarding clinical manifestations, the most frequent were those of a hyperadrenergic nature (agitation, aggressiveness, anxiety), possibly due to the predominance of cocaine and amphetamines among the drugs used (Galicia, Nogué, Sanjurjo & Miró, 2008; Galicia, Nogué, Sanjurjo & Miró, 2010; Noseda et al., 2021). However, there were different prevalences depending on sex in some specific clinical manifestations, even after controlling for the sociodemographic differences and the type of drugs consumed by each sex. Thus, men were observed to have a higher likelihood of presenting cardiovascular symptoms: chest pain, symptomatic hypertension and severe bradycardia. We do not know if this is related to more previous cardiovascular comorbidities in men (known or hidden), since comorbidity was not collected in the study. On the other hand, anxiety and vomiting were more frequent in women. It cannot be ruled out that these differences in clinical expression may be linked to an increased susceptibility to certain manifestations linked to sex. Earlier studies have shown, for instance, that women have a 1.5-1.7 times higher risk than men of presenting adverse reactions in relation to the use of medical drugs (Anderson, 2008; Rademaker, 2001).

A toxicological analysis was performed in 76% of the cases, without differences between the sexes. It could be considered that this percentage of toxicological tests is adequate since it has been shown that they are not essential for emergency management of intoxicated patients, with some authors suggesting that toxicological tests should be reserved for specific cases (Córdoba et al., 2020). The present study does not show there is a difference in application of this criterion depending on the sex of the patient. However, we believe that the importance of this toxicological determination goes beyond the clinical relevance it may have in, for example, revealing substances that the patient does not know they have consumed (Liakoni et al., 2018). This determination also has an epidemiological role that EDs should not ignore, given their key position when it comes to detecting new patterns of use or the introduction of new drugs on the market (as may be the case of NPS). Samples of these should moreover be kept during the treatment process for later analysis using specific methods since their identification is beyond the immunoassay techniques available in EDs (Fernández Alonso, Quintela Jorge & Santiago Sáez, 2016; Miró & Galicia, 2019; Observatorio Español de las Drogas y las Adicciones, 2020).

In relation to the treatment carried out in the ED, it was found that anxiolytic or sedative drugs were more frequently given to men, a fact that contrasts with their lower

prevalence of anxiety symptoms. This difference may have several explanations: the presence of more pronounced manifestations in men or a greater occurrence of agitation, psychotic symptoms, seizures or even hypertension, where benzodiazepines are used to control symptoms. Men also received more naloxone, which is more to be expected considering that in terms of absolute numbers they consumed more opiates or GHBs and presented more frequently in comatose states in the EDs (Sivilotti, 2016).

Men presented more serious intoxications, given their 59% higher risk of presenting combined AE compared to women. Among the AE, the need for endotracheal intubation was the only one that was significantly increased, with an increased risk of 92% compared to women. The latter is likely related to the increased presence of coma, opiates and GHB (Galicia et al., 2008). However, this greater severity of poisonings in men would be more linked to older age or the type of substances consumed by men. Thus, when adjusting for these factors, the differences decreased (the rise in combined AE decreased to 35% and that of orotracheal intubation to 37%) and lost statistical significance.

This study has limitations. First, despite being a prospective study, some data, in particular vital signs, were not recorded in the medical records. This is a general issue in EDs (Galicia, 2020; Miró et al., 2018; Roset Ferrer et al., 2020). We must highlight the clinical importance of this in general and especially in intoxicated patients, where it is absolutely essential to know and record both the temperature (missing in 35% of the patients in this series, and which allows cases of hyperthermia to be detected) and the respiratory rate (missing in 81%, and which allows bradypnea to be detected in cases of intoxication by GHB or opiates or tachypnea in cases of metabolic acidosis). Second, the diagnosis of the drug involved was based on clinical history and/or analytical identification, so that in some cases it was not possible to identify substances by either the patient or the analysis. As previously indicated, some of the drugs, such as GHB or new psychotropic substances, cannot be identified by immunoassay, the technique most used in EDs, and so these groups may have been underrepresented. It could also happen that the drug indicated by the patient was not actually the one involved, due to the use of other substances such as drug adulterants. Third, the identification of adverse events was made by the investigator of each centre, without external monitoring. The events under consideration are very objective and are probably subject to only small interpretive biases of little relevance. Fourth, despite being a large series, for some drugs, the number of cases with some symptoms or some AE was low, so a beta error may have been incurred by disregarding the existence of statistical significance in the differences found between men and women. Finally, and despite the fact that the participating centres were distributed across the country, only six autonomous communities were represented, which partially reduces the global vision of the problem in Spain.

In conclusion, this study shows that sex differences exist in drug intoxications treated in ED. There is a greater involvement of GHB in men and of benzodiazepines and alcohol in women. In the case of benzodiazepines, this is very evident in older patients. Cardiovascular symptoms prevail in men and anxiety and vomiting in women, a difference which cannot be attributed to sociodemographic variation or to the drugs used by each of the sexes. Men have more severe AD, which could be related to older age and the type and pattern of drug use, since when adjusting for these differences, the severity of intoxication episodes was not significantly different by sex.

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Conflict of interests

None of the authors of this study has declared a conflict of interest.

References

Anderson, G.D. (2008). Gender differences in pharmacological response. *International Review of Neurobiology*, *83*, 1–10. doi:10.1016/S0074-7742(08)00001-9.

Burillo-Putze, G., López-Hernández, A., Expósito-Rodríguez, M. & Dueñas-Laita, A. (2013). Sumisión química, oportunista o premeditada. *Medicina Clínica*, *140*, 139. doi:10.1016/j.medcli.2012.05.035.

Burillo-Putze, G. & Matos Castro, S. (2018). Los servicios de urgencias como atalaya de los patrones de uso de drogas y sus consecuencias clínicas. *Emergencias*, *30*, 377–379.

Córdoba, F., Iglesias Lepine, M. L., García Gibert, L., Gispert, M. À., Moreno, A. & Supervía, A. (2020). Grado de conocimiento de la detección de drogas en orina entre médicos que atienden a pacientes intoxicados. *Emergencias*, *32*, 451–452.

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2021). *Encuesta sobre alcohol y otras drogas en España, EDADES 2019/20.* Madrid: Ministerio de Sanidad. https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/2019-20_Informe_EDADES.pdf.

Delegación del Gobierno para el Plan Nacional sobre Drogas. (2020). *Encuesta sobre Uso de Drogas en Enseñanzas Secundarias en España (ESTUDES) 1994-2018.* Madrid: Ministerio de Sanidad. https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/sistemaInformacion/pdf/ESTUDES_2018-19_Informe.pdf.

Dines, A. M., Wood, D. M., Yates, C., Heyerdahl, F., Hovda, K. E., Giraudon, I.,… Euro-DEN Research Group (2015). Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN). *Clinical Toxicology, 53,* 893–900. doi:10.3109/15563650.2015.1088157.

ESPAD Group (2020). *ESPAD Report 2019: Results from the European school survey project on alcohol and other drugs*, Luxembourg: EMCDDA joint publications. Publications office of the European Union.

European Monitoring Centre for Drugs and Drug Addiction [EMCDDA]. (2020). E*uropean drug report 2020: Trends and developments.* Luxembourg: Publications office of the European Union.

Fernández Alonso, C., Óscar Quintela, J., Ayuso Tejedor, S., Santiago-Sáez, A. E. & González Armengol, J. J. (2019). Intoxicación aguda por nuevas drogas de abuso en probables casos de sumisión química oportunista o mixta y chemsex en pacientes con VIH atendidos en urgencias. *Emergencias*, *31*, 289–290.

Fernández Alonso, C., Quintela Jorge, O. & Santiago Sáez, A. S. (2016). Identificación de la droga de abuso flakka (α-PVP) como sospecha de sumisión química no probada en urgencias de un hospital terciario. *Medicina Clínica*, 147, 227–228. doi:10.1016/j.medcli.2016.03.028.

Fernández Egido, C., García Herrero, G., Romero García, R. & Marquina Santos, A. J. (2008). Intoxicaciones agudas en las urgencias extrahospitalarias. *Emergencias*, *20*, 328–331.

Galicia, M. (2020). Efectos adversos agudos en usuarios de drogas sintéticas: Una aproximación a la magnitud del problema en España. *Emergencias*, *32*, 7–8.

Galicia, M., Nogué, S., Casañas, X., Iglesias, M., Puiguriguer, J., Supervía, A.,… Miró, Ò. (2012). Multicenter assessment of the revisit risk for a further drug-related problem in the emergency department in cocaine users (MARRIED-cocaine study). *Clinical Toxicology*, *50*, 176–182. doi:10.3109/15563650.2012.658917.

Galicia, M., Nogué, S., Sanjurjo, E. & Miró, Ò. (2008). Evolución de las consultas urgentes relacionadas con el consumo de cocaína durante el periodo 2002-2007. *Emergencias*, *20*, 385–390.

Galicia, M., Nogué, S., Sanjurjo, E. & Miró, Ò. (2010). Consultas urgentes derivadas del consumo de éxtasis (3,4-metilenodioximetanfetamina) y derivados anfetamínicos: Perfil epidemiológico, clínico y evolutivo. *Revista Clínica Española*, *210*, 371–378. doi:10.1016/j.rce.2010.01.013.

Galicia, M., Nogué, S., To-Figueras, J., Echarte, J. L., Iglesias, M. L. & Miró, Ò. (2008). Intoxicaciones por éxtasis líquido atendidas en servicios de urgencias hospitalarios de la ciudad de Barcelona durante 2 años. *Medicina Clínica*, *130*, 254–258. doi:10.1157/13116549.

Hegazi, A., Lee, M. J., Whittaker, W., Green, S., Simms, R., Cutts, R.,… Pakianathan, M. R. (2017). Chemsex and the city: Sexualised substance use in gay bisexual and other men who have sex with men attending sexual health clinics. *International Journal of STD and AIDS*, *28*, 362–366. doi:10.1177/0956462416651229.

Liakoni, E., Yates, C., Dines, A. M., Dargan, P. I., Heyerdahl, F., Hovda, K. E.,… Euro-DEN Plus Research Group (2018). Acute recreational drug toxicity: Comparison of self-reports and results of immunoassay and additional analytical methods in a multicenter European case series. *Medicine*, *97*, e9784. doi:10.1097/MD.0000000000009784.

Miró, Ò. & Galicia, M. (2019). Sobre las fuentes de conocimiento del consumo de drogas y sus consecuencias. *Revista Española de Salud Pública*, *90,* 1-3.

Miró, Ò., Waring, W. S., Dargan, P. I., Wood, D. M., Dines, A. M., Yates, C.,… Euro-DEN Plus Research Group (2021). Variation of drugs involved in acute drug toxicity presentations based on age and sex: An

epidemiological approach based on European emergency departments. *Clinical Toxicology, 59,* 896-904. doi:10.1080/15563650.2021.1884693.

Miró, Ò., Yates, C., Dines, A. M., Wood, D. M., Dargan, P. I., Galán, I.,… Galicia, M. (2018). Comparación de las urgencias atendidas por drogas de abuso en dos servicios de urgencias españoles con las atendidas en tres áreas europeas distintas. *Emergencias*, *30*, 385–394.

Noseda, R., Schmid, Y., Scholz, I., Liakoni, E., Liechti, M. E., Dargan, P. I.,… Euro-DEN Research Group (2021). MDMA-related presentations to the emergency departments of the European Drug Emergencies Network plus (Euro-DEN Plus) over the four-year period 2014-2017. *Clinical Toxicology*, *59*, 131–137. doi:10.1080/15563650.2020.1784914.

Observatorio Español de las Drogas y las Adicciones. (2020). *Informe 2020. Alcohol, tabaco y drogas ilegales en España. Sistemas de alerta temprana. Esquema del sistema español de alerta temprana.* Madrid: Ministerio de Sanidad. https://pnsd.sanidad.gob.es/profesionales/sistemasAlerta/pdf/2020_Informe_Alertas.pdf.

Perelló, R., Aused, M., Saubí, N., Quirós, C., Blanco, J. L., Martínez-Rebollar, M.,… Nogué, S. (2018). Intoxicación aguda por drogas de abuso en el paciente VIH: Papel del chemsex. *Emergencias*, *30*, 405–407.

Puiguriguer, J., Nogué, S., Echarte, J. L., Ferrer, A., Dueñas, A., García, L.,… Burillo-Putze, G. (2013). Mortalidad hospitalaria por intoxicación aguda en España (EXITOX 2012). *Emergencias*, *25*, 467–471.

Rademaker, M. (2001). Do women have more adverse drug reactions? *American Journal of Clinical Dermatology*, *2*, 349–351. doi:10.2165/00128071-200102060-00001.

Roset Ferrer, C., Gomila Muñiz, I., Elorza Guerrero, M. Á., Puiguriguer Ferrando, J., Leciñena Esteban, M. Á., Tuero León, G.,… Barceló Martín, B. (2020). Intoxicaciones por anfetamina y metanfetamina atendidas en los servicios de urgencias: Características clínicas y utilidad de la confirmación analítica. *Emergencias*, *32*, 26–32.

Sivilotti, M. L. A. (2016). Flumazenil, naloxone and the "coma cocktail." *British Journal of Clinical Pharmacology*, *81*, 428–436. doi:10.1111/bcp.12731.

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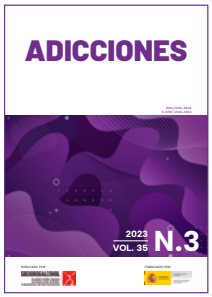

REVIEW

Economic evaluations of interventions aimed at the prevention, treatment and/or rehabilitation of alcohol-related disorders: A systematic review

Evaluaciones económicas de intervenciones dirigidas a la prevención, tratamiento y/o rehabilitación de trastornos por consumo de alcohol: Una revisión sistemática

Marta Trapero-Bertran*; Dolors Gil-Doménech**; Ana Magdalena Vargas-Martínez***.

* Departamento de Ciencias Básicas. Instituto Universitario de Pacientes. Universitat Internacional de Catalunya (UIC Barcelona).

** Facultad de Ciencias Económicas y Sociales. Universitat Internacional de Catalunya (UIC Barcelona).

*** Departamento de Enfermería. Facultad de Enfermería, Fisioterapia y Podología. Universidad de Sevilla (US). Universitat Internacional de Catalunya (UIC Barcelona).

Abstract

The aim of this systematic literature review is to identify economic evaluations of programmes or interventions aimed at the prevention, treatment and rehabilitation of alcohol use disorders, as well as to determine those types of programmes, treatments or interventions that are efficient. The systematic literature review was conducted by searching the following databases: National Health Service Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA), MEDLINE Ovid and PubMed. The search terms used were in English. No time restriction was applied. A data extraction form was used to draw information. The systematic review follows the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) on reporting systematic reviews. The interventions were classified into three categories: "A" treatments for people with alcohol use disorders (tertiary prevention); "B" treatments for people at risk for alcohol-related problems (secondary prevention); "C" policy legislation and enforcement interventions (primary prevention). Furthermore, the "A" interventions were subclassified into psychological, pharmacological and combined interventions. The review included 63 papers. In terms of treatments for people with alcohol use disorders, any psychosocial intervention compared to no intervention appeared to be a dominant strategy. In terms of treatments for people at risk of alcohol-related problems, brief intervention appears to be dominant or cost-effective when compared to no intervention. Advertising controls, tax increases, licensing, legal drinking age, and mass media campaigns seem to be dominant or cost-effective strategies compared to no intervention or random breath testing. Previous reviews have been extended by depicting alcohol programmes according to their efficiency. Despite this, the available studies in this regard have heterogeneous approaches and most do not adequately define the costs included in their analyses. Therefore, it is necessary to encourage the evaluation of the efficiency of these types of interventions to aid decision-making in public health.

Keywords: alcohol, systematic review, efficiency, cost-effectiveness, intervention classification

Resumen

El objetivo de esta revisión sistemática de la literatura es identificar evaluaciones económicas de programas o intervenciones dirigidas a la prevención, tratamiento y rehabilitación de trastornos por consumo de alcohol, así como determinar aquellos tipos de programas, tratamientos o intervenciones que son eficientes. Se realizó una revisión sistemática de la literatura mediante la búsqueda en las siguientes bases de datos: National Health Service Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA), MEDLINE Ovid and PubMed. Los términos de búsqueda utilizados fueron en inglés. No se aplicó ninguna restricción de tiempo. Se utilizó un formulario de extracción de datos para resumir la información. La revisión sistemática siguió las recomendaciones (PRISMA-P) sobre la presentación de informes de revisiones sistemáticas. Las intervenciones fueron clasificadas en tres categorías: «A» tratamientos para personas con trastornos por consumo de alcohol (prevención terciaria); «B» tratamientos para personas en riesgo de problemas relacionados con el alcohol (prevención secundaria); «C» legislación sobre políticas e intervenciones de aplicación (prevención terciaria). Además, las intervenciones «A» fueron subclasificadas en intervenciones psicológicas, farmacológicas y combinadas. Se incluyeron 63 documentos. En términos de tratamientos para personas con trastornos por uso de alcohol, cualquier intervención psicosocial en comparación con ninguna intervención parece ser una estrategia dominante. En términos de tratamientos para personas en riesgo de problemas relacionados con el alcohol, la intervención breve parece ser dominante o rentable en comparación con no hacer nada. Los controles publicitarios, las subidas de impuestos, las licencias, la edad legal para consumir alcohol y las campañas en los medios de comunicación parecen ser una estrategia dominante o rentable en comparación con ninguna intervención o prueba aleatoria de alcoholemia. Se han ampliado las revisiones anteriores al mostrar los programas de alcohol según criterios de eficiencia. A pesar de ello, los estudios disponibles al respecto tienen enfoques heterogéneos y la mayoría no define adecuadamente los costes incluidos en su análisis. Por tanto, es necesario continuar evaluando en términos de eficiencia este tipo de intervenciones para informar mejor la toma de decisiones en salud pública.

Palabras clave: alcohol, revisión sistemática, eficiencia, coste-efectividad, clasificación intervenciones

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■ **Send correspondence to:**
Marta Trapero-Bertran PhD. Universitat Internacional de Catalunya (UIC). Departamento de Ciencias Básicas. Instituto Universitario de Pacientes. Carrer de Josep Trueta, 08195 Sant Cugat del Vallès, Barcelona. Email: mtrapero@uic.es

Alcohol consumption ranks as a leading risk factor for mortality and disability around the world, representing 5.3% of all deaths and 5.1% of all disability-adjusted life years (DALY) worldwide (World Health Organization, 2018). Smyth et al. (2015) confirmed that alcohol misuse was associated with increased risk of mortality, cancer and injury and an insignificantly reduced risk of myocardial infarction. The amount and pattern of alcohol consumption can have different associations with health outcomes and costs. Three decades ago, Burke (1988) already estimated the economic impact of alcohol use disorder (AUD) and alcoholism quantifying losses of billions of dollars per year because of lost productivity and employment. Rehm et al. (2009) stated that the costs associated with alcohol amount to more than 1% of the gross national product in high-income and middle-income countries, with the costs of social harm constituting a major proportion in addition to health costs, and actions to reduce burden and costs associated with alcohol should be urgently increased.

Economic Evaluation (EE) is the most relevant tool to health care decision-makers (Goeree & Diaby, 2013) to compare alternative courses of action both in terms of their costs and health outcomes. There are four different types of EEs with the main difference being the way outcomes are measured, valued and included in the analysis (Drummond, Sculpher, Claxton, Stoddard & Torrance, 2015). With Cost-Effectiveness Analysis (CEA) alternatives are compared in terms of costs and outcomes, and outcomes are measured and valued in natural units collected in clinical trials or observational studies. In a Cost-Utility Analysis (CUA), expected costs and outcomes for each intervention are calculated, with the outcome measure mainly expressed as quality adjusted life years (QALYs), which combines quality of length and length of life into a single measure (Drummond et al., 2015). The results of an EE are presented in terms of an incremental cost-effectiveness ratio (ICER), which is literally the differences in mean expected costs divided by the difference in mean expected outcomes (Drummond et al., 2015). The ICER provides a measure of the expected cost needed to gain a unit of effect. When a program or an intervention improves the outcomes and lower (saves) costs then it is said that exists dominance (Drummond et al., 2015). During the past few years, economic evaluations have become more important as a source of information for decision makers in the public health field (Drummond et al., 2007; Williams, McIver, Moore & Bryan, 2008). It has been proven that the market itself does not achieve efficient solutions, so decision makers play a key role because they can decide how to allocate scarce resources (Drummond et al., 2015; Gold, Siegel, Russell & Weinstein, 1996; Kernick, 2003; Sloan & Hsieh, 2012). Therefore, to reduce the disease and injury burden associated with alcohol consumption, it is important to identify the cost-effective interventions to support national health strategies and initiatives to reduce harmful alcohol use.

Donaldson, Mugford & Vale (2002) argued for the value of systematic reviews of economic evaluations as a tool to promote evidence-informed health care. They suggest that the value of systematic review of economic evaluation evidence is not to generate a single authoritative result or recommendation about relative cost effectiveness but, rather, to help decision makers understand the structure of the resource allocation problem and potential impacts.

Some systematic reviews have been published, evaluating different types of programs, strategies or interventions such as psychological therapies (Meads, Ting, Dretzke & Bayliss, 2007) and pharmacological treatments (Ndegwa & Cunningham, 2009) from an efficiency point of view, trying to identify which service provision the National Health Service (NHS) should be promoting to reduce alcohol consumption. In addition, other systematic reviews of effectiveness, such as on mass media campaigns to reduce alcohol-impaired driving and alcohol-related crashes (Yadav & Kobayashi, 2015), community pharmacy interventions or alcohol management interventions (Brown et al., 2016) have been published, highlighting the most effective in terms of health outcomes. In addition, Barbosa, Godfrey & Parrott (2010) carried out a review of the methodology that was adopted in previous economic evaluations of alcohol treatment, and they offered research recommendations with a view to enhancing the consistency and harmonization of economic evaluation in the alcohol usage field. The added value of this new review on alcohol-related economic evaluations is the inclusion of programs distinguishing between treatments for people with alcohol use disorders, treatments for people at risk of alcohol-related problems , and policy, legislation and enforcement interventions. This implies mapping the efficiency of all available interventions to deal with this public health problem.

Therefore, the goal of this paper is to conduct a systematic literature review of economic evaluations of treatments for people with alcohol use disorders or at risk of alcohol-related problems and of policy legislation and enforcement interventions, considering the findings from previous literature reviews (Angus, Latimer, Preston, Li & Purshouse, 2014; Barbosa et al., 2010; Chisholm, Doran, Shibuya & Rehm, 2006; Hill, Vale, Hunter, Henderson & Oluboyede, 2017; Hoang et al., 2016; Kaner et al., 2017; Kelly, Abry, Ferri & Humphreys, 2020; Kruse et al., 2020; Ludbrook, 2004; Ludbrook et al., 2002; Mujoomdar & Spry, 2009; Poldrugo, Haeger, Comte, Walburg & Palmer, 2005; Rehm & Barbosa, 2018; Slattery et al., 2002; White, Skirrow, George & Memon, 2018). The specific objectives of this review are (a) to conduct a qualitative review of the methodological aspects of each of the identified studies; (b) to identify the most studied and efficient programs and strategies to treat people with alcohol use disorders or people at risk of alcohol-related problems; and (c) to group all existing interventions into the three categories stated before ("A": treatments for people

with alcohol use disorders; "B": treatments for people at risk of alcohol-related problems; "C": policy legislation and enforcement interventions).

Method

Search strategy

The systematic literature review was conducted by searching three databases: National Health Service Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA), MEDLINE Ovid and PubMed. All databases were searched from their inception to 24th July 2020, using keywords: (alcohol*:ti or drink*:ti or detoxificat*:ti) crossed with (cost benefit* or cost effect* or cost utilit* or cost minim* or unit* adj cost or cost*) for the NHS EED and Health Technology Assessment (HTA) searches; and (alcohol$[Title] or drink$[Title] or detoxificat$[Title]) and (cost$ benefit$ or cost$ effect$ or cost$ utilit$ or cost$ minim$ or unit$ adj cost$) for the MEDLINE and PubMed searches. The search terms used were in English.

Inclusion criteria

The inclusion criteria consisted of considering papers about economic evaluations related to humans, with no time restriction (search conducted till 24th July 2020), who undertake programmes for treating people with alcohol use disorders (classified as "A" in the data extraction tables), people at risk of alcohol-related problems (classified as "B" in the data extraction tables), and policy legislation and enforcement interventions (classified as "C" in the data extraction tables). Papers were excluded if they were review articles, were not full economic evaluations (comparative analysis of alternative courses of action in terms of both costs (resource use) and consequences (outcomes, effects) that aims to produce measures of incremental resource use, costs and/ or cost-effectiveness) (Drummond et al., 2015) providing an Incremental Cost-Effectiveness Ratio (ICER) as a result, did not use the term 'alcohol' as a drink, or did not focus on programmes associated with reducing or preventing alcohol consumption. Review papers were kept to check that identified papers by previous economic evaluation review were included. Papers included were those identified by the search strategy and some others obtained from citation tracking of identified key articles.

Data extraction and synthesis method

Data from included papers was extracted using the same structure as the standardised data extraction tool for economic evaluations in Joanna Briggs Institute for Evidence Based Practice (JBI-ACTUARI) (The Joanna Briggs Institute, 2014). The quality and validity of the included studies were subjected to double review by two independent reviewers using the standardised critical appraisal tools from the Joanna Briggs Institute from JBI-ACTUARI for economic evaluations (The Joanna Briggs Institute, 2014). Whenever there was a discrepancy, papers were reviewed a second time by both reviewers to reach a consensus. No additional data was extracted. The systematic review follows the recommendations of the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) on reporting systematic reviews (Moher et al., 2015)[1].

The data extracted will cover descriptive data about the (i) study population/participants, alcohol dependence level, intervention, comparator(s) and outcomes; (ii) study methods, including evaluation design type, analytic viewpoint(s); source of effectiveness data, prices and currency used for costing, time period of analysis; sensitivity testing; measures of resource use; cost and health effect/clinical and cost effectiveness; and, (iii) study context (geographical, year of publication, health care and broader service delivery setting and culture). Regarding the alcohol dependence, the Tenth Revision of the International Classification of Diseases and Health Problems (ICD-10) defines the dependence syndrome as being a cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value (World Health Organization, 1992). This concept is of much importance in the alcohol context in order to describe the importance and level of this abusive bahaviour and the potential consequences that they could have. Data on definition of alcohol dependence and people at risk of alcohol dependence was summarised. All existing interventions were classified according to treatment for people with alcohol use disorders; treatments for people at risk of alcohol related problems; and, policy, legislation and enforcement interventions. To do so, were considere some advices from policy makers, definitions developed by published reviews (Barbosa et al., 2010; Chisholm et al., 2006; Ludbrook, 2004; Ludbrook et al., 2002; Slattery et al., 2002) and results obtained from this systematic literature review.

Results

Description of included studies

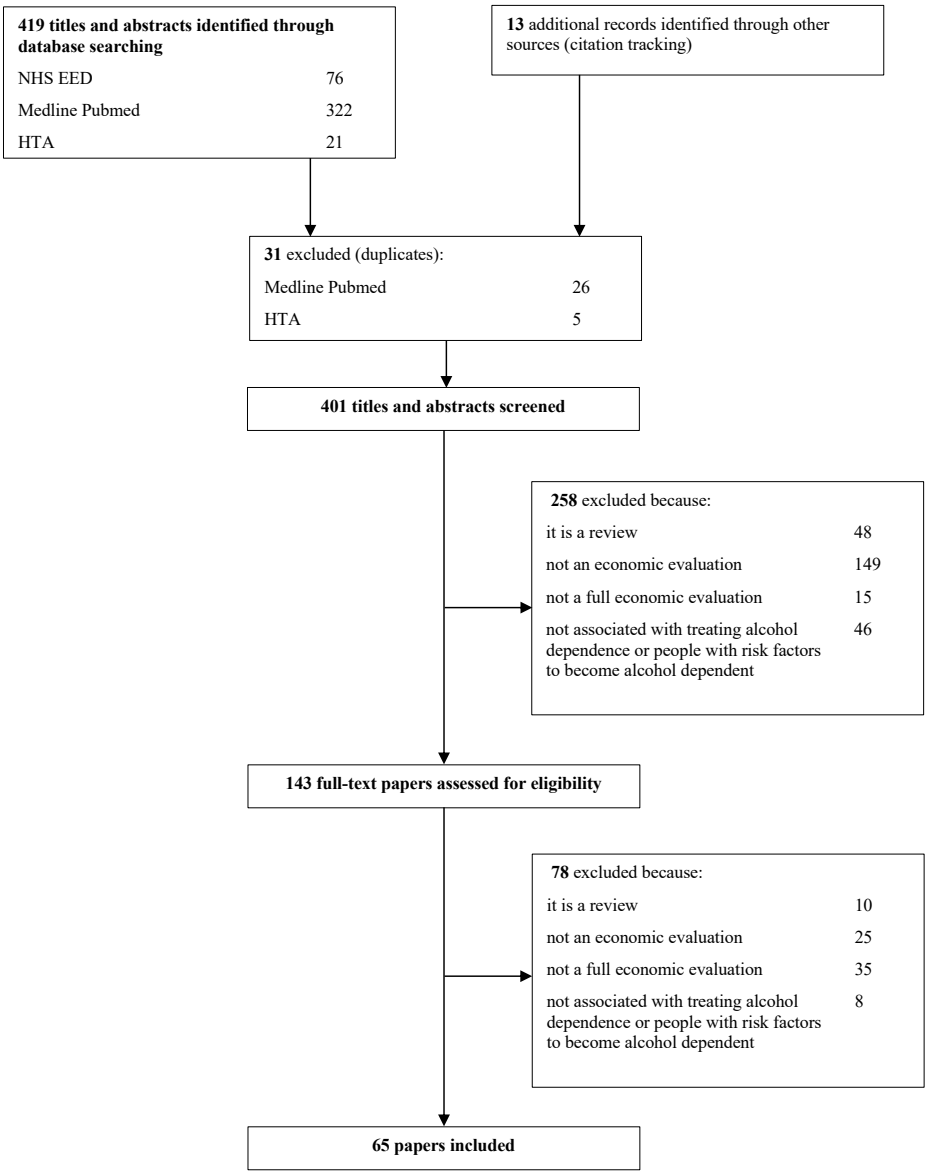
Figure 1 documents the flowchart of articles through the study and the reasons for exclusion. Finally, a total of 65 economic evaluations specifying 192 estimates for the ICER that met the initial inclusion criteria were included in the analysis. Fifhteen literature reviews (Angus et al., 2014; Barbosa et al., 2010; Chisholm et al., 2006; Hill et al., 2017; Hoang et al., 2016; Kaner et al., 2017; Kelly et al., 2020; Kruse et al. 2020; Ludbrook, 2004; Ludbrook et al., 2002; Mujoomdar & Spry, 2009; Poldrugo et al., 2005; Rehm & Barbosa, 2018; Slattery et al., 2002; White et al., 2018) were examined to check that all papers included in them were also included in our review. No additional stu-

dies were included because they were not economic evaluations or not full economic evaluations (they did not calculate the incremental cost-effectiveness ratio).

Characteristics of included studies

All these results refer to the 65 papers included in the systematic literature review. From these studies, there was one that evaluated a drug (Baclofen) as an intervention in uncomplicated alcohol-withdrawal syndrome. This study was also included in this systematic literature review because these people still have alcohol use disorders or being people at risk of alcohol-related problems. Of these 65 articles, 4 studies included interventions classified exclusively as primary prevention, 23 as secondary prevention (aimed at people with risky alcohol consumption), 24 as tertiary prevention (aimed at alcohol-dependent people) and 14 as secondary and tertiary prevention (aimed at people with risky alcohol consumption and dependent people). Almost seventy percent of papers (n = 44) were published in the last ten years (between 2010 and 2020). Only 9,2% of papers (n = 6) first appeared between 1991 and 2002. The last year of the search up to the date indicated produced five published studies. Appendix 1 contains a list of the 65 papers included in the present systematic literature review. See Table 1 for further details on the main characteristics of included Table 1 studies.

Figure 1
Flowchart of study identification and selection



Of the 65 articles included, 23.1% (n = 15) were from Europe (one of those was from Spain), 21.5% (n = 14) from the United States, 12.3% (n = 8) from Australia, 26.2% (n = 17) from the United Kingdom, 6.2% (n = 4) from India, and the remaining from Brazil, Estonia, and Italy. Four papers studied more than one country. The average age of populations, weighted by sample, included in the study was approximately 38 years, though only 46% of studies reported age. Most of the studies (73.8%; n = 48) reported the sample size; eighteen of those comprised a sample higher than 10,000; however, three comprised a sample lower than 100 people. The gender of the people was specified in 58.7% of the studies included in the economic evaluation; from those, 35.1% were men only. Only one study specified the socioeconomic status of the participants. Only two studies (3.2%) offered monetary compensation for participating in the study. Thirty-two (50.8%) studies were trial based, all randomised with the exception of two studies.

More than half of the studies (56.9%; n = 37) stated that the participants had alcohol dependence. However, only seventeen (47.2%) of those defined this condition, whose definition was based on in grams per day or week, or consumed units, drinks, per day/week, or based on AUDIT score, WHO criteria, the ICD-10, or based on the Diagnostic Interview Schedule for Psychoactive Substance Dependence (DSM). A high number of studies (n = 25; 39.7%) stated that their participants attributed health conditions to alcohol, among them, cardiovascular- (n = 19) and liver- (n = 14) related diseases and cancer (n = 14) the most frequent ones, followed by car accidents (n = 11). See Table 1 for further details.

Table 1
Main characteristics of included studies and definitions of alcohol dependence and people at risk of alcohol dependence

Authors	Sample size	Alcohol dependence*	Definition of alcohol dependence	Definition of people at risk of alcohol dependence	Type of EE (according to reviewers)	Perspective**
Agus A et al., 2019	8226	No dependence	No definition included	Heavy episodic drinking (HED)[a]	CEA	Funder
Angus C et al., 2014	ns	-	No definition included	No definition included	CUA	Funder
Barbosa C et al., 2010	608	Dependence	No definition included	Hazardous drinking: ≤54.99 g/day (women); ≤79.99 g/day (men); Harmful drinking: ≥55 g/day (women); ≥80 g/day (men)	CUA	Funder
Barbosa C et al., 2015	9835	ns	No definition included	No definition included	CEA; CUA	Provider; Social
Barbosa C et al., 2017	976	ns	No definition included	No definition included	CEA	Provider
Barrett B et al., 2006	290	Dependence	No definition included	Any man drinking more than 8 units of alcohol in any one session at least once a week; any woman drinking more than 6 units in any one session at least once a week	CEA	Social
Blankers M et al., 2012	136	Dependence	AUDIT Score >8 and a weekly consumption of more than 14 standard (10 g ethanol) drinking units	No definition included	CEA; CUA	Social
Brodtkorb T-H et al., 2016	100,000	Dependence	No definition included	Males/Females: Very high risk (>101 / >60 g per day) High risk (61-100 / 41-60 g per day) Meidum risk (41-60 / 21-40 g per day) Low risk (1-40 / 1-20 g per day)	CUA	Funder; Social
Byrnes JM et al., 2010	ns	No dependence	No definition included	No definition included	CUA	Funder
Chisholm D et al., 2004	ns	Dependence	No definition included	Hazardous and harmful alcohol consumption was defined as consuming on average more than 20 and 40 g of pure alcohol per day for females and males, respectively.	CUA	Social
Chisholm D et al., 2018	529	ns	No definition included.	Hazardous and harmful alcohol consumption was defined as consuming on average more than 20 and 40 g of pure alcohol per day for females and males, respectively.	CUA	ns
Cobiac L et al., 2009	ns	Dependence	No definition included	No definition included	CUA	Funder
Cordovilla-Guardia S et al., 2020	294	No dependence	No definition included	No definition included	CBA	Funder
Corry J et al., 2004	20463; 30999	Dependence	No definition included	No definition included	CEA	Funder
Coulton S et al., 2017	529	No dependence	No definition included	AUDIT Score >8 is indicative of hazardous alcohol use	CUA	Funder; Social
Cowell AJ et al., 2012	656	Dependence	No definition included	At least one heavy drinking episode[b]	CEA	Provider
Crawford MJ et al., 2015	797	ns	No definition included	Men who drink more than eight standard drinks on one occasion one a month or more, and women who drink more than six standard drinks on one occasion once a month or more (Modified-Single Alcohol Screening Questionnaire [M-SASQ])	CUA	Funder
Deluca P et al., 2020	3326	No dependence	No definition included	>ó= 3 on the AUDIT-C → high-risk drinkers <3 on the AUDIT-C→ low-risk drinkers or abstainers	CUA	Funder
Drost RM et al., 2016	690	No dependence	No definition included	No definition included	CEA	Funder; Social

Table 1 *(cont.)*

Authors	Sample size	Alcohol dependence*	Definition of alcohol dependence	Definition of people at risk of alcohol dependence	Type of EE (according to reviewers)	Perspective**
Drummond C et al., 2009	112	No dependence	No definition included	AUDIT score > or = 8	CUA	ns
Dunlap LJ et al., 2010	1379	Dependence	No definition included	No definition included	CEA	Patient
Dunlap LJ et al., 2020	101	Dependence	No definition included	No definition included	CEA	Patient
Gentilello LM et al., 2005	ns	Dependence	No definition included	Either a blood alcohol level ≥100 mg/dL or a positive result on a standard brief alcohol disorder screening questionnaire	CBA	Funder
Giles EL et al., 2019	443	Dependence	AUDIT score ≥8	AUDIT score ≥4 OR Scored positive on the A-SAQ (Adolescent Single Alcohol Questionnaire): ≥3 was considered for possible hazardous or harmful drinking.	CUA; CCA	Funder
Havard A et al., 2012	244	Dependence	No definition included	People who had alcohol consumption in the 6 hours prior to the onset of their condition or who perceived alcohol to be a contributing factor in the condition with which they presented in the emergency department.	CEA	Provider
Holm AL et al., 2014a	ns	No dependence	No definition included	Excess alcohol consumption[c].	CUA	Funder
Holm AL et al., 2014b	ns	No dependence	No definition included	Excess alcohol consumption[c]	CUA	Funder
Hunter R et al., 2017	763	No dependence	No definition included	AUDIT-C ≥5 for men or AUDIT-C ≥4 for women	CUA	Funder
Ingels JB et al., 2013	473	No dependence	No definition included.	No definition included.	CEA	
Kruger J et al., 2014	1445	No dependence	No definition included.	No definition included.	CUA	Funder
Kunz FM et al., 2004	194	Dependence	AUDIT score >8	People who have used alcohol in the past 12 months with a CAGE score ≥1	CEA	ns
Lai T et al., 2007	ns	Dependence	No definition included	No definition included	CUA	Funder
Laramée P et al., 2014	ns	Dependence	Alcohol-dependent people with high/ very high drinking risk levels (defined based on the WHO criteria for risk consumption on a single drinking day)[d]	No definition included	CEA; CUA	Funder
Laramée P et al., 2016	ns	Dependence	Alcohol-dependent people with high/ very high drinking risk levels[d]	No definition included	CUA	Funder
Li T et al., 2017	33560	No dependence	No definition included	No definition included	CEA; CBA	Funder
Millier A et al., 2017	824	Dependence	No definition included	No definition included	CUA	Social; Third-party payer
Moore SC et al., 2020	832	No dependence	No definition included	No definition included	CEA	Funder; Social
Moraes E et al., 2010	89	Dependence	No definition included	No definition included	CEA	Social
Mortimer D & Segal L 2005	ns	Dependence	No definition included	No definition included	CUA	Social
Nadkarni A et al., 2017a	316	No dependence	No definition included	Harmful drinking. AUDIT Score 12-19	CEA; CUA	Funder; Social
Nadkarni A et al., 2017b	278	No dependence	No definition included	AUDIT Score 12-19	CEA; CUA	Funder; Social
Nadkarni A et al., 2019	135	Dependence	AUDIT Score ≥20	No definition included	CEA	Funder; Social
Navarro HJ et al., 2011	17030	Dependence and no dependence	AUDIT Score ≥20	Risky drinkers (AUDIT Score 8–19, representing WHO categories of hazardous and harmful drinking)	CEA	ns
Neighbors CJ et al., 2010	84	Dependence	No definition included	No definition included	CEA; CUA	Provider; social
Olmstead TA et al., 2019	138	Dependence and/ or current alcohol abuse	DSM-IV TR (APA, 2000)[e]	No definition included	CEA	Provider
Palmer AJ et al., 2000	ns	No dependence	-	-	CEA	Funder
Purshouse RC et al.,2013	ns	Dependence	AUDIT Score >8	No definition included	CUA	Funder
Robinson E et al., 2020	ns	No dependence	No definition included	No definition included	CEA	Social
Reddy VK et al., 2014	60	Dependence	No definition included	No definition included	CEA	Funder; patient
Rychlik R et al., 2003	814	Dependence	No definition included	No definition included	CEA	ns

Table 1 *(cont.)*

Authors	Sample size	Alcohol dependence*	Definition of alcohol dependence	Definition of people at risk of alcohol dependence	Type of EE (according to reviewers)	Perspective**
Schädlich PK & Brecht JG, 1998	2000	Dependence	People who meet at least 5 DSM criteria for alcohol dependence and are alcohol-dependent according to the Munich Alcoholism Test.	No definition included	CEA	Funder
Schulz DN et al., 2014	1733	No dependence	No definition included	No definition included	CEA; CUA	Funder; Social
Slattery J et al., 2002	1000	Dependence	Definition of alcohol dependence based on the International Classification of Disease (ICD-10) diagnostic categories[f]	No definition included	CEA	Funder
Sluiter RL et al., 2018	ns	Dependence	No definition included	No definition included	CEA	Social
Smit F et al., 2011	1254000	Dependence	Alcohol dependence based on the WHO criteria[g]	No definition included	CBA; CUA	Funder
Solberg LI et al., 2008	4000000	No dependence	-	-	CUA	Funder; social
Sumnall H et al., 2017	12738	No dependence	No definition included	Heavy episodic drinking (HED)[a]	CEA	Social
Tariq L et al., 2009	1110000	Dependence	Alcohol dependence based on DSM-IV criteria[e]	"High risk groups are defined as women who drink 2 or more standard alcohol drinks (i.e., 20 grams ethanol) per day; and men who drink 4 or more standard alcohol drinks (i.e. .40 grams ethanol) per day; without meeting the DSM-IV criteria for alcohol dependency"	CEA; CUA	Funder
Torfs K & De Graeve D, 1991	65909	Dependence	Physical dependence on alcohol and drinking >200 g/day	No definition included	CEA	Funder
UKATT Research Team, 2005	608	Dependence	No definition included	No definition included	CUA	ns
van den Berg M et al., 2008	ns	No dependence	No definition included	Alcohol consumption risk levels based on the Environment Chronic Disease Model[h]	CEA; CUA	Funder
Watson J et al., 2013	422	Dependence	AUDIT score ≥20	AUDIT score ≥8	CUA	Funder
Weisner C et al., 2000	541	Dependence	Alcohol dependence based on the DSM-IV criteria[e]	No definition included	CEA	ns
Wutzke SE et al., 2001	ns	No dependence	No definition included	Alcohol consumption is classified according to the Australian National Health and Medical Research Council criteria[i]	CEA	Funder
Zarkin GA et al., 2008	1383	Dependence	Alcohol dependence is determined by DSM-IV criteria[e]	No definition included	CEA	Provider

Note. ns: information not specified; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; DSM: Diagnostic and Statistical Manual of Mental Disorders.
* The definition of dependence is cluster of physiological, behavioural, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviours that once had greater value (World Health Organisation, 1992).
**Funder perspective: taking into account the outcomes and costs of interest for the organisation funding the intervention; Social perspective: capturing all relevant outcomes and costs borne by providers and potential beneficiaries (society as a whole); Provider perspective: taking into account the outcomes and costs of interest for the organisation implementing the intervention (i.e., National Health System, University, etc.); Patient perspective: taking into account the outcomes and costs of interest for the patient.
[a] Heavy episodic drinking (HED): defined as the consumption of 6 or more units in a single episode for male students and 4.5 or more units for female students. [b] Heavy drinking episode: any man drinking 5 or more drinks on an occasion or any woman drinking 4 or more drinks on an occasion. [c] Excess alcohol consumption: Hazardous drinking→ 12-23.9 g/day for women and 24-35.9 d/day for men. Harmful drinking→ >24 g/day for women and >36 g/day for men. [d] Alcohol-dependent people with high/very high drinking risk levels are defined based on the WHO criteria for risk consumption on a single drinking day: ≥41 g/day for women; ≥61 g/day for men.
[e] Definition of alcohol dependence according to DSM-IV TR (APA, 2000). Reference: American Psychiatric Association (APA). (2000). DSM-IV-TR. Barcelona: Masson. [f] Definition of alcohol dependence based on the ICD-10. Reference: World Health Organization. ICD-10: International statistical classification of diseases and related health problems (10th revised ed Vol. 1) Geneva, Switzerland: Author; 1992. [g] Alcohol dependence is defined, based on the WHO criteria, as meeting "at least 3 of the following criteria: tolerance; withdrawal symptoms; impaired control; preoccupation with acquisition and/or use; persistent desire or unsuccessful efforts to quit; sustains social, occupational, or recreational disability; and use continues despite adverse consequences." [h] Definitions of alcohol consumption categories: moderate: fewer than two standard drinks (< 20 g) per day for women, and fewer than four standard drinks (< 40 g) per day for men; excessive: 2–4 standard drinks (20–40 g) per day for women, and 4–6 standard drinks (40–60 g) per day for men; dangerous: more than four standard drinks (> 40 g) per day for women, and more than six standard drinks (> 60 g) per day for men. [i] Alcohol consumption classification according to the Australian National Health and Medical Research Council (NHMRC) criteria (NHMRC, 1992). These criteria define safe drinking as less than 40 g (four standard drinks) for men and less than 20 g (two standard drinks) for women with two alcohol-free days per week. Drinking above these levels is defined as 'hazardous' and above 60 g and 40 g per day, respectively as 'harmful'.

Assessment of methodological quality of the included studies

The JBI ACTUARI was used to assess the quality of the included studies. All studies reached an acceptable level of quality to be included in the systematic review. Commonly, these results refer to the 192 ICERs produced by the systematic literature review. In relation to items measured through the JBI ACTUARI related to well-defined question/objective, comprehensive description of alternatives, identification of relevant costs and outcomes for each alternative and their adjustment for differential timing, clinical effectiveness, incremental analysis of costs and consequences, and sensitivity analysis, the assessment of the included studies is presented below. In general, all papers defined the research question and the programmes or interventions appropriately that were compared in the analysis. The description of alternatives was comprehensive, although on many occasions (49.2%), papers did not report the sample size of each arm and the duration of intervention. Fifty percent of papers took the funder perspective, mostly the National Health System, and only 18.8% adopted a social perspective. The lifetime horizon was used in 57.1% of studies, with a time horizon lower than one year not frequent. Costs and outcomes have been adjusted for differential timing in more than fifty percent of papers, presenting outcomes and costs not appropriately adjusted in 39.68% of papers. Clinical effectiveness was established, using mainly a quality-of-life measure (47.6%) followed by a clinical measure (39.7%) or both at the same time (12.7%). It is clear in all papers how they have derived the effectiveness estimate. Fourty-six percent of papers did not specify which types of costs were included in their analysis. Of those that specified types of costs, 79.4% of papers included the direct health care–related costs as well as different types of costs such as direct non-health-related costs, patient costs or intervention costs. Only ten papers (26.5%) included productivity losses. Informal care costs were included at three papers. From all papers specifying the use of the social perspective, 81.8% of those included costs related to loss of productivity. Costs and outcomes have been measured accurately, though in costs, in many instances, the use of resources has not been reported separately. It is important to report use of resources separately from costs/prices for transparency, comparability and transferability reasons. In order to understand and evaluate if the cost data used in the economic evaluation was sensible it is always easier if the resources are reported separately from the costs/prices. Almost 60% of studies (n = 35) were conducting a cost–utility analysis. Fourty-nine per cent of papers used a decision analysis to estimate costs and outcomes, 48.4% of them being models different from a decision tree and a Markov model. Fully 88.9% of papers conducted a sensitivity analysis, mostly a deterministic (57.1%) rather than a probabilistic (42.9%) one. Of those doing a probabilistic sensitivity analysis, the vast majority (79.2%) represented a cost-effectiveness acceptability curve.

Findings of the review

These results refer to the 192 ICERs produced by the systematic literature review. In summary, for both people with alcohol dependence and people with high risk factors to become alcohol dependent, psychological interventions were the most evaluated in terms of efficiency, which were shown to be cost-effective or dominant when compared to doing nothing. In relation to pharmacological interventions, which were aimed to people with alcohol dependence, the drugs most used and evaluated were nalmefene and acamprosate, followed by other opioids and opioid antagonists and other drugs such as baclofen and disfulfiram. The policy, legislation and enforcement interventions were mainly based on tax increases observing a tendency for dominance or cost-effectiveness when compared to no intervention.

The different economic evaluations found cover a range of interventions such as psychosocial interventions; pharmacological treatments; brief interventions; and policy and legislation or enforcement interventions. Other interventions have been also included such as residential treatment, random breath testing, GP telemarketing, etc. See Table 2 for definitions of the various programmes and interventions informed by this systematic literature review and four other previous published reviews (Barbosa et al., 2010; Chisholm et al., 2006; Ludbrook et al., 2002; Slattery et al., 2002) that already did tasks in terms of homogenisation of the taxonomy for treating people with alcohol use disorders or people at risk of alcohol-related problems.

All these different interventions have been classified according to the availability of efficiency evidence according to the objectives of the programmes. The classification used was also based on those previous published reviews (Barbosa et al., 2010; Chisholm et al., 2006; Ludbrook et al., 2002; Slattery et al., 2002) and this systematic review. You can consult the definition of these interventions in the supplemental material (Table S1), and the classification of the types of alcohol programs in Table 2.

Treatments for people with alcohol dependence (32.8%; n=63) have been the most evaluated compared to treatments for people at risk of alcohol-related problems (28.6%; n=55) and policy, legislation and enforcement interventions (22.9%; n = 44). These percentages have been calculated according to the total number of comparisons in terms of efficiency found (n=192). In addition, the remaining 15.3% of comparisons studied a combination of different types of interventions (n=29). For further details, see Table 3.

Regarding treatments for people with alcohol dependence (n=63), 29.5% were focused in psychosocial interventions; 9.8% in pharmacological interventions; 1.6% evaluated other interventions such as residential treat-

ment; and, the remaining 59.0% evaluated a combination of these types of interventions. In terms of psychosocial interventions, despite the low number of estimates in this case (n = 18), it seemed that when any of these types of interventions (i.e., motivational interviewing; behavioural self-control training; coping/social skills training; etc.) were compared to 'no intervention' then the intervention was dominant, which means that the intervention was more effective and less costlier than the comparison. In this line, it could be highlighted the study carried out by Slattery et al. (2002) who found that different psychosocial interventions for people with alcohol dependence were dominant resulting in savings between £923 and £1,643 per additional abstinent patient compared with standard treatment. However, no particular intervention showed a clear tendency in terms of efficiency when compared to another. The low number of economic evaluations on pharmacological interventions (n=7) and the heterogeneity of evidence found lead to the impossibility of establishing conclusions in terms of the efficiency for this type of programmes. Although the number of comparisons of exclusively pharmacological interventions was low, there were some economic evaluations of combined interventions that include drugs. So, these studies have been added to the pharmacological interventions. So, a total of 34 comparisons based mainly on treatment with acamprosate, an N-methyl-D-aspartate (NMDA) receptor modulator, and opioids or opioid antagonists such as nalmefene have been added. Despite the greater number of existing comparisons when including the combined interventions that included drugs, no conclusive results could be found related to acamprosate. The use of acamprosate exclusively for the treatment of alcohol dependence has been shown to be dominant or cost-effective in the 3 comparisons made with placebo. When used in combination with a psychological intervention and medical management, it was dominated by medical management and placebo, as well as by the combination of medical management, opioids or opioid antagonists,

Table 2
Types of alcohol programs for alcohol dependence (Source: own; and Barbosa et al., 2010; Chisholm et al., 2004; Ludbrook et al., 2002; Slattery et al., 2002)

A. Treatments for people with alcohol dependence	
Psychosocial interventions	**Pharmacological interventions**
Motivational Interviewing	Acamprosate
Motivational Enhancement Therapy	Opioids and opioid antagonists (i.e., Naltrexone, Nalmefene, etc.)
Social Behaviour and Network Therapy	Disulfiram
Behavioural Self Control Training	Lithium
Coping/Social Skills Training	Selective serotonin reuptake inhibitors
Marital, Couples or Family Therapy	Benzodiazepines
Moderation-oriented cue exposure	Baclofen
Relapse prevention	Beta-blockers
Longer intervention	Alpha and beta receptor agonists adrenergic
Cognitive Behavioural Therapy	
12-Step Facilitation Therapy	Other interventions (i.e., residential treatment)
Group Therapy	Combined interventions
Community Reinforcement Approach	
B. Treatments for people at risk of alcohol-related problems	
Brief interventions	
School-based interventions	
Family skills interventions program	
Other interventions (i.e., GP telemarketing, eHealth)	
Combined interventions	
SBIRT (Screening, Brief Intervention and Referral to Treatment)	
Stepped care	
AMPP (Alcohol Misconduct Prevention Program)	
AIMS (Alcohol intoxication management service)	
Community prevention initiatives	
C. Policy, legislation and enforcement interventions	
Drunk-driving legislation/enforcement (random breath testing)	
Advertising controls/bans	
Tax increases	
Licensing	
Legal drinking age	
Mass-media campaigns	
Combined interventions	
Server training	

Note. *Highlighted areas mean that authors have found evidence on efficiency of these interventions.

Table 3
Types of interventions compared (65 papers; 192 comparisons in terms of efficiency)

Intervention	Comparator (check general definitions of these interventions in Table 2)	Efficiency results*	References
A: Treatments for people with alcohol dependence (n=63)			
Psychosocial interventions (n=18)			
Motivational Interviewing (n=3)	Motivational Interviewing (+3 months) (n=1)	Dominated	Cowell AJ et al., 2012
	No intervention (n=1)	Dominant	Slattery J et al., 2002
	Brief intervention (n=1)	Cost-effective	Neighbors CJ et al., 2010
Motivational Enhancement Therapy (n=1)	Brief interventions (n=1)	Cost-effective	Mortimer D & Segal L, 2005
Social Behaviour and Network Therapy (n=2)	Motivational Enhancement Therapy (n=2)	Indifferent (both cost-effective) (n=1) Cost-effective (n=1)	Barbosa C et al., 2005; UKATT Research Team, 2005
Behavioural Self Control Training (n=1)	No intervention (n=1)	Dominant	Slattery J et al., 2002
Coping/Social Skills Training (n=1)	No intervention (n=1)	Dominant	Slattery J et al., 2002
Marital, Couples or Family Therapy (n=1)	No intervention (n=1)	Dominant	Slattery J et al., 2002
Moderation-Oriented Cue Exposure (n=1)	Behavioural Self Control Training (n=1)	Cost-effective	Mortimer D, Segal L, 2005
Relapse Prevention (n=1)	No intervention (n=1)	ns	Slattery J et al., 2002
Longer intervention (trained staff consultations) (n=1)	Brief interventions (n=1)	Not cost-effective	Holm AL et al., 2014a
eHealth intervention (n=1)	Current practice (a) (n=1)	Cost-effective	Smit F et al., 2011
Combined behavioural intervention (n=2)	Medical Management + placebo (n=2)	Dominated	Dunlap LJ et al., 2010; Zarkin GA et al., 2008
Provision of brief psychosocial interventions (3 visits) for persons with hazardous and harmful alcohol use (50% coverage). (n=2)	No intervention or Current situation (n=2)	Cost-effective	Chisholm D et al., 2018
Enhanced usual care (EUC) + Counselling for Alcohol Problems (CAP) (n=1)	EUC alone (n=1)	Cost-effective	Nadkarni et al., 2019
Pharmacological interventions (n=7)			
Acamprosate (n=4)	Placebo (n=3)	Dominant (n=1) ns (n=2) Cost-effective (n=1)	Rychlik R et al., 2003; Schädlich PK & Brecht JG, 1998; Slattery J et al., 2002; Torfs K & De Graeve D, 1991
	Standard care (n=1)		
Baclofen (n=1)	Benzodiazepines *(Chlordiazepoxide)* (n=1)	Dominated	Reddy VK et al., 2014
Opioid or opiate antagonists (n=1)	Placebo (n=1)	ns	Slattery J et al., 2002
Disulfiram (n=1)	Placebo (n=1)	ns	Slattery J et al., 2002
Other interventions (n=1)			
Residential treatment (n=1)	Drunk-driving legislation (n=1)	Not cost-effective	Cobiac L et al., 2009
Combined interventions (n=37)			
Motivational Interviewing + Home visits (beginning and end of treatment) (n=1)	Motivational Interviewing + Relapse prevention (n=1)	Cost-effective	Moraes E et al., 2010
Motivational Interviewing + Cognitive Behavioural Therapy + Therapist support (n=1)	Motivational Interviewing + Cognitive Behavioural Therapy (n=1)	Cost-effective	Blankers M et al., 2012
Psychosocial support + Opioid or opiate antagonists (Nalmefene) (n=2)	Psychosocial support (n=2)	Cost-effective; Dominant	Laramée P et al., 2014, 2016
Medical Management + combined behavioural intervention + Acamprosate (n=2)	Medical Management + placebo (n=1)	Dominated	Dunlap LJ et al., 2010
	Medical Management + Opioid or opiate antagonists + Acamprosate (n=1)	Dominated	Zarkin GA et al., 2008
Medical Management + combined behavioural intervention + placebo (n=2)	Medical Management + Opioid or opiate antagonists (n=1)	Dominated	Zarkin GA et al., 2008
	Medical Management + placebo (n=1)	Dominated	Dunlap LJ et al., 2010
Medical Management + combined behavioural intervention + Opioid or opiate antagonists (n=2)	Medical Management + Opioid or opiate antagonists + Acamprosate (n=1)	Dominated	Zarkin GA et al., 2008
	Medical Management + placebo (n=1)	Dominated	Dunlap LJ et al., 2010
Medical Management + combined behavioural intervention + Opioid or opiate antagonists + Acamprosate (n=2)	Medical Management + Opioid or opiate antagonists + Acamprosate (n=1)	Dominated	Zarkin GA et al., 2008
	Medical Management + placebo (n=1)	Dominated	Dunlap LJ et al., 2010
Medical Management + Opioid or opiate antagonists + Acamprosate (n=2)	Medical Management + placebo (n=1)	Cost-effective	Dunlap LJ et al., 2010
	Medical Management + Opioid or opiate antagonists (n=1)	Cost-effective	Zarkin GA et al., 2008

Table 3 *(cont.)*

Intervention	Comparator (check general definitions of these interventions in Table 2)	Efficiency results*	References
Medical Management + Opioid or opiate antagonists (n=2)	Medical Management + placebo (n=2)	Cost-effective	Dunlap LJ et al., 2010; Zarkin GA et al., 2008
Medical Management + Acamprosate (n=2)	Medical Management + placebo (n=1)	Dominated	Dunlap LJ et al., 2010
	Medical Management + Opioid or opiate antagonists (n=1)	Dominated	Zarkin GA et al., 2008
Opioid or opiate antagonists + Residential treatment (n=1)	Random breath testing (n=1)	Not cost-effective	Cobiac L et al., 2009
Group behavioral couples' therapy + individual-based treatment (n=8)	Standard behavioral couples' therapy + individual-based treatment (n=8)	Dominant or cost-effective	Dunlap LJ et al., 2020
Nalmefene + Psychosocial support (n=10)	Psychosocial support alone (n=2)	Cost-effective or dominant	Brodtkorb T-H et al., 2016; Millier A et al., 2017
	No treatment (n=4)	Cost-effective or dominant	
OPRM1 Screening: OPRM1 genotype-guided treatment allocation of naltrexone to G-allele carrying AUD patients (n=1)	No OPRM1 Screening: Random (non-genotype guided) treatment allocation to pharmacological treatment with naltrexone or acamprosate (n=1)	Cost-effective	Sluiter et al., 2018
B: Treatments for people at risk of alcohol-related problems (n=55)			
Brief interventions (n=26)			
Brief interventions (face-to-face) (n=19)	Brief intervention (+ 3 months) (n=1)	Dominated	Cowell AJ et al., 2012
	Random breath testing (n=1)	Cost-effective	Cobiac L et al., 2009
	No intervention (n=15)	Dominant (n=2) Dominant or cost-effective (n=3) Cost-effective (n=10)	Angus C et al., 2014; Chisholm D et al., 2004 (n=3); Gentilello LM et al., 2005; Lai T et al., 2007; Mortimer D & Segal L, 2005 (n=2); Purshouse RC et al., 2013; Solberg LI et al., 2008 (n=2); Tariq L et al., 2009; Wutzke SE et al., 2001 (n=2); Havard et al., 2012
	Control (b) (n=1)	Cost-effective	Wutzke SE et al., 2001
	Current situation (c) (n=1)	Cost-benefit	Cordovilla-Guardia S et al., 2020
Brief interventions (by phone) (n=1)	Brief interventions (face-to-face) (n=1)	Dominant	Holm AL et al., 2014b
Strong African American Families-Teen program (SAAF-T) (n=1)	Attention-control intervention (ACI) (n=1)	Cost-effective	Ingels JB et al., 2013
Personal feedback and Brief Advice (PFBA) (face-to-face) (n=2)	Control group (screening alone) (n=2)	Not cost-effective (n=2) (in the low-risk and high-risk trials)	Deluca P et al., 2020
Personal feedback + smartphone- or web-based brief intervention (eBI) (n=2)		Dominated (n=2) (in the low-risk and high-risk trials)	
Brief advice (face-to-face) + an offer of an appointment with an Alcohol Health Worker (AHW) (n=1)	Control treatment: general health information leaflet (n=1)	Not cost-effective	Crawford MJ et al., 2015
Other interventions (n=22)			
E-mail with a feedback report on personal drinking patterns (n=1)	E-mail with a feedback report on personal drinking patterns (+3 months) (n=1)	ns	Cowell AJ et al., 2012
eHealth intervention (n=1)	No intervention (n=1)	Cost-effective	Smit F et al., 2011
Non-Directive Reflective Listening (n=1)	Brief intervention (Assessment and feedback) (n=1)	Not cost-effective	Mortimer D & Segal L, 2005
A sequential web-based computer-tailored multisession program (n=1)	A simultaneous web-based computer-tailored multisession program (n=1)	Dominated (CUA)	Schulz DN et al., 2014
A sequential web-based computer-tailored multisession program (n=1)	Control (n=1)	Cost-effective (CEA) Dominated (CUA)	
A simultaneous web-based computer-tailored multisession program (n=1)		Cost-effective (CEA) Dominated (CUA)	
A theory-based online health behaviour intervention (U@Uni) (n=1)	Control (n=1)	Cost-effective	Kruger J et al., 2014
Brief Treatment (BT) (SBIRT service) (n=1)	Brief Intervention (BI) (SBIRT service) (n=1)	Cost-effective	Barbosa C et al., 2017
Alcohol intoxication management services (AIMSs) model (n=6)	Usual care (n=6)	Dominant or cost-effective	Moore SC et al., 2020
Facilitated access to an interactive website (n=1)	Face-to-face brief intervention delivered by a general practice (n=1)	Cost-effective	Hunter R et al., 2017
Alcohol Misconduct Prevention Program (AMPP) (n=3)	Historical control group (n=1)	Cost-effective and cost-benefit	Li T et al., 2017
Stepped care (n=2)	Control group minimal intervention (n=2)	Dominant or Cost-effective	Coulton S et al., 2017; Drummond C et al., 2009

Table 3 *(cont.)*

Intervention	Comparator (check general definitions of these interventions in Table 2)	Efficiency results*	References
Screening, Brief Intervention, and Referral to Treatment (SBIRT) in Emergency Departments (Trauma Centers included) (n=1)	SBIRT in Outpatient Medical Settings (Federally Qualified Health Centers or hospital outpatient clinics) (n=1)	Cost-effective	Barbosa C et al., 2015
Web-based computer-tailored school intervention based on I-Change model (n=1)	Care as usual (CAU) (n=1) (waiting list control condition)	Cost-effective for population subgroups	Drost RM et al., 2016
Combined interventions (n=7)			
Brief intervention + referral to alcohol treatment services (n=1)	Opportunistic identification and an information only control (n=1)	Cost-effective	Barrett B et al., 2006
Brief intervention + health information packet (n=1)	Health information packet (n=1)	Cost-effective	Kunz FM et al., 2004
Brief interventions + GP Telemarketing + GP Support (n=1)	Random breath testing (n=1)	Cost-effective	Cobiac L et al., 2009
Enhanced usual care (EUC) + Counselling for Alcohol Problems (CAP) (n=2)	EUC alone (n=2)	Dominant or Cost-effective	Nadkarni et al., 2017a, 2017b
A combined universal school and parental alcohol intervention called the Steps Towards Alcohol Misuse Prevention Programme (STAMPP) (n=1)	Control group: Education as normal (EAN) (n=1)	Cost-effective	Sumnall H et al., 2017
School-based universal alcohol harm reduction curriculum + brief parental intervention (n=1)	Education as normal (EAN) (n=1)	Cost-effective	Agus A et al., 2019
C: Policy, legislation and enforcement interventions (n=44)			
Advertising controls/bans (n=6)	Brief intervention (n=1)	Dominant	Holm AL et al., 2014b
	Random breath testing (n=1)	Dominant	Cobiac L et al., 2009
	No intervention or Current situation (c) (n=4)	Dominant o cost-effective (n=3) Dominated (n=1)	Chisholm D et al., 2004 (n=3); Lai T et al., 2007
Random breath testing (n=4)	Current situation (c) (n=1)	Dominated	Lai T et al., 2007
	No intervention (n=3)	Dominant o cost-effective	Chisholm D et al., 2004 (n=3)
A rate that maintains the current deadweight loss of taxation (n=1)	Existing taxation system (n=3)	Dominant	Byrnes JM et al., 2010
A rate that maintains existing taxation Revenue (n=1)		Dominant	
A rate equal to the existing rate applied to spirits (n=1)		Dominant	
Tax increases (n=11)	Brief intervention (n=1)	Dominant	Holm AL et al., 2014b
	Random breath testing (n=1)	Dominant	Cobiac L et al., 2009
	No intervention or Current situation (c) (n=8)	Dominant (n=1) dominant or cost-effective (n=4) cost-effective (n=2)	Chisholm D et al., 2004 (n=3); Holm AL et al., 2014a; Lai T et al., 2007; van den Berg M et al., 2008; Chisholm D et al., 2018
	Minimun unit floor price applied to all types of alcoholic drinks (n=1)	Dominant	Robinson E et al., 2020
Licensing (n=6)	Brief intervention (n=1)	Dominant	Holm AL et al., 2014b
	Random breath testing (n=1)	Cost-effective	Cobiac L et al., 2009
	No intervention or Current situation (c) (n=4)	Dominant (n=3) Dominated (n=1)	Chisholm D et al., 2004 (n=3); Lai T et al., 2007
Legal drinking age (n=2)	Brief intervention (n=1)	Cost-effective	Holm AL et al., 2014b
	Random breath testing (n=1)	Dominant	Cobiac L et al., 2009
Mass-media campaigns (n=3)	Random breath testing (n=3)	Cost-effective	Cobiac L et al., 2009; Chisholm D et al., 2018
Enactment and enforcement of drunk driving laws and blood alcohol concentration limits (via sobriety checkpoints) (n=2)	No intervention or Current situation (n=2)	Cost-effective	Chisholm D et al., 2018
Enactment and enforcement of restrictions on the physical availability of retailed alcohol (via reduced hours of sale) (n=2)	No intervention or Current situation (n=2)	Cost-effective	Chisholm D et al., 2018
Combined interventions (n=5)			
Tax increases + Advertising controls (n=4)	No intervention or Current situation (c) (n=4)	Cost-effective	Chisholm D et al., 2004 (n=3); Lai T et al., 2007
Tax increases + Random breath testing (n=1)	Current situation (c) (n=1)	Dominated	Lai T et al.,2007

Table 3 *(cont.)*

Intervention	Comparator (check general definitions of these interventions in Table 2)	Efficiency results*	References
A & B (n=22)			
Motivational Interviewing + Feedback report (n=1)	Motivational Interviewing + Feedback report (+ 3 months) (n=1)	Cost-effective	Cowell AJ et al., 2012
Group female-specific cognitive behavioral therapy (G-FS-CBT) (n=1)	Individual female-specific cognitive behavioral therapy (I-FS-CBT) (n=1)	Cost-effective	Olmstead TA et al., 2019
Motivational Enhancement Therapy + Brief interventions + Referral to local specialist alcohol services (n=1)	Brief intervention + Informative leaflet (n=1)	Dominant or cost-effective	Watson J et al., 2013
Brief interventions + 12-Step Facilitation Therapy + Marital, Couples or Family Therapy + Group Therapy + Pharmacological interventions (not specified the type) + Relapse prevention + Physician appointments (four times the intensity of interventions than the control group) (n=1)	Brief interventions + 12-Step Facilitation Therapy + Marital, Couples or Family Therapy + Group Therapy + Pharmacological interventions (not specified the type) + Relapse prevention + Physician appointments (n=1)	ns	Weisner C et al., 2000
Brief interventions + Cognitive Behavioural Therapy + Marital, Couples or Family Therapy + Acamprosate (n=2)	No intervention (n=2)	Cost-effective	Corry J et al., 2004 (n=2)
Self-reported contact for mental health problem + Cognitive Behavioural Therapy + Brief intervention + Acamprosate (n=2)	No intervention (n=2)	Cost-effective	Corry J et al., 2004 (n=2)
Acamprosate + Brief intervention (n=1)	Brief intervention (n=1)	Dominant	Palmer AJ et al., 2000
Brief intervention (weekly therapy) + Opioid or opiate antagonists (n=1)	Brief intervention + Placebo (n=1)	ns	Mortimer D & Segal L, 2005
Screening + Brief Intervention (BI) by a GP (n=11)	Screening alone (n=11)	Cost-effective	Navarro HJ et al., 2011
Brief intervention for alcohol problems (n=1)	Usual practice (n=1)	Cost-effective	Giles EL et al., 2019
B & C (n=7)			
Brief intervention + Tax increases (n=1)	Current situation (c) (n=1)	Dominated	Lai T et al., 2007
Tax increases + Advertising controls + Brief intervention (n=4)	No intervention or Current situation (c) (n=4)	Dominated (n=1) ns (n=3)	Chisholm D et al., 2004 (n=3); Lai T et al., 2007
Tax increases + Advertising controls + Random breath testing + Licensing + Brief intervention (n=1)	Current situation (c) (n=1)	Cost-effective	Lai T et al., 2007
Tax increases + Advertising controls + Licensing + Brief intervention (n=1)	Current situation (c) (n=1)	Dominated	Lai T et al., 2007

Note. (a)"Current practice" is defined as usual care in the Netherlands,. Authors do not specify in what usual care consists of.
(b) "Control" is defined as a strategy in which there is no initial training and no ongoing support on programme implementation.
(c) "Current situation" is defined as a "do nothing counterfactual", a situation where no interventions exist.
ns: information not specified.
*Dominant: the new intervention or treatment is found to be less costly and more effective, so it will be getting more health for less cost. This means the new intervention or treatment dominates the comparator. Dominated: the new intervention or treatment is found to be less effective and more costly, so it means the new intervention or treatment is dominated by the comparator.

and acamprosate. Therefore, when used in combination with an opioid or opioid antagonist, it was cost-effective or dominant. Likewise, when the combination of medical management with acamprosate was compared with medical management and placebo, as well as with medical management and opioids or opioid antagonists, it turned out to be dominated by the latter combinations. However, in relation to use of nalmefene combined with psychological therapy, it demonstrated its cost-effectiveness or dominance compared with psychological therapy alone or placebo in the 12 comparisons found in this review (Brodtkorb, Bell, Irving & Laramée, 2016; Laramée, Bell, Irving, & Brodtkorb, 2016; Laramée et al., 2014; and Millier et al., 2017). The same applies to the economic evaluation of combined interventions in this case (see Table 3).

In terms of treatments for people with high risk factors to become alcohol dependent brief intervention has been the largest evaluated (47.8%). When comparing this intervention to no intervention, in spite of the low amount of evidence, it seemed that brief intervention (mainly focused in brief advice in this case) could be a dominant or cost-effective strategy. Similarly, when this type of intervention was applied in different settings, for instance, according to the study carried out by Barbosa, Cowell, Bray & Aldridge (2015), the combined intervention known as SBIRT which includes brief intervention results in costs savings and improvements in health in both emergency departments and outpatient settings, being more cost-effective, which means that it provides better effectiveness at a lower cost, in emergency departments than in outpatient settings. No other conclusions could be withdrawn from other interventions

or combined interventions (e.g. brief intervention + referral to alcohol treatment services) in terms of efficiency due to the inconsistency of evidence found (see Table 3).

In the case of policy, legislation and enforcement interventions, and acknowledging there could be a tendency for interventions such as advertising controls, random breath testing, Tax increases, and licensing, for dominance or cost-effectiveness when compared to no intervention. For instance, in the study carried out by Chisholm et al. (2018), a 50% increase in consumption tax rates resulted in a low cost of implementation (less than I $ 0.10 per capita), a level of impact in health translated into more than 500 years of healthy life gained by one million inhabitants and a very favorable level in terms of the cost-effectiveness ratio, which is less than I $ 100 per year of healthy life gained, this being the strategy of most profitable intervention among those evaluated (see Table 3).

Discussion

Some previous literature reviews on the measures to reduce alcohol misuse have been published before (Angus et al., 2014; Barbosa et al., 2010; Chisholm et al., 2006; Hill et al., 2017; Hoang et al., 2016; Kaner et al., 2017; Kelly et al., 2020; Kruse et al., 2020; Ludbrook, 2004; Ludbrook et al., 2002; Meads et al., 2007; Mujoomdar & Spry, 2009; Ndegwa & Cunningham, 2009; Poldrugo et al., 2005; Rehm & Barbosa, 2018; Slattery et al., 2002; White et al., 2018; Yadav & Kobayashi, 2015); however, no one has addressed the question of identifying which programme or intervention was more efficient in terms of treatments for people with AUD, although Ludbrook (2004) looked at all possible alcohol-related approaches, spanning from treatment to prevention, and individual-level interventions to population approaches. In addition, Rehm and Barbosa (2018) concluded that the economic research to date is relatively scarce and not always rigorous. Thus, there is a need for this information, to inform the policy debate when determining the level of resource input necessary to tackle alcohol problems. Combining treatment/early intervention and policy interventions offers readers an overview of the range of choices for impacting AUD, and their potential for cost-effectiveness. This paper defines a starting point for decision makers by allowing them to prioritise classes of interventions that have a greater potential for being efficient. This analysis also points to areas (medication-assisted treatment) where additional economic evaluations are needed.

Although, in this systematic review of economic evaluations of interventions for people with alcohol use disorders or people at risk of alcohol-related problems, not much evidence has been found in terms of efficiency, some careful conclusions might be drawn. Unfortunately, the wide variety of outcome measures and costs does not allow decision makers to choose the intervention that is most efficient. It is impossible to determine whether differences in the cost per unit (e.g., QoL) gained are truly due to differences in efficiency of the interventions rather than to differences in the methods used for the comparisons, thus, most of the conclusions that can be drawn are limited to the interventions included in each separate study. However, this information could be helpful to clinical practice in terms of raising the importance of the need for evaluating all interventions in terms of efficiency. It also shows which interventions have been more commonly evaluated and which are the most important variables for taking in account in order to conduct economic evaluations on alcohol -related programs. In relation to the studies evaluating the efficiency of pharmacological interventions related to alcohol dependence, conclusions could be established regarding the use of nalmefene but not in relation to acamprosate due to the controversial and different results obtained in the studies found. Recently, Avanceña, Miller, Uttal, Hutton & Mellinger (2020) have carried out an economic evaluation based on the existing literature finding that the use of Acamprosate and naltrexone, as well as the use of Baclofen, gabapentin, and topiramate, compared to doing nothing, are cost-saving interventions in patients with alcohol-related cirrhosis.

Regarding conclusions referring to brief intervention, this recommendation was already established for Scotland (Ludbrook, 2004) some time ago. This result held in our review. Despite this, several authors (Falcón et al., 2018) describe barriers to implementing screening and brief intervention for alcohol consumption in some settings such as hospital emergency departments. Something to highlight was that not many drug-related studies to quit alcohol or help reduce alcohol intake have been evaluated from an efficiency point of view. Therefore, there is a need for the pharmaceutical industry, which produces drugs that reduce alcohol intake, to invest in measuring and evaluating the efficiency of their products to reduce alcohol intake and decrease relapse to heavy drinking. Additionally, no study aimed at improving cognitive functioning in patients with cognitive deterioration associated with alcohol use who are undergoing treatment for alcohol dependency has been identified in this systematic review. Nevertheless, authors such as Frías-Torres et al. (2018) suggest how cognitive rehabilitation therapy could improve this condition.

Other reviews of economic evaluations focused on pharmacological interventions, such as the use of Naltrexone (Mujoomdar & Spry, 2009), policy instruments (Chisholm et al., 2006), screening and brief interventions (Angus et al., 2014) and assessment of methods for economic evaluations of treatments for AUD (Barbosa et al., 2010) exist. However, they did not really assess the efficiency of those programs. This review still online presents the conclusions from Brown et al. (2016) who showed that there was a dearth of evaluations that assessed the effectiveness of

pharmacy-based interventions for alcohol management. The present study included all references these reviews provided, with the exception of some that were not full economic evaluations and thus did not provide an ICER (Alwyn, John, Hodgson & Phillips, 2004; Babor et al., 2006; Bischof et al., 2008; Humphreys & Moos, 1996; Lock et al., 2006; Long, Williams & Hollin, 1998; Nalpas et al., 2003; Pettinati et al., 1999; Shakeshaft, Bowman, Burrows, Doran & Sanson-Fisher, 2002; Sobell et al., 2002). In addition, it encourages the idea of thinking, in all these interventions, in terms of treating people with alcohol dependence; treating people at risk of alcohol-related problems, and policy, legislation and enforcement interventions. Therefore, if decision makers were thinking of implementing a potential programme in a particular country, the recommendable interventions according to the efficiency criteria would be any psychosocial intervention, brief interventions for people at risk of alcohol-related problems, and advertising controls, tax increases, licensing, legal drinking age, and mass media campaigns. Thus, the information generated by this systematic review would help in order to decide in which interventions invest public health resources to address rehabilitation of alcohol-related disorders.

In line with policy, legislation and enforcement interventions, given the favourable findings in terms of the incremental cost-effectiveness ratio, it seems to be recommendable for countries to promote these types of interventions in order to improve the efficiency of this public health problem. It is surprising the lack of economic evaluations of the preventive intervention based on a "minimum price per unit" or "minimum unit price" (MUP). On the one hand, Lonsdale, Hardcastle & Hagger (2012) concluded through focus groups that a series of objections were raised by the participants related to scepticism about whether the MUP is an effective means to reduce alcohol consumption, the perception that the policy "punishes" the moderate drinker and related to the concern that this measure may exacerbate existing social problems. On the other hand, the study´participants expressed that this measure could work if it would be part of a broader campaign that included other educational activities. Additionally, Purshouse, Meier, Brennan, Taylor & Rafia (2010) concluded that The Sheffield alcohol policy model (Holmes et al., 2014) predicts that the establishment of an MUP would reduce alcohol-related harms to a greater extent than overall increases in taxes, with nearly twice the number of deaths prevented.

In addition, there was an interest to compare the efficiency of different interventions according to the level of alcohol dependence (i.e. efficiency of interventions targeted at those with moderate-to-severe alcohol dependence as compared to interventions targeted at less severe alcohol problems). However, the definitions used across studies for grading the alcohol dependence has been different (i.e. people with an AUDIT score >8; people drinking >200 g/day). Therefore, without a homogeneous definition it is not possible to study the impact on results according to different grades of alcohol dependence. In relation to the observed trend in the use and efficiency of interventions such as advertising controls, random breath testing, Tax increases, and licensing, it seems to be recommendable for countries to promote these types of interventions in order to improve the efficiency of this public health problem. There is a need for further research in order to characterise cost-effectiveness thresholds in the substance use field. In order to do so, more evidence in terms of cost-effectiveness needs to be provided of all these different interventions to tackle the alcohol dependence. However, there is a need to evaluate how much society is willing to pay for these types of interventions and the improvement on health outcomes generated. Thus, willingness to pay studies or discrete choice experiments could be used in order to explore this question.

One of the limitations of this review is the limited number of studies found from which to draw conclusions. Ideally, these conclusions should have been drawn according to the study country to ensure the applicability of the results to each particular context. Therefore, this review continues to suggest that further research needs to be conducted to evaluate the efficiency of interventions and programmes to reduce alcohol misuse around the world. Barbosa et al. (2010) pointed out some years ago that this type of literature was still rather sparse, and further research is required to fill the gaps. There is still a need to use common methodology in future economic evaluations of alcohol treatment, to produce more stable cost-effectiveness estimates and to inform decisions for resource allocation to efficient alcohol treatment. Another issue raised by this systematic literature review is that very few studies considered direct costs for the patient, productivity losses, and other costs, mainly referring to external effects such as criminal justice, fire services or accident fatality in studies for treating alcohol use disorders or people at risk of alcohol-related problems.

Not only is there a need for further research in efficiency but also in the effectiveness of different programmes or interventions. According to Yadav & Kobayashi (2015), despite the additional decade of evidence, available studies were heterogeneous in their approaches, so no conclusions about the effectiveness of mass media campaigns could be made. More studies in terms of effectiveness and cost-effectiveness are needed to evaluate programmes related to alcohol intake. In addition, there was also a need to report the cost methodology of the different studies better (Bray, Zarkin, Hinde & Mills, 2012). Costs related to the evaluation of programmes such as alcohol screening and brief intervention in medical settings might present large differences because the cost methodology was not commonly established.

In fact, there is a need to foster an evaluation culture among those responsible for delivering services and to design some guidelines in promoting this evaluation culture along this public health programme (Ludbrook, 2004). Careful attention needs to be paid in terms of evaluating efficiency of alcohol-related programs.

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Conflict of interests

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References

Alwyn, T., John, B., Hodgson, R. J. & Phillips, C. J. (2004). The addition of a psychological intervention to a home detoxification programme. *Alcohol and Alcoholism*, *39*, 536–541. doi:10.1093/alcalc/agh092.

Angus, C., Latimer, N., Preston, L., Li, J. & Purshouse, R. (2014). What are the implications for policy makers? A systematic review of the cost-effectiveness of screening and brief interventions for alcohol misuse in primary care. *Frontiers in Psychiatry*, *5,* 114. doi:10.3389/fpsyt.2014.00114.

Avanceña, A., Miller, N., Uttal, S. E., Hutton, D. W. & Mellinger, J. L. (2020). Cost-effectiveness of alcohol use treatments in patients with alcohol-related cirrhosis. *Journal of hepatology*. Advance publication online. doi:10.1016/j.jhep.2020.12.004.

Babor, T. F., Higgins-Biddle, J. C., Dauder, D., Burleson, J. A., Zarkin, G. A. & Bray, J. (2006). Brief interventions for at-risk drinking: Patient outcomes and cost-effectiveness in managed care organizations. *Alcohol and Alcoholism*, *41*, 624–631. doi: 10.1093/alcalc/agl078.

Barbosa, C., Cowell, A., Bray, J. & Aldridge, A. (2015). The cost-effectiveness of alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) in emergency and outpatient medical settings. *Journal of Substance Abuse Treatment, 53*, 1–8. doi:10.1016/j.jsat.2015.01.003.

Barbosa, C., Cowell, A., Dowd, W., Landwehr, J., Aldridge, A. & Bray, J. (2017). The cost-effectiveness of brief intervention versus brief treatment of Screening, Brief Intervention and Referral to Treatment (SBIRT) in the United States. *Addiction, 112* (Supl. 2), 73–81. doi:10.1111/add.13658.

Barbosa, C., Godfrey, C. & Parrott, S. (2010). Methodological assessment of economic evaluations of alcohol treatment: What is missing? *Alcohol and Alcoholism*, *45*, 53–63. doi:10.1093/alcalc/agp067.

Bischof, G., Grothues, J. M., Reinhardt, S., Meyer, C., John, U. & Rumpf, H. J. (2008). Evaluation of a telephone-based stepped care intervention for alcohol-related disorders: A randomized controlled trial. *Drug and Alcohol Dependence*, *93*, 244–251. doi:10.1016/j.drugalcdep.2007.10.003.

Bray, J. W., Zarkin, G. A., Hinde, J. M. & Mills, M. J. (2012). Costs of alcohol screening and brief intervention in medical settings: A review of the literature. *Journal of Studies on Alcohol and Drugs, 73*, 911–919. doi:10.15288/jsad.2012.73.911.

Brodtkorb, T-H., Bell, M., Irving, A.H. & Laramée, P. (2016). The cost effectiveness of nalmefene for reduction of alcohol consumption in alcohol-dependent patients with high or very high drinking-risk levels from a UK societal perspective. *CNS Drugs, 30,* 163-177. doi:10.1007/s40263-016-0310-2.

Brown, T. J., Todd, A., O'Malley, C. L., Moore, H. J., Husband, A. K., Bambra, C.,… Summerbell, C. D. (2016). Community pharmacy interventions for public health priorities: A systematic review of community pharmacy-delivered smoking, alcohol and weight management interventions. *BMJ Open, 6,* e009828. doi:10.1136/bmjopen-2015-009828.

Burke, T. R. (1988). The economic impact of alcohol abuse and alcoholism. *Public Health Reports, 103*, 564–568.

Chisholm, D., Doran, C., Shibuya, K. & Rehm, J. (2006). Comparative cost-effectiveness of policy instruments for reducing the global burden of alcohol, tobacco and illicit drug use. *Drug and Alcohol Review*, *25*, 553–565. doi:10.1080/09595230600944487.

Chisholm, D., Moro, D., Bertram, M., Pretorius, C., Gmel, G., Shield, K. & Rehm, J. (2018). Are the "best buys" for alcohol control still valid? An update on the comparative cost-effectiveness of alcohol control strategies at the global level. *Journal of Studies on Alcohol and Drugs, 79*, 514–522.

Chisholm, D., Rehm, J., Van Ommeren, M. & Monteiro, M. (2004). Reducing the global burden of hazardous alcohol use: A comparative cost-effectiveness analysis.

Journal of Studies on Alcohol, *65*, 782–793. doi: 10.15288/jsa.2004.65.782.

Cobiac, L., Vos, T., Doran, C. & Wallace, A. (2009). Cost-effectiveness of interventions to prevent alcohol-related disease and injury in Australia. *Addiction*, *104*, 1646–1655. doi:10.1111/j.1360-0443.2009.02708.x.

Donaldson, C., Mugford, M. & Vale, L. (Eds.). (2002). *Evidence-based health economics: From effectiveness to efficiency in systematic review*. London: BMJ Publishing Group.

Drummond, M., Sculpher, M., Claxton, K., Stoddard, G. L. & Torrance, G. W. (2015). *Methods for the economic evaluation of health care programmes* (4th ed.). United Kingdom: Oxford University Press.

Drummond, M., Weatherly, H., Claxton, K., Cookson, R., Ferguson, B., Godfrey, C. & Rice, N. (2007). *Assessing the challenges of applying standard methods of economic evaluation to public health interventions (2nd ed.)*. York: Public Health Research Consortium.

Dunlap, L. J., O'Farrell, T. J., Schumm, J. A., Orme, S. S., Murphy, M. & Murchowski, P. M. (2020). Group versus standard behavioral couples' therapy for alcohol use disorder patients: Cost-effectiveness. *Journal of Studies on Alcohol and Drugs, 81*, 152–163. doi:10.15288/jsad.2020.81.152.

Dunlap, L. J., Zarkin, G. A., Bray, J. W., Mills, M., Kivlahan, D. R., McKay, J. R.,… Tonigan, J. S. (2010). Revisiting the cost-effectiveness of the COMBINE study for alcohol dependent patients: The patient perspective. *Medical Care*, *48*, 306–313. doi:10.1097/mlr.0b013e3181ca3d40.

Falcón, M., Navarro-Zaragoza, J., García-Rodríguez, R. M., Nova-López, D., González-Navarro, M. D., Mercadal, M.,… Luna Ruiz-Cabello, A. (2018). Perceived barriers to implementing screening and brief intervention for alcohol consumption by adolescents in hospital emergency department in Spain. *Adicciones, 30*, 189-196. doi:10.20882/adicciones.896.

Frías-Torres, C., Moreno-España, J., Ortega, L., Barrio, P., Gual, A. & Teixidor López, L. (2018). Remediation therapy in patients with alcohol use disorders and neurocognitive disorders: A pilot study. *Adicciones, 30,* 93-100. doi:10.20882/adicciones.757.

Goeree, R. & Diaby, V. (2013). Introduction to health economics and decision-making: Is economics relevant for the frontline clinician? *Best Practice and Research: Clinical Gastroenterology*, *27*, 831–844. doi: 10.1016/j.bpg.2013.08.016.

Gold, M. R., Siegel, J. E., Russell, L. B. & Weinstein, M. C. (1996). *Cost-effectiveness in health and medicine*. New York: Oxford University Press.

Hill, S. R., Vale, L., Hunter, D., Henderson, E. & Oluboyede, Y. (2017). Economic evaluations of alcohol prevention interventions: Is the evidence sufficient? A review of methodological challenges. *Health Policy, 121*, 1249–1262. doi:10.1016/j.healthpol.2017.10.003.

Hoang, V. P., Shanahan, M., Shukla, N., Perez, P., Farrell, M. & Ritter, A. (2016). A systematic review of modelling approaches in economic evaluations of health interventions for drug and alcohol problems. *BMC Health Services Research, 16*, 127. doi: 10.1186/s12913-016-1368-8.

Holmes, J., Meng, Y., Meier, P. S., Brennan, A., Angus, C., Campbell-Burton, A., … Purshouse, R.C. (2014). Effects of minimum unit pricing for alcohol on different income and socioeconomic groups: A modelling study. *Lancet, 383*, 1655–64. doi:10.1016/S0140-6736(13)62417-4.

Humphreys, K. & Moos, R. (1996). Reduced substance-abuse-related health care costs among voluntary participants in Alcoholics Anonymous. *Psychiatric Services*, *47*, 709–713. doi:10.1176/ps.47.7.709.

Kaner, E. F., Beyer, F. R., Garnett, C., Crane, D., Brown, J., Muirhead, C.,… Michie, S. (2017). Personalised digital interventions for reducing hazardous and harmful alcohol consumption in community-dwelling populations. *Cochrane Database of Systematic Reviews, 9*, CD011479. doi:10.1002/14651858.CD011479.pub2.

Kelly, J. F., Abry, A., Ferri, M. & Humphreys, K. (2020). Alcoholics anonymous and 12-step facilitation treatments for alcohol use disorder: A distillation of a 2020 Cochrane review for clinicians and policy makers. *Alcohol and Alcoholism, 55,* 641-651. doi:10.1093/alcalc/agaa050.

Kernick, D. P. (2003). Introduction to health economics for the medical practitioner. *Postgraduate Medical Journal*, *79*, 147–150. doi:10.1136/pmj.79.929.147.

Kruse, C. S., Lee, K., Watson, J. B., Lobo, L. G., Stoppelmoor, A. G. & Oyibo, S. E. (2020). Measures of effectiveness, efficiency, and quality of telemedicine in the management of alcohol abuse, addiction, and rehabilitation: Systematic review. *Journal of Medical Internet Research, 22*, e13252. doi: 10.2196/13252.

Laramée, P., Bell, M., Irving, A. & Brodtkorb, T. H. (2016). The Cost-effectiveness of the integration of nalmefene within the UK healthcare system treatment pathway for alcohol dependence. *Alcohol and Alcoholism, 51*, 283–290. doi:10.1093/alcalc/agv140.

Laramée, P., Brodtkorb, T.-H., Rahhali, N., Knight, C., Barbosa, C., Francois,… Rehm, J. (2014). The cost-effectiveness and public health benefit of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: A Markov model. *BMJ Open, 4,* e005376. doi:10.1136/bmjopen-2014-005376.

Lock, C. A., Kaner, E., Heather, N., Doughty, J., Crawshaw, A., McNamee, P.,… Pearson, P. (2006). Effectiveness of nurse-led brief alcohol intervention: A cluster randomized controlled trial. *Journal of Advanced Nursing*, *54*, 426–439. doi:10.1111/j.1365-2648.2006.03836.x.

Long, C., Williams, M. & Hollin, C. (1998). Treating alcohol problems: A study of programme effectiveness and cost effectiveness according to length and delivery of treatment. *Addiction*, *93*, 561–571. doi:10.1046/j.1360-0443.1998.93456111.x

Lonsdale, A. J., Hardcastle, S. J. & Hagger, M. S. (2012). A minimum price per unit of alcohol: A focus group study to investigate public opinion concerning UK government proposals to introduce new price controls to curb alcohol consumption. *BMC Public Health, 12*, 1023. doi:10.1186/1471-2458-12-1023.

Ludbrook, A. (2004). *Effective and cost-effective measures to reduce alcohol misuse in Scotland: An update.* Edinburgh: Scottish Executive Health Department.

Ludbrook, A., Godfrey, C., Wyness, L., Parrott, S., Haw, S., Napper, M. & van Teijlingen, E. (2002). *Effective and cost-effective measures to reduce alcohol misuse in Scotland: A literature review.* Edinburgh: Scottish Executive Health Department.

Meads, C., Ting, S., Dretzke, J. & Bayliss, S. (2007). *A systematic review of the clinical and cost-effectiveness of psychological therapy involving family and friends in alcohol misuse or dependence*. Report Number 65. Birmingham, Department of Public Health and Epidemiology, West Midlands Health Technology Assessment Collaboration.

Millier, A., Laramée, P., Rahhali, N., Aballéa, S., Daeppen, J. B., Rehm, J. & Toumi, M. (2017). Cost-effectiveness of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: A microsimulation model. *Journal of Studies on Alcohol and Drugs, 78,* 867–876. doi:10.15288/jsad.2017.78.867.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M.,… the PRISMA-P Group (2015). Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. *Systematic Reviews*, *4*, 1. doi:10.1186/2046-4053-4-1.

Mujoomdar, M. & Spry, C. (2009). *Naltrexone for the treatment of alcohol dependence: A review of the clinical and cost-effectiveness*. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). https://www.cadth.ca/sites/default/files/pdf/L0076_Naltrexone_for_alcohol_dependence.pdf.

Nalpas, B., Combescure, C., Pierre, B., Ledent, T., Gillet, C., Playoust, D.,… Daurès, J. P . (2003). Financial costs of alcoholism treatment programs: A longitudinal and comparative evaluation among four specialized centers. *Alcoholism, Clinical and Experimental Research*, *27*, 51–56. doi:10.1097/01.ALC.0000047301.72437.10.

Ndegwa, S. & Cunningham, J. (2009). *Naltrexone in combination with acamprosate for the treatment of alcohol dependence: a review of the clinical and cost-effectiveness*. Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH). https://www.cadth.ca/media/pdf/L0123_Naltrexone_and_Acamprosate_final.pdf.

Pettinati, H. M., Meyers, K., Evans, B. D., Ruetsch, C. R., Kaplan, F. N., Jensen, J. M. & Hadley, T. R. (1999). Inpatient alcohol treatment in a private healthcare setting: Which patients benefit and at what cost? *American Journal on Addictions*, *8*, 220–233. doi:10.1080/105504999305839.

Poldrugo, F., Haeger, D. A., Comte, S., Walburg, J. & Palmer, A. J. (2005). A critical review of pharmacoeconomic studies of acamprosate. *Alcohol and Alcoholism, 40*, 422–430. doi:10.1093/alcalc/agh171.

Purshouse, R. C., Meier, P. S., Brennan, A., Taylor, K. B. & Rafia, R. (2010). Estimated effect of alcohol pricing policies on health and health economic outcomes in England: An epidemiological model. *Lancet, 375*, 1355–64. doi:10.1016/S0140-6736(10)60058-X.

Rehm, J. & Barbosa, C. (2018). The cost-effectiveness of therapies to treat alcohol use disorders. *Expert review of Pharmacoeconomics & Outcomes Research*, *18*, 43–49. doi:10.1080/14737167.2018.1392241.

Rehm, J., Mathers, C., Popova, S., Thavorncharoensap, M., Teerawattananon, Y. & Patra, J. (2009). Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. *Lancet, 373*, 2223-2233. doi:10.1016/S0140-6736(09)60746-7.

Shakeshaft, A. P., Bowman, J. A., Burrows, S., Doran, C. M. & Sanson-Fisher, R. W. (2002). Community-based alcohol counselling: A randomized clinical trial. *Addiction*, *97*, 1449–1463. doi:10.1046/j.1360-0443.2002.00199.x.

Slattery, J., Chick, J., Cochrane, M., Craig, J., Godfrey, C., Macpherson, K. & Parrot, S. (2002). *Health Technology Assessment of Prevention of Relapse in Alcohol Dependence. Consultation Assessment Report. Scotland: Health Technology Board for Scotland.* https://www.drugsandalcohol.ie/19424/1/Health_Technology_Assessment_Prevention_of_relapse_in_alcohol_dependence.pdf.

Sloan, F. A. & Hsieh, C.-R. (2012). *Health Economics*. United States of America: The Massachusetts Institute of Technology (MIT) Press.

Smyth, A., Teo, K. K., Rangarajan, S., O'Donnell, M., Zhang, X., Rana, P.,… PURE Investigators (2015). Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: A prospective cohort study. *Lancet*, *6736*, 1–10.. doi:10.1016/S0140-6736(15)00235-4.

Sobell, L. C., Sobell, M. B., Leo, G. I., Agrawal, S., Johnson-Young, L. & Cunningham, J. A. (2002). Promoting self-change with alcohol abusers: A community-level mail intervention based on natural recovery studies. *Alcoholism: Clinical and Experimental Research*, *26*, 936–948.

The Joanna Briggs Institute (JBI) (2014). *Joanna Briggs Institute for Evidence Based Practice Reviewers' manual 2014. The Systematic Review of Economic Evaluation Evidence.* Australia, The Joanna Briggs Institute, The University of Adelaide. https://nursing.lsuhsc.edu/JBI/docs/ReviewersManuals/Economic.pdf.

White, P., Skirrow, H., George, A. & Memon, A. (2018). A systematic review of economic evaluations of local authority commissioned preventative public health interventions in overweight and obesity, physical inactivity, alcohol and illicit drugs use and smoking cessation in the United Kingdom. *Journal of Public Health, 40*, e521–e530. doi:10.1093/pubmed/fdy026.

Williams, I., McIver, S., Moore, D. & Bryan, S. (2008). The use of economic evaluations in NHS decision-making: A review and empirical investigation. *Health Technology Assessment, 12*, 1-175. doi:10.3310/hta12070.

World Health Organization. (1992). *The ICD-10 Classification of Mental and Behavioural Disorders*: Clinical descriptions and diagnostic guidelines. Geneva, World Health Organization.

World Health Organization (2018). *Global status report on alcohol and health 2018*. Geneva, World Health Organization.

Yadav, R.-P. & Kobayashi, M. (2015). A systematic review : Effectiveness of mass media campaigns for reducing drink-driving and alcohol-related crashes. *BMC Public Health*, *15*, 857. doi:10.1016/j.amepre.2004.03.002.

Appendices

Appendix 1 Papers included in the systematic review (n=65)

Agus, A., McKay, M., Cole, J., Doherty, P., Foxcroft, D., Harvey, S.,… Sumnall, H. (2019). Cost-effectiveness of a combined classroom curriculum and parental intervention: Economic evaluation of data from the Steps Towards Alcohol Misuse Prevention Programme cluster randomised controlled trial. *BMJ Open, 9*, e027951. doi:10.1136/bmjopen-2018-027951.

Angus, C., Scafato, E., Ghirini, S., Torbica, A., Ferre, F., Struzzo, P.,… Brennan, A. (2014). Cost-effectiveness of a programme of screening and brief interventions for alcohol in primary care in Italy. *BMC Family Practice, 15*, 26. doi:10.1186/1471-2296-15-26.

Barbosa, C., Cowell, A., Bray, J. & Aldridge, A. (2015). The Cost-effectiveness of Alcohol Screening, Brief Intervention, and Referral to Treatment (SBIRT) in emergency and outpatient medical settings. *Journal of Substance Abuse Treatment, 53*, 1–8. doi: 10.1016/j.jsat.2015.01.003.

Barbosa, C., Cowell, A., Dowd, W., Landwehr, J., Aldridge, A. & Bray, J. (2017). The cost-effectiveness of brief intervention versus brief treatment of Screening, Brief Intervention and Referral to Treatment (SBIRT) in the United States. *Addiction, 112 (Supl. 2)*, 73–81. doi:10.1111/add.13658.

Barbosa, C., Taylor, B., Godfrey, C., Rehm, J., Parrott, S. & Drummond, C. (2010). Modelling lifetime QALYs and health care costs from different drinking patterns over time: a Markov model. *International Journal of Methods in Psychiatric Research, 19*, 97–109. doi:10.1002/mpr.306.

Barrett, B., Byford, S., Crawford, M. J., Patton, R., Drummond, C., Henry, J. A. & Touquet, R. (2006). Cost-effectiveness of screening and referral to an alcohol health worker in alcohol misusing patients attending an accident and emergency department: A decision-making approach. *Drug and Alcohol Dependence, 81*, 47–54. doi:10.1016/j.drugalcdep.2005.05.015.

Blankers, M., Nabitz, U., Smit, F., Koeter, M. W. J. & Schippers, G. M. (2012). Economic evaluation of internet-based interventions for harmful alcohol use alongside a pragmatic randomized controlled trial. *Journal of Medical Internet Research, 14*, e134. doi:10.2196/jmir.2052.

Brodtkorb, T-H., Bell, M., Irving, A.H. & Laramée, P. (2016). The cost effectiveness of nalmefene for reduction of alcohol consumption in alcohol-dependent patients with high or very high drinking-risk levels from a UK societal perspective. *CNS Drugs*, *30*, 163-177. doi:10.1007/s40263-016-0310-2.

Byrnes, J. M., Cobiac, L. J., Doran, C. M., Vos, T. & Shakeshaft, A. P. (2010). Cost-effectiveness of volumetric alcohol taxation in Australia. *Medical Journal of Australia, 192*, 439–443. doi:10.5694/j.1326-5377.2010.tb03581.x.

Chisholm, D., Moro, D., Bertram, M., Pretorius, C., Gmel, G., Shield, K. & Rehm, J. (2018). Are the "best buys" for alcohol control still valid? An update on the comparative cost-effectiveness of alcohol control strategies at the global level. *Journal of Studies on Alcohol and Drugs, 79*, 514–522.

Chisholm, D., Rehm, J., Van Ommeren, M. & Monteiro, M. (2004). Reducing the global burden of hazardous alcohol use: A comparative cost-effectiveness analysis. *Journal of Studies on Alcohol, 65*, 782–793. doi:10.15288/jsa.2004.65.782.

Cobiac, L., Vos, T., Doran, C. & Wallace, A. (2009). Cost-effectiveness of interventions to prevent alcohol-related disease and injury in Australia. *Addiction, 104*, 1646–1655. doi:10.1111/j.1360-0443.2009.02708.x.

Cordovilla-Guardia, S., Ortega-Ortega, M., Epstein, D., Fernández-Mondéjar, E. & Vilar-López, R. (2020). Economic analysis of brief motivational intervention following trauma related to drugs and alcohol. *Nursing Research, 69*, 358–366. doi:10.1097/NNR.0000000000000455.

Corry, J., Sanderson, K., Issakidis, C., Andrews, G. & Lapsley, H. (2004). Evidence-based care for alcohol use disorders is affordable. *Journal of Studies on Alcohol, 65*, 521–529. doi:10.15288/jsa.2004.65.521.

Coulton, S., Bland, M., Crosby, H., Dale, V., Drummond, C., Godfrey, C.,…Wu, Q. (2017). Effectiveness and cost-effectiveness of opportunistic screening and stepped-care interventions for older alcohol users in primary care. *Alcohol and Alcoholism, 52*, 655–664. doi:10.1093/alcalc/agx065.

Cowell, A. J., Brown, J. M., Mills, M. J., Bender, R. H. & Wedehase, B. J. (2012). Cost-effectiveness analysis of motivational interviewing with feedback to reduce drinking among a sample of college students. *Journal of Studies on Alcohol and Drugs, 73*, 226–37. doi:10.15288/jsad.2012.73.226.

Crawford, M. J., Sanatinia, R., Barrett, B., Byford, S., Dean, M., Green, J.,… Lingford-Hughes, A. (2015). The clinical and cost-effectiveness of brief advice for excessive alcohol consumption among people attending sexual health clinics: A randomised controlled trial. *Sexually Transmitted Infections, 91*, 37–43. doi:10.1136/sextrans-2014-051561.

Deluca, P., Coulton, S., Alam, M. F., Boniface, S., Donoghue, K., Gilvarry, E.,…Drummond, C. (2020). *Screening and brief interventions for adolescent alcohol use disorders presenting through emergency departments: A research programme including two RCTs.* Southampton (UK): National Iinstitute for Health Research (NIHR) Journals Library. doi:10.3310/pgfar08020

Drost, R. M., Paulus, A. T., Jander, A. F., Mercken, L., de Vries, H., Ruwaard, D. & Evers, S. M. (2016). A web-based computer-tailored alcohol prevention program for adolescents: Cost-effectiveness and intersectoral

costs and benefits. *Journal of Medical Internet Research, 18*, e93. doi:10.2196/jmir.5223.

Drummond, C., Coulton, S., James, D., Godfrey, C., Parrott, S., Baxter, J.,… Peters, T. (2009). Effectiveness and cost-effectiveness of a stepped care intervention for alcohol use disorders in primary care: Pilot study. *British Journal of Psychiatry, 195*, 448–456. doi:10.1192/bjp.bp.108.056697.

Dunlap, L. J., O'Farrell, T. J., Schumm, J. A., Orme, S. S., Murphy, M. & Murchowski, P. M. (2020). Group versus standard behavioral couples' therapy for alcohol use disorder patients: Cost-effectiveness. *Journal of Studies on Alcohol and Drugs, 81*, 152–163. doi:10.15288/jsad.2020.81.152.

Dunlap, L. J., Zarkin, G. A., Bray, J. W., Mills, M., Kivlahan, D. R., McKay, J. R.,…Tonigan J. S. (2010). Revisiting the cost-effectiveness of the COMBINE study for alcohol dependent patients: The patient perspective. *Medical Care, 48*, 306–313. doi:10.1097/mlr.0b013e3181ca3d40.

Gentilello, L. M., Ebel, B. E., Wickizer, T. M., Salkever, D. S. & Rivara, F. P. (2005). Alcohol interventions for trauma patients treated in emergency departments and hospitals: A cost benefit analysis. *Annals of Surgery, 241*, 541–550. doi:10.1097/01.sla.0000157133.80396.1c.

Giles, E. L., McGeechan, G. J., Coulton, S., Deluca, P., Drummond, C., Howel, D.,… Newbury-Birch, D. (2019). *Brief alcohol intervention for risky drinking in young people aged 14–15 years in secondary schools: The SIPS JR-HIGH RCT*. Southampton (UK): National Iinstitute for Health Research (NIHR) Journals Library.

Havard, A., Shakeshaft, A. P., Conigrave, K. M. & Doran, C. M. (2012). Randomized controlled trial of mailed personalized feedback for problem drinkers in the emergency department: The short-term impact. *Alcoholism: Clinical and Experimental Research, 36*, 523–531. doi:10.1111/j.1530-0277.2011.01632.x.

Holm, A. L., Veerman, L., Cobiac, L., Ekholm, O. & Diderichsen, F. (2014a). Cost-effectiveness of changes in alcohol taxation in Denmark: A modelling study. *Cost Effectiveness and Resource Allocation, 12*, 1–13. doi:10.1186/1478-7547-12-1.

Holm, A. L., Veerman, L., Cobiac, L., Ekholm, O. & Diderichsen, F. (2014b). Cost-effectiveness of preventive interventions to reduce alcohol consumption in Denmark. *PLoS One, 9*, e88041. doi:10.1371/journal.pone.0088041.

Hunter, R., Wallace, P., Struzzo, P., Vedova, R. D., Scafuri, F., Tersar, C.,… Freemantle, N. (2017). Randomised controlled non-inferiority trial of primary care-based facilitated access to an alcohol reduction website: Cost-effectiveness analysis. *BMJ Open, 7*, e014577. doi:10.1136/bmjopen-2016-014577.

Ingels, J. B., Corso, P. S., Kogan, S. M. & Brody, G. H. (2013). Cost-effectiveness of the strong African American families-teen program: 1-year follow-up. *Drug and Alcohol Dependence, 133*, 556–561. doi:10.1016/j.drugalcdep.2013.07.036.

Kruger, J., Brennan, A., Strong, M., Thomas, C., Norman, P. & Epton, T. (2014). The cost-effectiveness of a theory-based online health behaviour intervention for new university students: An economic evaluation. *BMC Public Health, 14*, 1011. doi:10.1186/1471-2458-14-1011.

Kunz, F. M., French, M. T. & Bazargan-Hejazi, S. (2004). Cost-effectiveness analysis of a brief intervention delivered to problem drinkers presenting at an inner-city hospital emergency department. *Journal of Studies on Alcohol, 65*, 363–370. doi:10.15288/jsa.2004.65.363.

Lai, T., Habicht, J., Reinap, M., Chisholm, D. & Baltussen, R. (2007). Costs, health effects and cost-effectiveness of alcohol and tobacco control strategies in Estonia. *Health Policy, 84*, 75–88. doi:10.1016/j.healthpol.2007.02.012.

Laramée, P., Bell, M., Irving, A. & Brodtkorb, T. H. (2016). The cost-effectiveness of the integration of nalmefene within the UK healthcare system treatment pathway for alcohol dependence. *Alcohol and Alcoholism, 51*, 283–290. doi:10.1093/alcalc/agv140.

Laramée, P., Brodtkorb, T.-H., Rahhali, N., Knight, C., Barbosa, C., Francois,… Rehm, J. (2014). The cost-effectiveness and public health benefit of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: A Markov model. *BMJ Open, 4*, e005376. doi:10.1136/bmjopen-2014-005376.

Li, T., Waters, T. M., Kaplan, E. K., Kaplan, C. M., Nyarko, K. A., Derefinko, K. J.,… Klesges, R. C. (2017). Economic analyses of an alcohol misconduct prevention program in a military setting. *Military Medicine, 182*, e1562–e1567. doi:10.7205/MILMED-D-16-00098.

Millier, A., Laramée, P., Rahhali, N., Aballéa, S., Daeppen, J. B., Rehm, J. & Toumi, M. (2017). Cost-effectiveness of nalmefene added to psychosocial support for the reduction of alcohol consumption in alcohol-dependent patients with high/very high drinking risk levels: A microsimulation model. *Journal of Studies on Alcohol and Drugs, 78*, 867–876. doi:10.15288/jsad.2017.78.867.

Moore, S.C., Allen, D., Amos, Y., Blake, J., Brennan, A., Buykx, P.,…Young, T. (2020). *Evaluating alcohol intoxication management services: the EDARA mixed-methods study.* Southampton (UK): National Iinstitute for Health Research (NIHR) Journals Library.

Moraes, E., Campos, G. M., Figlie, N. B., Laranjeira, R. & Ferraz, M. B. (2010). Cost-effectiveness of home visits in the outpatient treatment of patients with alcohol dependence. *European Addiction Research, 16*, 69–77. doi:10.1159/000268107.

Mortimer, D. & Segal, L. (2005). Economic evaluation of interventions for problem drinking and alcohol depen-

dence: Cost per QALY estimates. *Alcohol and Alcoholism, 40*, 549–555. doi:10.1093/alcalc/agh192.

Nadkarni, A., Weiss, H. A., Velleman, R., McCambridge, J., McDaid, D., Park, A. L.,… Patel, V. (2019). Feasibility, acceptability and cost-effectiveness of a brief, lay counsellor-delivered psychological treatment for men with alcohol dependence in primary care: An exploratory randomized controlled trial. *Addiction, 114*, 1192–1203. doi:10.1111/add.14630.

Nadkarni, A., Weiss, H. A., Weobong, B., McDaid, D., Singla, D. R., Park, A. L.,… Patel, V. (2017a). Sustained effectiveness and cost-effectiveness of Counselling for Alcohol Problems, a brief psychological treatment for harmful drinking in men, delivered by lay counsellors in primary care: 12-month follow-up of a randomised controlled trial. *PLoS Medicine, 14*, e1002386. doi:10.1371/journal.pmed.1002386.

Nadkarni, A., Weobong, B., Weiss, H. A., McCambridge, J., Bhat, B., Katti, B.,… Patel, V. (2017b). Counselling for Alcohol Problems (CAP), a lay counsellor-delivered brief psychological treatment for harmful drinking in men, in primary care in India: A randomised controlled trial. *Lancet, 38*9, 186–195. doi:10.1016/S0140-6736(16)31590-2.

Navarro, H. J., Shakeshaft, A., Doran, C. M. & Petrie, D. J. (2011). The potential cost-effectiveness of general practitioner delivered brief intervention for alcohol misuse: Evidence from rural Australia. *Addictive Behaviors, 36*, 1191–1198. doi:10.1016/j.addbeh.2011.07.023.

Neighbors, C. J., Barnett, N. P., Rohsenow, D. J., Colby, S. M. & Monti, P. M. (2010). Cost-effectiveness of a motivational intervention for alcohol-involved youth in a hospital emergency department. *Journal of Studies on Alcohol and Drugs, 71*, 384–394. doi:10.15288/jsad.2010.71.384.

Olmstead, T. A., Graff, F. S., Ames-Sikora, A., McCrady, B. S., Gaba, A. & Epstein, E. E. (2019). Cost-effectiveness of individual versus group female-specific cognitive behavioral therapy for alcohol use disorder. *Journal of Substance Abuse Treatment, 100*, 1–7. doi:10.1016/j.jsat.2019.02.001.

Palmer, A., Neeser, K., Weiss, C., Brandt, A., Comte, S. & Fox, M. (2000). The long-term cost-effectiveness of improving alcohol abstinence with adjuvant acamprosate. *Alcohol and Alcoholism, 35*, 478–492. doi:10.1093/alcalc/35.5.478.

Purshouse, R. C., Brennan, A., Rafia, R., Latimer, N. R., Archer, R. J., Angus, C. R., … Meier, P. S. (2013). Modelling the cost-effectiveness of alcohol screening and brief interventions in primary care in England. *Alcohol and Alcoholism, 48*, 180–188. doi:10.1093/alcalc/ags103.

Reddy, V. K., Girish, K., Lakshmi, P., Vijendra, R., Kumar, A. & Harsha, R. (2014). Cost-effectiveness analysis of baclofen and chlordiazepoxide in uncomplicated alcohol-withdrawal syndrome. *Indian Journal of Pharmacology, 46*, 372–377. doi:10.4103/0253-7613.135947.

Robinson, E., Nguyen, P., Jiang, H., Livingston, M., Ananthapavan, J., Lal, A. & Sacks, G. (2020). Increasing the price of alcohol as an obesity prevention measure: The potential cost-effectiveness of introducing a uniform volumetric tax and a minimum floor price on alcohol in Australia. *Nutrients, 12*, 603. doi:10.3390/nu12030603.

Rychlik, R., Siedentop, H., Pfeil, T. & Daniel, D. (2003). Cost-effectiveness of adjuvant treatment with acamprosate in maintaining abstinence in alcohol dependent patients. *European Addiction Research, 9*, 59–64. doi:10.1159/000068810.

Schädlich, P. K. & Brecht, J. G. (1998). The cost effectiveness of acamprosate in the treatment of alcoholism in Germany: Economic evaluation of the prevention of relapse with acamprosate in the management of alcoholism (PRAMA) study. *PharmacoEconomics, 13*, 719–730. doi:10.2165/00019053-199813060-00008.

Schulz, D. N., Smit, E. S., Stanczyk, N. E., Kremers, S. P., de Vries, H. & Evers, S. M. (2014). Economic evaluation of a web-based tailored lifestyle intervention for adults: Findings regarding cost-effectiveness and cost-utility from a randomized controlled trial. *Journal of Medical Internet research, 16*, e91. doi:10.2196/jmir.3159.

Slattery, J., Chick, J., Cochrane, M., Craig, J., Godfrey, C., Macpherson, K. & Parrot, S. (2002). *Health Technology Assessment of Prevention of Relapse in Alcohol Dependence. Consultation Assessment Report.* Scotland: Health Technology Board for Scotland. https://www.drugsandalcohol.ie/19424/1/Health_Technology_Assessment_Prevention_of_relapse_in_alcohol_dependence.pdf.

Sluiter, R. L., Kievit, W., van der Wilt, G. J., Schene, A. H., Teichert, M., Coenen, M. & Schellekens, A. (2018). Cost-effectiveness analysis of genotype-guided treatment allocation in patients with alcohol use disorders using naltrexone or acamprosate, using a modeling approach. *European Addiction Research, 24*, 245–254. doi:10.1159/000494127.

Smit, F., Lokkerbol, J., Riper, H., Majo, M. C., Boon, B. & Blankers, M. (2011). Modeling the cost-effectiveness of health care systems for alcohol use disorders: How implementation of ehealth interventions improves cost-effectiveness. *Journal of Medical Internet Research, 13*, e56. doi:10.2196/jmir.1694.

Solberg, L. I., Maciosek, M. V. & Edwards, N. M. (2008). Primary care intervention to reduce alcohol misuse. Ranking its health impact and cost effectiveness. *American Journal of Preventive Medicine, 34*, 143-152. doi:10.1016/j.amepre.2007.09.035.

Sumnall, H., Agus, A., Cole, J., Doherty, P., Foxcroft, D., Harvey, S.,… Percy, A. (2017). *Steps Towards Alcohol Misuse Prevention Programme (STAMPP): A school- and community-based cluster randomised controlled trial.* Southhampton

(UK): National Iinstitute for Health Research (NIHR) Journals Library.. doi:10.3310/phr05020.

Tariq, L., van den Berg, M., Hoogenveen, R. T. & van Baal, P. H. M. (2009). Cost-effectiveness of an opportunistic screening programme and brief intervention for excessive alcohol use in primary care. *PLoS One, 4*, e5696. doi:10.1371/journal.pone.0005696.

Torfs, K. & De Graeve, D. (1991). *A cost-effectiveness analysis of AOTAL, a drug used to prevent relapse in weaned alcoholics.* SESO Working Papers, 1991003. Belgium: University of Antwerp, Faculty of Business and Economics. UKATT Research Team. (2005). Cost effectiveness of treatment for alcohol problems: Findings of the randomised UK alcohol treatment. *BMJ, 331*, 544–548. doi:10.1136/bmj.331.7516.544.

Van den Berg, M., van Baal, P. H., Tariq, L., Schuit, A. J., de Wit, G. A. & Hoogenveen, R. T. (2008). The cost-effectiveness of increasing alcohol taxes: A modelling study. *BMC Medicine, 6*, 36. doi:10.1186/1741-7015-6-36.

Watson, J. M., Crosby, H., Dale, V. M., Tober, G., Wu, Q., Lang, J.,… AESOPS Trial Team (2013). AESOPS: A randomised controlled trial of the clinical effectiveness and cost-effectiveness of opportunistic screening and stepped care interventions for older hazardous alcohol users in primary care. *Health Technology Assessment, 17*, 1-158. doi:10.3310/hta17250.

Weisner, C., Mertens, J., Parthasarathy, S., Moore, C., Hunkeler, E. M., Hu, T. & Selby, J. V. (2000). The outcome and cost of alcohol and drug treatment in an HMO: Day hospital versus traditional outpatient regimens. *Health Services Research, 35*, 791–812.

Wutzke, S. E., Shiell, A., Gomel, M. K. & Conigrave, K. M. (2001). Cost effectiveness of brief interventions for reducing alcohol consumption. *Social Science & Medicine, 52*, 863–870. doi:10.1016/s0277-9536(00)00189-1.

Zarkin, G. A., Bray, J. W., Aldridge, A., Mitra, D., Mills, M. J., Couper, D. J. & Cisler, R. A. (2008). Cost and cost-effectiveness of the COMBINE study in alcohol-dependent patients. *Archives of General Psychiatry, 65*, 1214–1221. doi:10.1001/archpsyc.65.10.1214.

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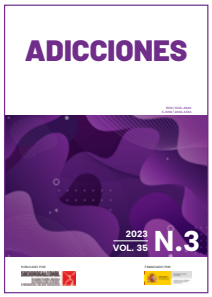

REVIEW

Impact of the legalisation of recreational cannabis use

Impacto de la legalización del consumo recreativo del cannabis

Manuel Isorna*; Francisco Pascual**; Ester Aso***; Francisco Arias****.

* Universidad de Vigo. Facultad Ciencias Educación y Trabajo Social. Ourense. Grupo PsiComBi. Grupo Ibero Ciência.

** UCA-Alcoi. Grupo Ibero Ciência. Socidrogalcohol. Grupo Investigación Prevengo UMH.

*** Unitat de Farmacologia, Departament de Patologia i Terapèutica Experimental, Facultat de Medicina i Ciències de la Salut, Institut de Neurociències, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona.

**** Programa de Alcohol y Patología Dual. Hospital Doce de Octubre, Madrid. Grupo Ibero Ciência. Socidrogalcohol.

Abstract

In recent years, there have been important legislative changes in many countries regarding the use of cannabis for medicinal and/or recreational purposes, which have facilitated access to it. Uruguay, Canada and some of the US states are the only jurisdictions that have legalised recreational consumption, applying different legislative models. The aim of this review is to analyse the effects that the legalisation of recreational cannabis has had on its use and its consequences. In general, the evidence accumulated to date indicates that the legalisation of cannabis has been associated with a decrease in the price of the substance, higher concentration of THC (potency), greater diversity of presentations for consumption, lower risk perception and an increase in consumption in adults and moderately in adolescents (even though it is illegal for them to consume), as well as an increase in the adverse consequences derived from cannabis consumption on public health. There has been a decrease in drug-related arrests, but the illegal market continues to be frequently used. No increase in the demand for treatment due to cannabis consumption has been detected. Therefore, these legislative changes have so far failed to achieve their main objectives, which were to suppress the illegal market and protect the most vulnerable groups, while on the contrary, they seem to imply an increase in some of the negative aspects associated with cannabis consumption. However, taking into account that most of these legislative changes have entered into force relatively recently, a longer follow-up period is required to be able to draw definitive conclusions.

Keywords: cannabis, legalisation, recreational use, consequences of consumption, public health

Resumen

En los últimos años se han producido importantes cambios legislativos en numerosos países respecto al consumo de cannabis con fines medicinales y/o recreativos, que han facilitado su accesibilidad. Actualmente, Uruguay, Canadá y algunos estados de EE.UU. han legalizado el consumo recreativo, aplicando distintos modelos legislativos. El objetivo de la presente revisión es analizar los efectos que ha tenido la legalización del cannabis recreativo sobre su consumo y sus consecuencias. En general, las evidencias indican que la legalización se ha asociado a un descenso en el precio, mayor concentración de THC (potencia), mayor diversidad de presentaciones para su consumo, una menor percepción de riesgo y un incremento en el consumo en adultos y de forma moderada en adolescentes (aunque sea ilegal el consumo para ellos), así como un aumento de las consecuencias adversas derivadas del consumo en la salud pública. Se ha producido un descenso en los arrestos relacionados con el consumo, pero el mercado ilegal sigue utilizándose de forma habitual. No se ha detectado un incremento de la demanda de tratamiento por este consumo. Por el momento, estos cambios legislativos no han conseguido alcanzar sus objetivos principales que eran suprimir el mercado ilegal y proteger a los grupos más vulnerables, mientras que, por el contrario, parecen implicar un incremento de algunos aspectos negativos asociados al consumo de cannabis. Sin embargo, teniendo en cuenta que la mayoría de estos cambios legislativos han entrado en vigor hace relativamente poco tiempo, se requiere un periodo de seguimiento mayor para poder extraer conclusiones definitivas.

Palabras clave: cannabis, legalización, uso recreativo, consecuencias del consumo, salud pública

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■ **Send correspondence to:**
Dr. Manuel Isorna Folgar. Universidad de Vigo. Facultad Ciencias Educación y Trabajo Social. Campus As Lagoas, 32004, Ourense.
Email: isorna.catoira@uvigo.es

The last two decades have seen a growing number of countries introduce legislative changes governing the use of cannabis and its derivatives. In general, these legal modifications favouring sales and decriminalizing consumption have come about after a referendum to consult the population. Governments have thus responded to social and political pressure for legalization resulting from the growing acceptance of the potential therapeutic benefit of cannabis among citizens of these countries. These changes have generated a political and social debate in many countries, including Spain, about the desirability of decriminalization and legalization and thereby also regulating the sale of cannabis for "recreational" use.

Among the main arguments put forward by defenders of recreational cannabis legalization (Degenhardt et al., 2013; Felson, Adamczyk & Thomas, 2019; The NORML Foundation, 2021) the following can be highlighted:

- Cannabis is commonly used by young adults and causes less harm to health than other legal drugs such as alcohol, tobacco and opioids.
- The consequences of criminalizing cannabis use are more harmful to the user than the use itself as it can lead to arrest and a criminal record.
- Criminalization of cannabis use disproportionately affects minority or disadvantaged populations. In many countries, being penalized for violations related to use reduces future employment opportunities, thereby increasing social inequalities, although this may not be the case in Spain.
- Legalization of cannabis is a better social policy than criminalization because:
  a. It reduces or eliminates the illicit market, thereby reducing organized crime and the police resources needed to control or eradicate illegal trafficking.
  b. It allows control to be exercised over the cannabis-using population, minimizing access of the most vulnerable population segments in particular, such as adolescents, and controlling the quality of the product used in terms of delta^{9}-tetrahydrocannabinol (THC) content, the main psychoactive cannabis compound, and contaminants (fungi, pesticides, heavy metals), thus leading to an improvement in public health.
  c. It benefits the state financially by allowing revenues to be raised in the form of taxes on the production and sale of cannabis products.

The main argument against legalizing cannabis for recreational purposes is the potentially negative impact on public health (Isorna, 2017; National Academies of Sciences, Engineering, and Medicine, 2017; Nazif-Muñoz, Oulhote & Ouimet, 2020; Steinemann, Galanis, Nguyen & Biffl, 2018), given the possibility that:

- Cannabis use may increase and the risk perception in the population may decrease, leading to subsequent increases in high-risk consumption patterns and associated disorders, mainly in vulnerable groups.
- Traffic and work accidents related to cannabis use may increase.
- The incidence of respiratory diseases, mental disorders and poisonings may rise.
- The use of alcohol, tobacco and other drugs may increase.

While several studies have tried to analyze some of these consequences separately in states where cannabis has already been legalized for all uses (Chung et al., 2019; Grigsby, Hoffmann & Moss, 2020; Hall & Lynskey, 2020; Nazif-Muñoz et al., 2020; Steinemann et al., 2018), there has been no studies addressing all consequences globally and possible repercussions in all countries where it has been legalized.

The objectives of this review are therefore: 1) to present the current situation at a global level regarding the legalization of cannabis; 2) update the existing evidence on the impact of cannabis legalization in various areas of public health in countries where recreational use has been legalized, and 3) analyze whether the legal market has led to changes in how cannabis is used.

Material and methods

A PubMed database search was conducted with the keywords "cannabis" OR "marijuana" AND "legalization" over the last 10 years. The search was conducted on January 5, 2021.

The inclusion criteria were: original or review articles focusing on the changes that recreational cannabis legalization has caused in the way it is used, consequences for public and user health, changes in the prevalence of use and changes in the product and forms of use. Articles written in English or Spanish were considered for inclusion.

Letters to the editor, comments from authors on legalization and studies carried out prior to legalization in those states where it then became legalized were excluded.

The initial search obtained 1,877 references, of which 562 articles were chosen after reviewing abstracts and being assessed for inclusion by the 4 authors of the present study. Likewise, the reference lists of the selected articles were considered and three articles published after the date of the search were included. The final selection contained 109 articles considered to meet the inclusion criteria.

In addition, information on the status of cannabis legalization was obtained by consulting government sources and official bodies in each of the countries included in the study.

Results

1. Current situation of cannabis legalization

Figure 1 shows the current situation worldwide regarding the legalization of medicinal and/or recreational cannabis to date. Only three nations, Uruguay, the USA (not at federal level) and Canada, have passed laws decriminalizing the production and use of cannabis and regulating distribution among the adult population for recreational purposes. Below is a summary of the regulatory models adopted by each of these countries.

Uruguay

This was the first country to fully legalize production, distribution, marketing and use of cannabis for both medicinal and recreational purposes. In 2013, a law (19,172) was passed that allowed people aged over 18 years to register in a state database as cannabis users and thereby obtain permission to use it legally (República de la Presidencia Oriental de Uruguay, 2014). Article 4 of this law defined its main objectives: "*The purpose of this law is to protect the inhabitants of the country from the risks inherent in involvement with illegal trade and drug trafficking, seeking, through state intervention, to tackle the devastating health, social and economic consequences of the problematic use of psychoactive substances, as well as to reduce the incidence of drug trafficking and organized crime*". Three ways of obtaining the product were considered: private production (up to 6 female plants/household), membership of a club of cannabis producers (maximum 45 members, 99 cultivated plants and maximum annual production of 480g/person) or purchase of cannabis in pharmacies licensed to supply it with state-regulated pricing (up to 40g/month). However, the advertising of cannabis-related products and the sale of edible products containing this substance were not allowed. Despite being pioneers in proposing this highly regulated and state-controlled cannabis management model, it has not been fully implemented successfully to date due, according to the authorities, to a production deficit, financial constraints or the scarcity of authorized points of sale, among other reasons. Thus, only 1.3% of the country's pharmacies have obtained a license to sell cannabis and only 27.3% and 38.4% of Uruguayan users of recreational and medicinal cannabis, respectively, say that they acquire it through any of the legal channels, according to the latest national survey published on drug use (Observatorio Uruguayo de Drogas, 2019). The same survey revealed that up to 84% of users in the last 12 months were not registered as users in the state database (Observatorio Uruguayo de Drogas, 2019).

USA

Although cannabis remains an illegal substance at the federal level, most states have laws that allow medical cannabis to be used under prescription, and up to 16 states, plus the District of Columbia (DC), have also legalized production, processing and recreational use in the population aged over 21 years (Figure 2). Colorado and Washington were

Figure 1

Visual summary of the legalization of cannabis for medical (green) and recreational (orange) use worldwide. The year given is when legal modifications allowing this use were introduced. The situation in the USA (light orange), where cannabis has been legalized in many states but not at federal level, is detailed in Figure 2. Information obtained from government sources in each country and the United Nations Office on Drugs and Crime (UNODC, 2020)

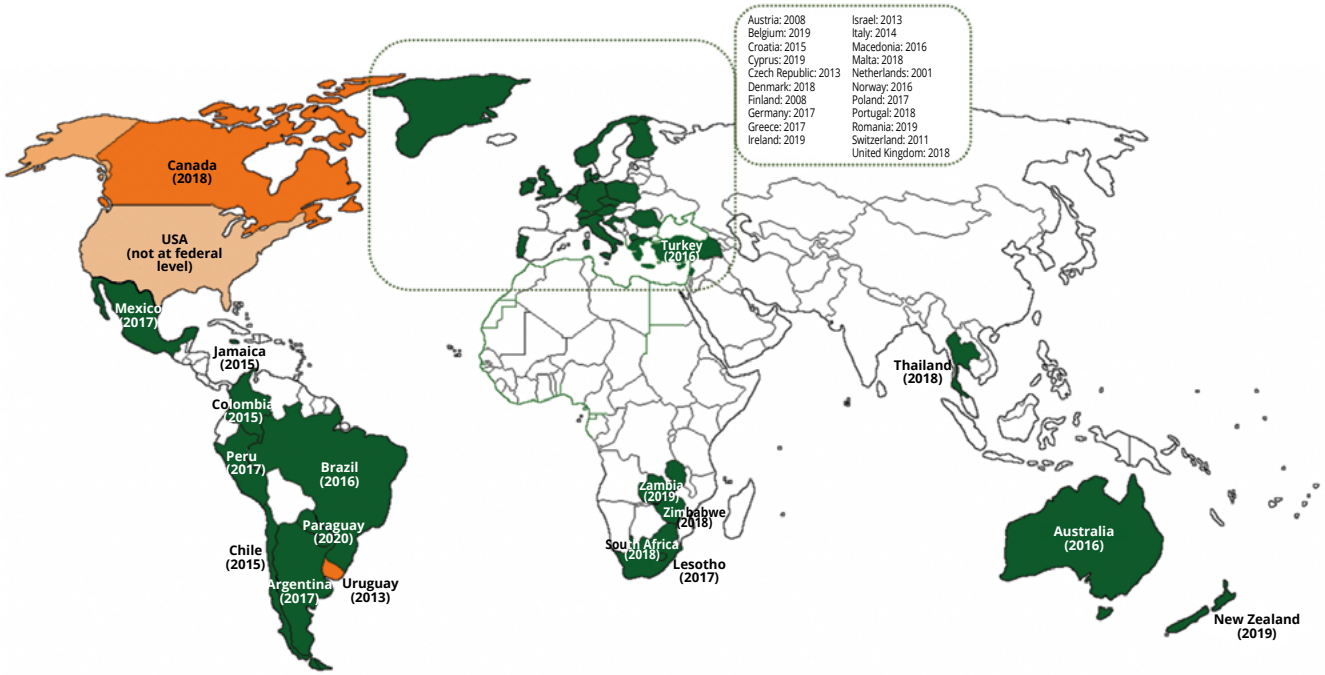


Figure 2

Current status of cannabis legalization for medical (green) and recreational (orange) use in the USA. The year given is when the legal modifications allowing this use were introduced. In most states where cannabis has not been legalized for any use (white), the processing and use of cannabidiol (CBD) products is allowed. Information obtained from government sources (Department of Justice, The United States)

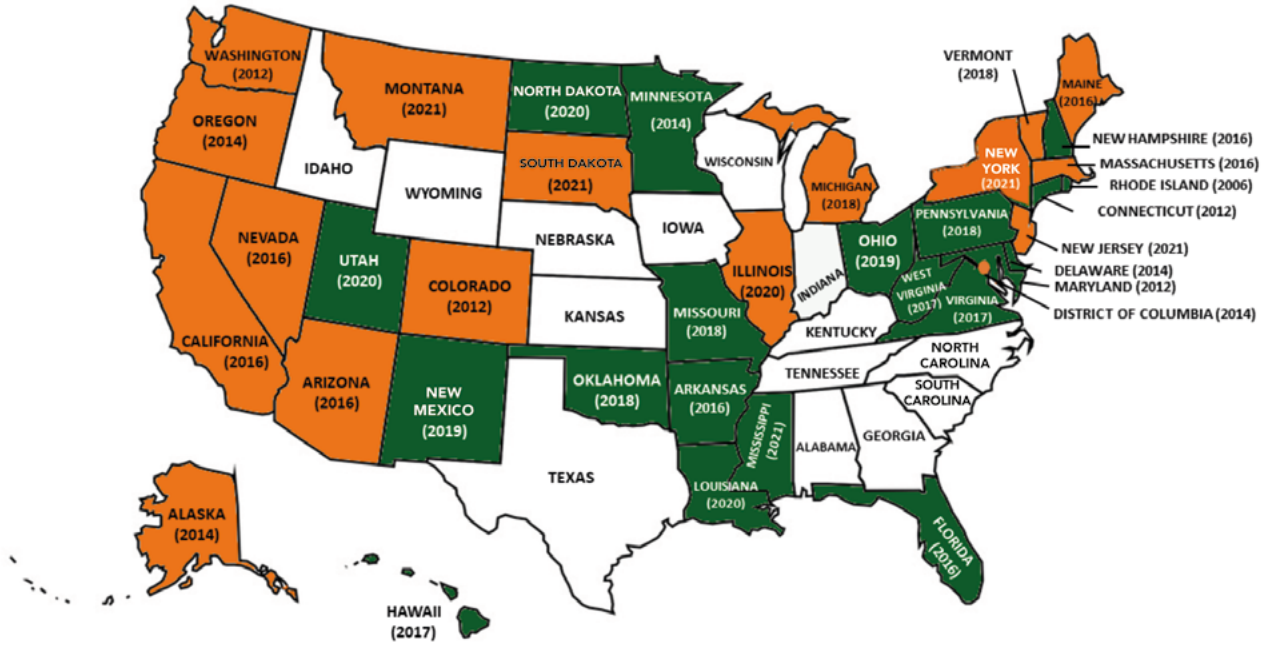
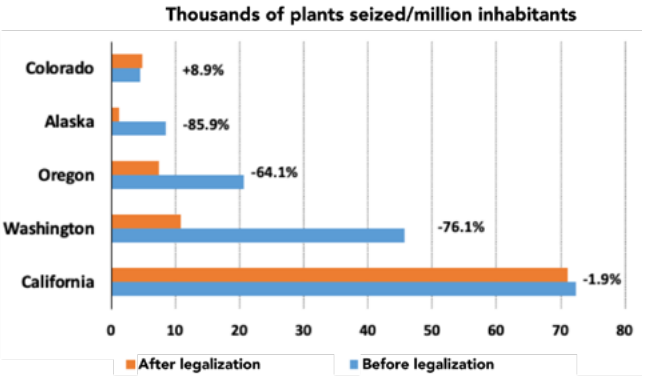


Figure 3

Average annual seizures (expressed in thousands of plants) carried out by the DEA, within the program for the reduction/ eradication of illegal cannabis cultivation in the USA (Drug Enforcement Administration, 2020), before (blue) or after (orange) cannabis legalization in each state between 2011-2019. Standardized data per million inhabitants (according to the United States Census Bureau, 2021) are included for states in which recreational cannabis was legalized in 2012 (Colorado and Washington) or in 2014 (Alaska and Oregon), plus California (legalized recreational cannabis in 2016) as it is the most populous state and where cannabis has traditionally been most cultivated and used



the first states to permit recreational use in 2012, followed by Oregon and Alaska in 2014; for this reason, most studies focussing on the consequences of cannabis legalization are based on data collected in these states. There is no single model in the USA for regulating recreational cannabis. For example, while the production of cannabis for personal use is legal in Vermont and DC, selling this substance remains illegal. Following the commercial models initiated in Colorado, California or Washington, however, most states chose to authorise companies to produce and sell cannabis for profit through networks of dispensaries licensed for the retail sale of cannabis and related products, which are then taxed on their sale price. Many of these states have limited the amount of cannabis an adult can legally carry to 28.5g (Hall et al., 2020). These models drive a thriving cannabis industry in the US, with a significant business volume which is growing annually. While the sector had a turnover of 8 billion dollars in 2017, this reached 11 billion the following year and it is estimated that these figures may double in just four years (Heinrich, 2018). The legal cannabis industry has an interest in promoting cannabis use and employs marketing strategies common to other business sectors, including the increasing use of social media (Cavazos-Rehg et al., 2019; Krauss et al., 2017).

According to data published by the US *Drug Enforcement Administration* (DEA), the government agency responsible for combating drug trafficking, seizures of illegal cannabis

crops have dropped significantly in some of the states that have legalized recreational cannabis in adults the longest, such as Alaska, Oregon or Washington. However, they have remained stable or even increased in key states in the cannabis movement such as California or Colorado (Figure 3) (Drug Enforcement Administration, 2020).

Canada

In October 2018, the Canadian government passed the *Cannabis Act (S.C. 2018, c.16)*, thus becoming the second country to legalize cannabis for recreational purposes (Government of Canada, 2018, 2020). The main motivation behind this law was to eliminate the illicit cannabis market and regulate the production and sale of this substance to protect public health and young people especially. The government of each of the provinces and territories licenses and regulates cannabis producers and collects taxes. Unlike the prevailing model in the USA, Canada prohibits cannabis advertising except under very restrictive conditions guaranteeing that minors have no access to the promotion of the products, and it is mandatory for products to be sold with health warnings. Provincial government regulation is comparable to that of alcohol sales, with retail sales of cannabis for profit allowed for licensed distributors, who in many cases also distribute alcohol.

According to data published by the Canadian government in the first nationwide survey on cannabis use that covered a full year after the legalization and regulation of recreational cannabis sales, cannabis use increased slightly (2% more of the population acknowledged using it in the last 12 months), especially among the population over 25 years of age, as well as the use of cannabis of legal origin. Nevertheless, only 37% of users acknowledged that they always purchase the product from legal sources, while up to 20% always obtained cannabis illegally (Government of Canada, 2021).

2. Effects of legalization on the product

2.1. Impact on potency (THC concentration)

The market for recreational cannabis has evolved towards greater product diversity and potency (Orens, Light, Lewandowski, Rowberry & Saloga, 2018). In the US, average THC potency in these types of products increased from 8.9% in 2008 to 17.1% in 2017, while the THC:CBD ratio increased dramatically from 23 in 2008 to 104 in 2017 (Chandra et al., 2019; ElSohly, Chandra, Radwan, Gon & Church, 2021). According to data from the DEA, the last ten years have seen a general increase in the potency of illicit cannabis in the USA, from approximately 10% in 2009 to 14% in 2019, although this increase has been observed in all states and the number of samples received in the last 5-6 years has decreased due to the legalization of marijuana for medical or recreational purposes in many USA states (ElSohly et al., 2021). In 2016, in response to this rise, the state of Colorado proposed to limit all types of cannabis products to 15-16% THC, but this initiative failed (Shi, Cao, Shang & Pacula, 2019). Estimates in Canada suggest similar (or greater) increases in cannabis potency. Specifically, a study based on monitoring the potency of legal and illegal cannabis products in the two months after the federal legalization of cannabis use for non-medical purposes found an average THC concentration of 16.1% in the legal market and 20.5% in the illegal market (Mahamad, Wadsworth, Rynard, Goodman & Hammond, 2020).

In the states where it has been legalized, despite clear differences between "medicinal" and "recreational" use (mainly in leisure or recreational sites), average THC concentration advertised in online stores for medicinal purposes (19.2% ± 6.2) is similar to that marketed for recreational purposes (21.5% ± 6.0) when compared between states with different programs, or between medicinal programs and recreational programs within the same states (Cash, Cunnane, Fan & Romero-Sandoval, 2020). Lower CBD concentrations are found in products with higher THC, irrespective of medicinal or recreational use, with THC content greater than 15% (between 70.3% and 91.4% of products) (Cash et al., 2020).

It therefore appears that legalization has coincided with an overall increase in the potency of cannabis in general, with illegal cannabis being the one with the highest THC content (Mahamad et al., 2020).

2.2. Impact of legalization on the price of cannabis

In Canada, a year before cannabis was fully legalized, the mean price in legal establishments per gram of marijuana was CA$7.43, down from CA$9.06 per gram in 2010 (Statistics Canada, 2018). Once legalized, the same body estimated the average price at CA$6.80 in 2018, with provincial averages ranging between CA$5.86 and CA$9.51 per gram (Statistics Canada, 2018). Another study found that prices decreased between 9% and 27% as purchase volume increased (Mahamad & Hammond, 2019). Regarding the price of illegal cannabis, according to the *Price of Weed* database in the pre-legalization period (2011-2015), the average street price per gram was CA$7.69, in a period when medical cannabis (which was legal) cost an average of two dollars more per gram (Public Safety Canada, 2017). Currently the average street price of cannabis (illegal sale) paid by users is approximately CA$6.22 per gram (Sikorski, Leos-Toro & Hammond, 2021). In Canada, four out of ten consumers claim to buy cannabis on the illegal market, probably due to the price difference compared to the legal market. There are two possible explanations for this fact: the first is that while a gram of legal marijuana costs an average of CA$9.51, the illegal market price is 51% lower, at CA$6.51, (Mahamad

Table 1
Changes in the increase in THC levels (potency)

Author (year)	Place	Method	Results	Observations
Cash et al. (2020)	USA	Study comparing differences in supply and sales between medicinal and recreational cannabis in 653 dispensaries.	The mean THC concentration advertised online in medicinal programs was similar (19.2% ± 6.2) to recreational programs (21.5% ± 6.0) when comparing states with different programs.	The lowest CBD concentrations were found in products with more THC.
Chandra et al. (2019)	USA	Longitudinal study (2008-2017) of police seizures of cannabis.	Mean THC:CBD ratio increased from 23 in 2008 to 104 in 2017. Increase in the proportion of seized hash oil samples and their average THC concentration (6.7-55.7%) from 2008 to 2017.	Trends in the last decade suggest that cannabis is becoming an increasingly potent product in the USA.
ElSohly et al. (2021)	USA	Analysis of 14,234 cannabis plant samples by the DEA in the last 10 years.	Illicit cannabis potency rose from approx. 10% in 2009 to approx. 14% in 2019.	The last two years saw a decrease in the THC:CBD ratio.
Mahamad, et al. (2020)	Canadá	Study of 185 legal and 944 illegal retailers.	Marijuana prices fell and potency increased. The mean price of legal marijuana was 19% higher than illegal products.	In the 2 months after legalization, illegal cannabis was less expensive and had higher THC on the label than legal cannabis.
Orens et al. (2018)	Colorado	Study of prices, potency, patterns of use in dispensaries.	Mean prices for adult use cannabis products and derivatives fell significantly from 2014 to 2017.	Trends reflect an increasingly competitive market. Producers and sellers improved their operations.
Shi et al. (2019)	EE.UU.	Assessment of sales in cannabis dispensaries.	The best-selling product is marijuana for smoking. Sales of cannabis-infused concentrates, edibles and beverages, etc., also increased.	THC rose from 3.4% in 1993 to 8.8% in 2008 and more dramatically after cannabis legalization from 16% to almost 20% during 2014-2017.

et al., 2020). Taxes account for approximately one dollar of the price paid in authorized stores. Added to this, the number of cannabis stores in Canada today is around 400, meaning that for every 100,000 residents there is only one shop; in Colorado this indicator is 10 stores per 100,000 inhabitants (Mahamad et al., 2020; Orens et al., 2018). Taxes based on the level of THC in edibles and cannabis extracts have been proposed in Canada, but applying these taxes could be challenging due to costs and difficulties in checking THC concentrations in cannabis products (Mahamad et al., 2020; Orens et al., 2018).

In the USA, data from household surveys and the dispensaries themselves indicate that prices fell by as much as 50% in the first states to legalize recreational cannabis (Smart, Caulkins, Kilmer, Davenport & Midgette, 2017); prices fluctuated within the states themselves between urban or mountainous areas, and in states bordering others in which it is not legalized, with prices ranging from $11.75 to $5.79 and at an average of $6.92 per gram (Department of Revenue Colorado, 2019; Hunt & Pacula, 2017; Wilson, Freeman & Mackie, 2019).

In Colorado, mean prices declined significantly from 2014 to 2017. The largest falls were seen in cannabis concentrates (hash oil, *dabs*) which fell 47.9%, from $41.43 to $21.57 per gram. The price of a gram of marijuana decreased 62%, from $14.05 to $5.34., while the price of food products and herbal tea packages containing 100 mg of THC remained relatively constant at around $18, with no clear trend over time. This same trend was also observable in medical cannabis, with the average price per gram of medical cannabis falling by 40.9% from $5.55 to $3.28 per gram between 2014 and 2017. Over the same period, the price of concentrates on the medical cannabis market fell by 34.6%, from $25.83 to $16.89 per gram. Medical infused edibles sold in 100mg THC packages consistently cost around $9, with a slight downward trend over time (Orens et al., 2018) (Table 2).

In Uruguay, the fixed purchase price of cannabis is set by the government in order to compete with the black market. The sale price of the 5-gram presentation in the 14 pharmacies dispensing cannabis is 350 Uruguayan pesos (about €6.63) (Instituto de regulación y control del cannabis, 2021).

2.3. Changes in post-legalization presentation, forms and patterns of use

The supply of new high-THC products, such as cannabis concentrates, vaping oils, edibles, and beverages, is more prevalent in Canada and "legal" states of the USA than in "illegal" states (Goodman, Wadsworth, Leos-Toro & Hammond, 2020) (Table 3). In a study on the use of cannabis among young people in Canada, the USA and

Table 2
Effects of legalization on taxes and the price of cannabis

Author (year)	Place	Method	Results	Comments
Department of Revenue Colorado (2019)	Colorado	Analysis of prices in state dispensaries.	Prices fell steadily every year after legalization.	
Hunt and Pacula (2017)	USA Colorado and Washington	Longitudinal surveys on prices paid by consumers and data extracted from websites on prices in three states with medical marijuana that eventually legalized recreational marijuana.	Different prices according to state. Colorado: recreational $9.94 and $7.98 medical. Orlando: no differences, $8.51 for medical vs $8.63 recreational. Washington quite similar, $10.65 medical versus $10.40 recreational.	Differences between marijuana prices at dispensaries and consumer self-reports. Dispensaries used strategies to attract consumers.
Mahamad et al. (2020)	Canada	Availability, price and potency of legal and illegal cannabis in Canada following the legalization of recreational cannabis.	Marijuana prices fell, potency increased. The mean price of legal marijuana was 19% higher than that of illegal.	
Orens et al. (2018)	Colorado	Report. Longitudinal study.	Prices of recreational and medical cannabis and all its derivatives fell steadily from 2014 to 2107.	Greater falls (47.9%) in cannabis concentrates, from $41.43 to $21.57.
Sikorski et al. (2021)	Canada	Online survey sampling Canadians aged 16-30 (N = 868).	Mean marijuana use was 17.8 g/month, 17.4 g/ month, and 9.4 g/month among medically licensed and non-medically licensed cannabis users.	31.5% and 13.2% of current users reported knowing the levels of THC and of CBD, respectively, in their cannabis.
Smart et al. (2017)	Washington	Analysis of data available from Washington's cannabis traceability system from July 7, 2014 to September 30, 2016.	The market share of extracts for inhalation increased by 145.8% between October 2014 and September 2016 and now represents 21.2% of sales.	Mean THC level of cannabis extracts is more than triple that of cannabis flowers (68.7% vs. 20.6%).
Statistics Canada (2018)	Canada	Survey.	The price of non-medical cannabis fell from $9.06 in 2010 to $7.43 in 2017.	The price of medical cannabis went from $9.06 in 2010 to $8.18 in 2017.

England, Hammond, Wadsworth, Reid and Burkhalter (2021) showed that while the prevalence of the use of oils/ liquids for vaping and the use of cannabis extracts (oil, wax and shatter) increased in all countries, the increase was significantly greater in Canada and the USA. Thus, the prevalence of vaping oils/liquids in the USA increased from 24.2% in 2017 to 52.1% in 2019.

In Uruguay, on the other hand, no edibles, oils, creams or alternative products are permitted, and pharmacies can only sell cannabis buds produced by the two companies contracted by the government (Cerdá & Kilmer, 2017).

After legalization, the most common method of use in Canada continues to be smoking, with estimates ranging between 84% and 95%. However, ingesting edibles made with cannabis oil has been gaining in popularity (Borodovsky, Crosier, Lee, Sargent & Budney, 2016), with use estimated at between 18% and 49%. In addition to traditional cannabis edibles (i.e., baked goods), other THC oral products such as candies, oils and tinctures, have become common in legal retail markets (Spindle, Bonn-Miller & Vandrey, 2019). Both therapeutic and recreational users who do not want to be exposed to cannabis smoke may demand edible cannabis products (Gourdet, Giombi, Kosa, Wiley & Cates, 2017), and it has been suggested that edibles reduce respiratory risks associated with the use of smoked cannabis (Russell, Rueda, Room, Tyndall & Fischer, 2018). However, a major concern with edible consumption is the delayed and often unpredictable onset and duration of psychotropic effects as a result of the slower and more variable absorption of THC (Huestis, 2007).

Several studies in the USA have revealed a relationship between the legalization of cannabis use (medicinal and/or recreational) and an increase in the probability of consuming new presentations among young people, especially edibles and vaping (Borodovsky et al., 2016; Borodovsky et al., 2017; Shi & Liang, 2020). In this sense, the legalization of home cannabis cultivation increases the probability that people will make cannabis edibles at home, while the authorization of sale in cannabis dispensaries increases the likelihood of this type of product being purchased (Borodovsky & Budney, 2017).

Another way of using cannabis that has become popular in states where it has been legalized is vaporization (Borodovsky et al., 2016), with use estimated to range from 13% to 45% (Government of Canada, 2018). Vaporization devices typically operate at temperatures that do not burn the cannabis product, but rather "*aerosolize the cannabinoids*" for inhalation, thus likely exposing the user to less toxicity (Spindle et al., 2019). However, the use of cannabis concentrates in vaporizers has been linked to increased

risk of lung injury and other acute damage (Borodovsky, Cavazos-Rehg, Bierut & Grucza, 2020). It is worth noting that concerns about vaping have been raised as a result of recent lung injuries and deaths linked to vaporizer use, such as the series of 98 cases in Wisconsin and Illinois documented in 2019 (Ghinai et al., 2019).

With legalization, other new trends in cannabis use have also gained popularity, such as the combustion and inhalation of cannabis concentrates such as waxes, "*dabs*" and "*shatter*" (Goodman et al., 2020; Spindle et al., 2019). These products tend to have very high THC concentrations, are commonly used for the increased THC-induced "*high*", and have been associated with a number of acute harms (Matheson & Le Foll, 2020). *Dabbing* usually results in very high and immediate doses of THC (Al-Zouabi, Stogner, Miller & Lane, 2018), and the use of "*dabs*" has been linked to cases of acute psychosis, cardiotoxicity and respiratory failure, even though exact causality remains uncertain (Al-Zouabi et al., 2018).

Table 3
Impact of legalization on the presentations, forms and patterns of use

Author (year)	Place	Method	Results	Comments
Al-Zouabi et al. (2018)	USA	Review of studies related to THC through butane extraction.	The use of butane-extracted hash oil consumed by "dabbing" had high THC content and the presence of impurities such as unpurged butane.	Public educational campaigns can focus on dispelling inaccuracies and false sense of security linked to amateur production.
Borodovsky and Budney (2017)	USA	Online survey of adult users.	Users in states where cannabis is legal have grown more at home and have used and purchased more edibles.	Those who have grown cannabis are more likely to make edibles than those who have never done so.
Borodovsky et al. (2017)	USA	Online survey of young cannabis users aged 14 to 18.	States where cannabis is legal and with the highest number of dispensaries were linked to a higher likelihood of trying vaping and edibles.	Laws appear to influence the probability and age at which young people try alternative methods of using cannabis.
Cerdá et al. (2017)	Washington and Colorado versus other states	Compares use in the month before and after legalization versus the other states, national survey (MTF).	Use in Washington increased in 13-15-year-olds, but not in Colorado and not in 17-year-olds.	Low risk perception. Short period after legalization.
Ghinai et al. (2019)	Illinois and Wisconsin	Interviews with nicotine and cannabis vape users.	A high percentage of patients reported using Dank Vape cartridges, which appears to be a highly counterfeited brand.	Lung injuries associated with e-cigarettes after use of products containing THC and nicotine.
Goodman et al. (2020)	Canada and USA	Cross-sectional survey.	Users in legal states significantly were more likely to consume products high in THC than users in illegal states of the USA or Canada and more likely to drive after cannabis use.	
Gourdet et al. (2017)	Alaska, Colorado, Oregon and Washington	Review of official data and surveys.	Wide variation in the regulation of labelling and packaging of THC edibles in the 4 states.	There are inherent difficulties in the enforcement of laws on the labelling, packaging and manufacture of edibles.
Hammond, Chaney, Hendrickson, and Sharma, (2020)	USA	Review (2008/2017).	Legalization has had mixed effects on the health of US adolescents, including the potential benefits of decriminalization and negative outcomes such as rise in car crashes, ED visits, and hospitalizations.	
Matheson and Le Foll (2020)	Colorado	Review.	Review of the increase in acute harms linked to high potency cannabis in states where it is legal.	
Spindle et al. (2019)	USA	Review of new products for use after legalization.	Vaporized cannabis provided higher concentrations of cannabinoids and produced stronger effects, compared to equivalent doses of smoked cannabis.	Delayed effects after use increases the likelihood of acute overdose incidents.
Shi y Liang (2020)	USA	Analysis of data at national level, 2010-17.	Increase in cannabis exposures reported to the poison data system after commercialization of recreational cannabis. Increased availability and accessibility among minors, possibly through purchase by third parties.	Price reduction. Enabled marketing activities at the point of sale. Increased the appeal of cannabis products. The availability of cannabis-derived products increased as did, in turn, the use of alternative methods of use.

At the same time, with legalization, the cannabis industry has commercialized a plethora of diverse products, such as topicals (lotions, balms, creams, etc.), sublingual sprays, and even rectal and vaginal suppositories (Spindle et al., 2019). Very little is known about the use of these new cannabis-derived products (Matheson & Le Foll, 2020).

3. Impact on cannabis use

According to Budney and Borodovsky (2017), the legalization of cannabis use has led to a series of sales and distribution opportunities that may involve increasing use and the possible development of cannabis use disorder (CUD). They highlight the following:

- Greater availability.
- More accessibility.
- Lower cost.
- More power.
- Greater variety of presentation (vapes, foods, extracts, oils ...).
- Higher concentration of THC.

- Lower perception of risk.
- Normalization of use.
- Advertising.
- Greater social and family acceptance.
- Earlier start of consumption due to greater accessibility and lower perception of risk.

Legalization implies potentially increased use among existing consumers and the likelihood that non-users will try it. Thus, over 10% of non-consumers expressed an intention to try it after legalization in the United States (Palamar, Ompad & Petkova, 2014), similar to the data from the ESTUDES survey in Spain (Observatorio Español de las Drogas y las Adicciones, 2020). In Canada, 18.5% of those aged over 15 years, especially the youngest (15-24), also said they intended to try it or increase use after legalization (Sandhu, Anderson & Busse, 2019).

3.1. Changes in risk perception among users and the general population

The broader use and greater availability of cannabis associated with legalization may lead to a decrease in the perception of the harm produced by it, a perception which is already generally low, as indicated in surveys in Spain such as ESTUDES (Observatorio Español de las Drogas y las Adicciones, 2020). A lower perception of risk regarding the use of a substance is associated with an increase in use (Budney & Borodovsky, 2017).

This lower perception of risk, both of the development of addiction and secondary mental problems, occurs specifically among users rather than non-users, as detected in an online survey in 2017 prior to legalization in Canada with subjects aged between 16-30 years (Leos-Toro, Fong, Meyer & Hammond, 2020). This same trend was observed in another survey conducted at national level in the USA in states where it had been legalized compared to those where it had not (Okaneku, Vearrier, McKeever, LaSala & Greenberg, 2015). In Canada, users also reported greater ease in recovering from addiction without the need for treatment (Cunningham, 2020).

In a qualitative study with students in Nevada, it was shown that there was majority support for legalization, a sense of greater security and less social (acceptance by others) and legal risk (legal problems derived from use) in this social segment for a short time after legalization, although, paradoxically, the black market continued to be used due to its lower prices and age restrictions (Amroussia, Watanabe & Pearson, 2020). A survey among students in Washington in 2014 also indicated that legalization led to a more positive attitude towards cannabis and greater intention to use, and could lead abstinent subjects or occasional users to a more frequent use of cannabis (Clarke, Dodge & Stock, 2018). In addition, legalization for recreational purposes made subjects consider that use was more beneficial for the management of pain or affective symptoms (Steigerwald et al., 2020). Surveys conducted by Fleming, Guttmannova, Cambron, Rhew and Oesterle (2016) and Brooks-Russell et al. (2019) also observed this decrease in risk perception among young people in Colorado.

Legalization may also lead to changes in the perception of risk on the part of parents and more permissive attitudes towards use by children. A study by Kosterman et al. (2016) in Washington, interviewing 395 parents between 1985 and 2014, revealed an increase in the approval of adult use and a decrease in the perception of use-related harm. However, its use by young people was negatively perceived. In addition, parents were seen to increase use, with 34% having used it during the previous year. Interestingly enough, quite a few parents were unaware of the legal age for cannabis use.

3.2. Changes in consumption in adolescents and young people

One of the major concerns in connection with legalization is the potential increase in use among young people, given their greater vulnerability and possible repercussions at academic, cognitive and mental-health levels, although in all states and countries where it has been legalized, cannabis use is prohibited at this life stage (under 18 in Uruguay and Canada, under 21 in the USA).

A considerable number of studies have assessed the impact of medical cannabis legalization on use among young people (Anderson & Rees, 2014; Anderson, Hansen, Rees & Sabia, 2019; Cerdá, Wall, Keyes, Galea & Hasin,

2012; Choo et al., 2014; Harper, Strumpf & Kaufman, 2012), generally reporting few repercussions. One meta-analysis indicates that there is no association between the legalization of medical cannabis and its use in adolescents (Sarvet et al., 2018). However, the advertising of cannabis products for therapeutic uses in some states may be influencing the perception of risk. A California study found that adolescents who had seen medical marijuana advertisements on billboards, magazines, or other media in the past three months were more likely to use cannabis and had a greater intention to do so up to a year later (D'Amico, Miles & Tucker, 2015).

In addition, despite the specific prohibition in minors, there is an interest in discovering whether legalization of recreational use influences the use by this population given the possibility that the legal market may be accessed through friends or family and in an environment of greater normalization and lower risk perception, which could favour its use. Melchior et al. (2019) in a recent meta-analysis concluded that measures liberalizing use led to increased consumption. These authors point out that with the legalization of medical cannabis, there was no clear effect on use by young people (three studies indicated a decrease and four an increase) but with the legalization of recreational cannabis, a slight increase was observed. It is argued that this increased consumption may be due to changes in the information regarding use, lower risk perception, greater availability and a decrease in legal and illegal market prices (Table 5). Other studies, such as that by Kerr, Bae, Phibbs and Kern (2017), have found increased rates of marijuana use in Oregon relative to other states without legalization, but only among students who reported recent heavy alcohol use.

A 2018 survey of young people aged 16-19 years on vaping and ways of smoking tobacco and cannabis showed higher cannabis use in Canada (16.65%) and the USA (13.8%) than in the United Kingdom (9%) in any of its forms (Hammond et al., 2021). This seems to indicate that greater previous use existed in countries where it has been legalized, which may favour the positive attitude towards legalization or a lower perception of risk (Brooks-Russell et al., 2019; Fleming et al., 2016).

Most studies (Table 5) were based on online surveys or obtained data from previous surveys, but the different methodologies of these surveys may explain part of the discrepancy in the results. Dilley et al. (2019), evaluating information from two different surveys, observed disparate results. While a survey used in the study by Cerdá and Kilmer (2017) detected a 4% increase in use among 15-year-old students, another survey carried out in state schools found a 2% decrease in 13- and 15-year-old students and no change among 17-year-old students in both. Midgette and Reuter (2020) also point out the importance of the cited sources, indicating considerable disparities in the prevalence figures between states and the doubts about the representativeness of some surveys, but nevertheless concluding that legalization does not influence the prevalence of use in adolescents.

It appears that the developments seen after legalization depend on the level of previous use, with greater increases among existing users (Rusby, Westling, Crowley & Light, 2018). In addition, changes regarding use will likely be perceived several years after legalization takes place, with potentially a stronger effect after five years (Shi et al., 2019).

Table 4
Changes in risk perception associated with the legalization of recreational cannabis

Author (year)	Place	Method	Results	Comments
Amroussia et al. (2020)	Nevada	Focus groups, 32 students, 18-24 years old, three groups (non-, occasional, regular users). Topics: legalization, harm reduction, acceptance, purchasing security.	Greater social and family acceptance. Greater accessibility. More security when buying, more reliability, more variety. Legalization not considered to affect use. Legalization does not eliminate illegal market. Black market used for reasons of cost and age restriction. Those under 21 are also supplied by the legal market through friends and family.	More positive attitude towards cannabis and more intention to use. Non-users thought they might try it in the future as it was legal. They showed little knowledge of regulation but supported legalization. The sense of security was higher.
Clarke et al. (2018)	Washington	Student surveys in 2014.	More positive attitude towards cannabis and more intentions to use.	
Kosterman et al. (2016)	Washington	Interviews with 395 parents from 1985 to 2014.	Increased approval of adult use and decrease in the perception of harm related to use; however, negative perception of use by young people maintained. Increase in use observed among using parents, with 34% having used it during the previous year.	
Steigerwald et al. (2020)	USA, divided into states with and without legalization.	National survey, N=16.280, 56.3% responded (9,003).	In legal states, use was felt to be more beneficial for pain, anxiety-depression management, improved appetite, and safer than tobacco.	

Table 5
Changes in use among adolescents and young adults

Author (year)	Place	Method	Results	Comments
Anderson et al. (2019)	USA, differentiating between states with and without legalization.	Survey of risk behaviours in young students. 1993-2017. N = 1,414,826.	Fall in use. No change in legal medical cannabis. 8% drop in recreational cannabis use and lower frequency of use.	Greater difficulty for adolescents to buy illegal cannabis as vendors are replaced by dispensaries that require proof of age.
Brooks-Russell et al. (2019)	Colorado	Student survey in 2013 (prior to implementation) and 2015 (18 months after implementation).	Little change in use (previous month and lifetime) but decrease in risk perception among adolescents.	
Cerdá and Kilmer (2017)	Washington and Colorado versus other states	Use compared in the month before and after legalization versus the other states, by national survey (MTF survey).	Use in Washington increased in 13-15-year-olds, but not in Colorado and not in 17-year-olds. Little perception of risk.	Low risk perception. Short period after legalization.
Cerdá et al. (2020)	USA, national	National survey of drug use, 2008-2016. N = 505,796. Assessed use before and after legalization. Groups: 12-17 years, 18-25 years and over 26 years.	CUDs in 12-17-year-olds increased from 2.18 to 2.72%; 25% higher than in states without legalizing recreational use.	Noticeable moderate but consistent increase in use and CUDs.
Estoup et al. (2016)	Washington	262 students in school interventions for drug use between 2010-15.	No increase in use (three-month use) after legalization.	
Graves et al. (2019)	Washington	Youth surveys 2010-16, 76,000 young people annually.	Greater use among young workers than non-workers, increase in 17-year-olds, decrease in 13-15-year-olds.	
Harpin et al. (2018)	Colorado	Students aged 11-17 years, survey in 2013 and 2014, n = 24,171.	No changes in previous-month use, greater perception of availability.	
Jones et al. (2018)	Colorado	Students (22-24 years old), n = 14. 13 cross-sectional surveys between 2013-15.	No changes in lifetime use after legalization. Cannabis use in Colorado higher than the national average.	
Kerr et al. (2017)	Oregon versus other states	Cross-sectional surveys in 2014 and 2016. Students aged 18-26. N = 10,924.	Greater increase in previous-month use in Oregon among alcohol users.	
Laqueur et al. (2020)	Uruguay (legal 2013, available 2017 through dispensaries, cultivation, registered clubs)	Student survey 2014-2018, comparison with Chile.	Greater perception of availability, no changes in risk perception, no changes in use. Recognizes that it may not reflect long-term changes.	Different model from USA, use in over-18-year-olds, limited quantities, no advertising, state control, no private companies.
Mason et al. (2016)	Washington	Survey of 238 14-year-old students followed-up between 2010 and 2012.	No increase in previous-month use.	Small sample and short period after legalization. Effect of medical cannabis legalization also assessed.
Mennis and Stahler (2020)	Colorado and Washington	National treatment database for CUD. SAMHSA, 2008-17. 12-17-year-olds.	No differences in treatment for CUD between states with and without legalization.	Higher %age of CUD treatment in Colorado and Washington prior to legalization versus other states. Then, further fall in Col. and Wash. due to changes in attitudes and risk perception.
Melchior et al. (2019)	USA	Meta-analysis: Includes 13 articles, 20 studies on medical cannabis legalization and 8 impact studies on recreational cannabis legalization.	Slight rise in use among adolescents after legalization of recreational use.	Short period of observation.
Miller et al. (2017)	Washington	Survey 2005-2015, with 2,069 students per year, average age 20 years.	Rise in previous-month use, up 2-3.5%, also more days of use. Higher among women, blacks, Hispanics. No change in other drugs.	
Parnes et al. (2018)	Colorado	Student surveys in 2013-2015, 5,241 students.	Rise in use, higher in those over 21 years, more 'try-it' behaviours, no changes in previous-month use. Encourages students from other states to go to Colorado.	Cannabis tourism, lower price after legalization. Displacement of student users from other states.
Rusby et al. (2018)	Oregon	Two cohorts of students before and after legalization, 13-15-year-olds.	Rise in use among young people already using, not in non-users.	
Sarvet et al. (2018)	USA	Review of 2,999 articles from 17 bibliographic sources.	Comparing states with and without legalization of medical cannabis, higher rates of use already existed in states where medical marijuana was legalized.	Prevalence of adolescent use did not increase in states with medical cannabis up to 2014.
Shi and Liang (2020)		Survey in 38 countries, 172,894 adolescents.	Greater liberalization of use is associated with higher use by adolescents; correlation after 5 years of legislative change.	

Table 6
Changes in use among adults

Author (year)	Place	Method	Results	Comments
Bae and Kerr (2020)	USA, comparison of states with and without recreational cannabis legalization	National survey administered in 2008 and 2018, 18-26-year-old students, 234,669 in states with legalization, 599,605 in states without legalization. Self-reports	Higher prevalence of previous-month use (OR = 1.23) and frequent use (OR = 1.18) than in non-legalized states, greater in women and those aged over 21 years age.	Greater increase after the first and second year of legalization, but more evident effect after more years of post-legalization (at 5-6 years post-legalization OR approx. 2).
Cerdá et al. (2020)	USA	National survey of drug use in the USA 2008-2016. N = 505,796. Evaluation before and after legalization. Three age groups: 12-17 years, 18-25 and over 26 years.	Increase in CUD in 12-17-year-olds from 2.18 to 2.72%, 25% more than in states without legalizing recreational use. No changes in 18-25-year-olds. In those over 26, increased frequency of previous-month use from 2.13 to 2.62%, and increase in CUD from 0.9 to 1.23%.	Highlights slight increase in use and moderate but consistent in CUD, and in 2016 (thus latest data), despite short assessment period.
Doran et al. (2021)	California	Survey of 563 young people (aged 18-29 years) in 2015, 3-year follow-up.	No changes in use, increase in women and decrease in men.	Not enough time for legalization to develop.
Everson et al. (2019)	Washington	Use survey, 2009 and 2016.	Greater increase in use with greater proximity to retail outlets. Use increased between 2009 and 2016, did not change immediately after legalization.	
Goodman et al. (2020)	USA (states with legal and illegal cannabis) and Canada	Online survey in 2018, n = 27,024, Age range 16-65 years.	In legal states 11.3% vs 7.4% of daily, 18.2% vs 11.6% of weekly and 25% vs 16.8% of monthly use.	Also, greater variety of products in legal states. Data from Canada similar to non-legal states in the USA as Canada had not yet legalized.
Goodwin et al. (2021)	USA	Cross-sectional national survey from 2004 to 2017, measuring use in adults with children.	Previous-month use in 2017: 11.9% in states with recreational cannabis legalization, 9.3% with medical cannabis and 6.1% illegal. Daily use: 4.2%, 3.2% and 2.3% respectively.	Recreational legalization increased use in adults with children at home. Effect of legalization for medicinal purposes had a more mixed effect.
Hammond et al. (2020)	USA and Canada	Online survey, age range 16-65 years, 27,169 subjects.	Non-users of cannabis: 43.5% in Canada (still illegal), 45.4% in illegal USA, 38.5% in legal USA. Daily use 8.9%, 7.4% and 11.3% respectively.	Data from the first wave of the survey aiming to assess changes over time.
Kerr et al. (2017)	Oregon	10,924 university students. Survey between 2012-2016.	Increase in cannabis use between 2012 and 2015 in all students. Greater increase in use in Oregon than in control states for those who reported alcohol use.	
Rotermann (2020)	Canada	Survey of use in 2018-2019, before and after legalization.	Use increased from 14.9% to 16.8% in the last 3 months after legalization, more in men and those aged over 25. Stable daily use at 6%.	52% obtained cannabis from legal sources, buying from illegal sources decreased from 51.7% to 40.1% in the first year of legalization.
Rotermann (2019)	Canada	Survey of use in 2018-2019, before and after legalization	Before legalization, use decreased in 15-17-year-olds, was stable in 18-24-year-olds and increased in 25-64-year-olds. After legalization, consumption increased from 14 to 18%, more in men.	Use increased but short period of implementation of legalization.
Steigerwald et al. (2020)	USA differentiating between states with and without legalization.	National survey, N=16,280, 56.3% responded (9,003).	Previous-year cannabis use 20% vs 12% in non-legal, 20% more frequent in states with legal than non-legal use.	Greater use of different varieties.

Regarding adolescent treatment admissions for cannabis use, no increase was noted in Colorado and Washington after the legalization of recreational cannabis. According to Mennis and Stahler (2020), this may be due either to the fact that cannabis use among young people has not increased, or because CUD levels have not changed despite the increase in use. The authors found changes in attitude and risk perception regarding cannabis use. Along similar lines, an assessment of the first three years of legalization in Colorado (Ghosh et al., 2017) did not find that consumption increased among young people but that the perception of risk decreased. Likewise, another study carried out in the same state suggests that there were no differences in use (if anything, frequent use decreased) but there was a decrease in risk perception among adolescents (Brooks-Russell et al., 2019). The results obtained in Washington follow a similar pattern, with no increase in use among adolescents but a decrease in their perception of risk (Fleming et al., 2016).

3.3. Changes in adult use

Studies focusing on the effect of medical cannabis legalization in the USA indicate that use and CUD in adults have increased (Cerdá et al., 2020). Using data from

surveys conducted in the same country from 1991 to 2013 (studies by NLAES and NESARC), Hasin et al. (2017) point out that legal medical cannabis increased the prevalence of illegal use and CUD. Thus, in a national survey on drug use in the United States, Mauro et al. (2019) revealed a rise in use among both sexes in those aged over 26 years.

In any case, it is important to consider that short-term effects do not predict long-term changes (Hall et al., 2019) since such changes do not occur immediately after legalization (Everson, Dilley, Maher & Mack, 2019). Short-term changes may not anticipate changes once the market stabilizes as it takes one to two years for dispensaries to function properly after legalization and, furthermore, many states have strong markets for medicinal cannabis that can affect this process of demand (Smart & Pacula, 2019) (Table 6).

An increase in use among cancer patients has also been described after the legalization of "recreational" use (Pergam et al., 2017), in line with the lack of separation between the possible medicinal properties of cannabis and its "recreational" use. In a survey of cancer patients in Canada, just after the legalization of recreational cannabis, an increase in cannabis use was noted from 23% to 29%, but difficulties were reported in obtaining certain products only available on the illicit market and at high cost (Hawley, Gobbo & Afghari, 2020).

3.4. Changes in the demand for treatment for CUD and cannabis dependence

It has been plausibly hypothesized that rising cannabis use will cause an increase in the incidence of CUD and the demand for treatment for this reason. If this were the case, it would probably be an association that would become observable after several years. It has been noted that two years after legalization, the demand for such treatment in Washington has decreased, but this was also in line with other states where "recreational" use had not been legalized (Hall & Lynskey, 2020). An assessment of adolescent treatment admissions (12-17 years) up to 2017 found that there were no changes in Colorado and Washington compared to other states; this can probably be explained by changes in attitude and risk perception (Mennis & Stahler, 2020). However, an analysis of such admissions between 1992 and 2016 indicates that the demand for treatment for cannabis as the main drug or concomitantly with alcohol increased among adolescents, and at a faster rate than treatment for other substances (Standeven, Scialli, Chisolm & Terplan, 2020). A review of the field indicates that greater social acceptance and lower risk perception may result in treatment not being requested (Sahlem, Tomko, Sherman, Gray & McRae-Clark, 2018). It is thus too early to draw firm conclusions regarding this aspect (Table 7).

It has been observed that after several years of medical cannabis legalization, a higher frequency of CUD was noted, especially in states permitting dispensaries and collective cultivation. The demand for CUD treatment is increasing both globally and for young people (Smart & Pacula, 2019), and a link has been established between higher density of medical cannabis dispensaries in California and CUD hospitalizations (Mair, Sumetsky, Kranich & Freisthler, 2021).

3.5. Impact on the consumption of other drugs

Another aspect of interest is whether the legalization of recreational use can influence the use of other substances by a substitution effect, by changes in the risk perception of other drugs or by concomitant use. For example, using data from a national survey in the USA from 2004-2017, Kim et al. (2021) pointed to the frequent co-use of cannabis and

Table 7
Demand for treatment of CUD and cannabis dependence

Author (year)	Place	Method	Results	Comments
Mair et al. (2021)	California	Spatial analysis of the data on discharges after admissions for cannabis use (2013-2016).	The density of medical cannabis dispensaries seems to be positively linked to hospitalizations for cannabis use disorder in the same year, but not the following year.	
Mennis and Stahler (2020)	Washington and Colorado	Admission registry SAMHSA TEDS-A for adolescents aged 12-17 years (2008/2017).	Treatment admissions for cannabis use in adolescents did not increase in Colorado and Washington after recreational legalization.	This may be due to: 1) adolescent use did not increase, 2) CUD did not increase (even if use did). 3) Demand for treatment changed due to changes in attitudes and risk perceptions towards cannabis use.
Sahlem et al. (2018)	USA	Review analysed public health results in the USA	Only 17% of cannabis users self-identify as medical users.	Medical users were more likely to use daily. They generally considered themselves less healthy and tended to be older compared to recreational users. In recent years there was a decrease in people seeking treatment for CUD.
Standeven et al. 2020	USA	Data analysis from 1996 to 2016. Shows adolescents and young adults.	Data on treatment/ admissions episodes for adolescents (12-17 years) and young adults (18-24 years) admitted for CUD treatment since 1992/2016 (N = 3,794,213).	Admissions for CUD treatment were the highest (38%) (followed by heroin and alcohol) in 2016. Being adolescent, non-Hispanic black male (with concurrent alcohol use) was associated with admission for CUD treatment compared to other substances.

Table 8
Impact on the use of other drugs

Author (year)	Place	Method	Results	Comments
Alley et al. (2020)	USA	Four-year cross-sectional survey 2008/2018 in colleges and universities. Sample: 18-26-year-old college students attending college in states that did and did not implement legalization in 2018.	Recreational cannabis legalization was associated with lower prevalence of binge drinking among college students aged 21 and over and increasing abuse of sedatives among minors.	Recreational cannabis legalization did not change secular trends in the use of other substances.
Doran et al. (2021)	California	Survey of 563 young people (aged 18-29 years) in 2015, 3-year follow-up.	No changes in use, increase in women and decrease in men.	Not enough time for legalization to develop.
Nicksic et al. (2020)	USA	2016 and 2017, national survey on tobacco in young people.	Among young people aged 19-21 cannabis use in sometime e-cigarette (EC) users increased.	Medical and recreational cannabis laws and the absence of legal minimum age for sale of EC were positively associated with cannabis in sometime EC users.
Subbaraman and Kerr (2020)	USA	Cross-sectional samples between 2014 and 2016 (N = 5,492).	No significant changes observed in the overall sample in any of the measures of alcohol use between 2014-2016, but prevalence of cannabis use increased from 25% to 31.7%, prevalence of alcohol-related harm in the home decreased significantly from 2.1% to 1%, and the prevalence of alcohol-related financial harms decreased from 1.5% to 0.8%.	
Veligati et al. 2020	USA	Tax revenue in 50 states. Comparison between states with medicinal and recreational cannabis.	No statistically significant associations were found between medical or recreational cannabis legalization policies and per capita alcohol or cigarette sales.	No evidence was found of a causal association between the legalization of recreational or medical cannabis and changes in per capita alcohol or cigarette sales.

alcohol. The legalization of medical cannabis was linked to an increase in such polydrug use in people aged over 50 years, and the legalization of "recreational" cannabis was also more clearly associated with the increase in co-use of alcohol and cannabis, with an increase in cannabis use alone and a decrease in alcohol use alone also being observed.

Furthermore, in a survey conducted in 2018 among American students aged 18-26 comparing states with and without legalization, Alley, Kerr and Bae (2020) revealed a decrease in binge drinking among those over 21 years of age in states with cannabis legalization, an increase in the use of sedatives in minors and no change in the use of stimulants or opioids. Similarly, data from several surveys conducted in Washington between 2014-2016 showed an increase in cannabis use from 25% to 31.7%, but there were no changes in the year immediately after legalization regarding the concomitant use of cannabis and alcohol or total alcohol consumption, although there was an increase in concomitant use in those aged over 50 years (Subbaraman & Kerr, 2020).

At the same time, after another review of the relationship between cannabis use and alcohol in the US under current cannabis policy, Guttmannova et al. (2016) considered that there was evidence for both a substitution (cannabis substituting alcohol in states with a more liberal cannabis policy) and a complementary effect (an increase in both uses after liberalization); however, their data came from studies focused on the decriminalization of cannabis use and legalization for medicinal purposes, without data on the effects of recreational cannabis legalization.

With regard to tobacco, in a survey of 563 young people aged 18-24 in California (where cannabis has been legal since 2016) between 2015-2018, Doran, Strong, Myers, Correa and Tully (2021) observed an increase in its use and also in electronic cigarettes associated with the legalization of cannabis, but the assessment period after legalization was short. Along similar lines, Nicksic, Do and Barnes, (2020), in a survey on tobacco use in the USA, observed that the legalization of cannabis was associated with greater use of cannabis derivatives in electronic cigarettes and this form was linked to an increase in tobacco use and low risk perception regarding this use. Similarly, Wang, Ramo, Lisha and Cataldo (2016a) found that there was an increase in the concomitant use of tobacco and cannabis, especially in the youth population in the USA states where the use of cannabis was legalized for medicinal purposes.

Conversely, research such as that of Veligati et al. (2020) analyzing alcohol and tobacco sales in the USA and differentiating by states with and without recreational cannabis legalization, found no link between the sale of tobacco or alcohol. Kerr, Bae and Koval (2018) reported a decline in tobacco use in Oregon after legalization, but no effect on alcohol or other illicit drugs.

Data is therefore not consistent, and this was pointed out in a review on the uncertain impact of cannabis legalization on alcohol and tobacco use (Smart & Pacula, 2019). Regarding opioids, the same review argued that the findings of the initial study showing a positive effect of medicinal cannabis in reducing mortality from opioids, which has had a significant media impact, could not be corroborated in later studies and, likewise, that no corresponding evidence was

Table 9
Effects of legalization on use among pregnant women

Author (year)	Place	Method	Results	Comments
Barbosa-Leiker et al. (2020)	Washington	Qualitative study in 14 pregnant women and 5 postpartum.	Continuous use during pregnancy, low perception of risk. Use to manage pregnancy discomfort and anxiety as an alternative to medication.	
Castro et al. (2020)	Uruguay	Cross-sectional and analytical study. 577 pregnant women, 319 interviews conducted in 2013 and 258 in 2016.	In 2013, 5 women reported smoking marijuana (1.57%) during pregnancy, while in 2016 there were 28 (10.85%). Cannabis and alcohol use during pregnancy increased, tobacco use decreased. Cannabis use before pregnancy: 12.85% in 2013 and 30% in 2016, during pregnancy: 1.6% in 2013 and 10.85% in 2016.	
Crume et al. (2018)	Colorado (legal in 2012, first dispensary 2014)	Cross-sectional study, 3,207 responded, 2014-2015, monitoring system.	5.7% used during pregnancy and 5% when breastfeeding, higher than estimated for the USA (around 3.6%). Prenatal use was associated with low birth weight.	
Lee et al. (2020)	California	Retrospective study of 466 women between 2016 and 2018.	Increase in all types of cannabis use from 6% to 11% during pregnancy just after legalization.	
Ng et al. (2020)	Nueva Jersey	Cross-sectional survey of 1,133 pregnant women.	Most of the pregnant women surveyed showed little knowledge about the risks of cannabis during pregnancy and indicated that they would be more likely to use during pregnancy if it were legalized.	Additional research is needed to clarify the associated risks.
Skelton et al. (2020)	USA	Self-reported questionnaire. Logistic regression: sample of 7,258 women.	Greater chance of childhood exposure to cannabis in states where it is legalized.	
Whitehill et al. (2019)	Massachusetts	Longitudinal study of 218 telephone calls.	Cases of pediatric exposure to cannabis increased in Massachusetts after medical marijuana was legalized in 2012.	States that legalize should strengthen regulations to prevent unintentional exposure among children and prevent use among adolescents.
Wolf et al. (2020)	Emergency Departments USA	Qualitative exploratory (2008-2017) using data collected by focus group nurses.	Increase in patients with cyclical vomiting syndromes and greater difficulty in managing associated behaviours.	Proposal to standardize the formulation, dosage and labelling of cannabis products.
Yeung et al. (2020)	Alberta	Longitudinal study. Registry of histories.	Canadian cannabis legalization was associated with small increases in cannabis-related ED visits in urban Alberta and calls to a poison control centre.	

found with the legalization of "recreational" cannabis (Smart & Pacula, 2019). However, Kropp et al. (2020) reported a fall in the use of opioids for chronic pain in Colorado after the legalization of cannabis, but, conversely, Alcocer (2020) showed that recreational cannabis legalization did not lead to a decrease in the opioid crisis in the same state.

Regarding the impact of recreational cannabis legalization on fatal opioid overdose deaths, Chihuri and Li (2019) concluded that while a slight reduction in opioid prescription may be observed, no evidence of a decrease in mortality from overdose was found. A similar conclusion about the limited impact on opioid use was drawn by another review focused primarily on studies of medical cannabis legalization (Wendelboe et al., 2019). Therefore, not enough evidence exists yet to show that the use of other drugs changes after cannabis legalization.

3.6. Impact of legalization on the consumption of pregnant women and children's exposure to cannabis

Pregnant women make up another group at special risk of the deleterious effects of cannabis use on the foetus, so it is interesting to assess the risk perception of this group. In a survey of pregnant women who attended a health centre in New Jersey, 4.5% of them used cannabis during pregnancy and had little knowledge of the risks of use during pregnancy, and 90% indicated that they would be more likely to use during pregnancy if it were legal (Ng, Rice, Ananth & Brandt, 2020). In general, it is observed that there is an increase in use among pregnant women, a low perception of risk for the foetus and it is seen as an alternative to alleviate pregnancy distress, which contrasts with a greater awareness of the negative effects of other drugs on pregnancy (Table 9).

At the same time, it has been shown that there is a greater likelihood of child exposure to cannabis during pregnancy in the states where it is legalized (Skelton, Hecht & Benjamin-Neelon, 2020). In Washington state, a percentage of pregnant women who used cannabis prior to gestation reported continuing to use it daily during pregnancy and postpartum to care for themselves and their baby (Barbosa-Leiker et al., 2020).

In Uruguay, between 2013 and 2016, a significant rise in self-declared cannabis use during pregnancy was observed; while 1.57% of women reported smoking cannabis in 2013, this was 10.85% in 2016. The same trend was also noted in the consumption of alcoholic drinks during pregnancy, rising from 23.8% in 2013 to 35.3% in 2016. The consumption of cocaine and cocaine base paste remained stable during this period. However, tobacco use fell significantly in the same period, although it remains the most frequently used drug by pregnant women in Uruguay, at 39.9% in 2016 (Castro et al., 2020).

4. Impact on emergency hospital admissions

With regard to emergency hospitalizations, data found by Wang, Davies, Halmo, Sass and Mistry (2018) in Colorado show a significant increase in emergency admissions for cannabis use, increasing by 1.8 per 1,000 visits in 2009 to 4.9 in 2015. Similarly, calls to Colorado's regional poison centre remained constant from 2000 to 2009; in 2010, however, after the liberalization of medical cannabis, the number of calls for cannabis exposure increased significantly from 42 to 93. In 2014, after recreational legalization, calls again rose sharply by 79.7%. The over-17 age group also made more calls after 2014 (Wang et al., 2017). In Canada, cannabis legalization was associated with slight increases in cannabis-related emergency department visits in urban Alberta and calls to the poison control centre (Yeung, Weaver, Janz, Haines-Saah & Lang, 2020).

In a study carried out in Colorado (Sokoya et al., 2018), an increase in facial trauma related to the effects of cannabis intoxication was found, although this increase was higher in older patients compared to the period prior to legalization, with fractures of the maxilla and base of the skull being the most frequent. It may in general be concluded that there is an increase in acute harm associated with high-potency cannabis in states where cannabis is legal (Matheson & Le Foll, 2020).

A further relevant aspect to investigate is the impact that cannabis legalization could have among the pediatric population, as it increases the likelihood that minors are exposed to this substance. Thus, cases of accidental pediatric exposure to cannabis increased in Massachusetts after medical marijuana was legalized in 2012, despite the use of child-resistant packaging and warning labels (Whitehill et al., 2019). A recent review found an increase in pediatric patients with cyclic vomiting syndromes, mainly caused by the ingestion of edible cannabis products. The main reason for this is attributed to high concentrations of THC in plants grown for medicinal cannabis and the new palatability of cannabis when infused or incorporated into sweet foods, such as candies and baked goods, thus contributing to pediatric exposures being more likely and to children repeatedly going to the pediatric EDs after consuming such cannabinoids (Wolf, Perhats, Clark, Frankenberger & Moon, 2020). A review was also carried out in Colorado comparing pediatric emergencies for accidental ingestion of cannabis before and after legalization and showing a clear increase after legalization (Wang et al., 2016b).

As in almost all aspects analyzed in this section, additional research is needed (Degenhardt et al., 2013; Felson et al., 2019).

Trends in states that have legalized cannabis and presented a growing prevalence of cannabis use, coinciding at the same time with declining risk perception, should alert pediatricians; they should be prepared to tackle the management and prevention of unintentional cannabis ingestion in childhood, as well as problematic use in adolescents (Grigsby et al., 2020).

Table 10
Impact on emergency hospitalizations

Author (year)	Place	Method	Results	Comments
Auger et al. (2020)	Canada	Longitudinal study of patient registry, hospitalized children.	Legalization of cannabis in Canada did not increase the risk of short-term cannabis-related hospitalization among older girls and boys.	In children aged 10-14, legalization may have contributed to an increased risk in children under 15 years of age.
Roberts (2019)	Colorado	Longitudinal study.	Important health consequences of cannabis legalization, especially in in emergency departments and hospitals.	The most worrying: psychosis, suicide and abuse of other substances. Increase in fatal vehicle collisions, adverse effects on cardiovascular/ pulmonary systems, accidental pediatric exposure.
Rylander et al. (2014)	Colorado	Mixed regression model. Generalized linear modelling techniques (longitudinal).	Medical cannabis legalization may not have an adverse impact on suicide rates.	However, this conclusion must be examined in light of the study's limitations and may not be generalizable to people with severe mental illness.
Grigsby et al. (2020)	USA	Review (2008-2017).	The rising prevalence of children with cannabis use coincides with decreasing risk perceptions of harm from cannabis products.	Pediatricians must be ready to address the management and prevention of unintentional ingestion during childhood.
Sokoya et al. (2018)	Colorado	Retrospective review.	Maxillary and skull base fractures increased significantly after legalization.	No significant differences were observed in the proportion of patients living in urban and rural counties before and after legalization.
Wang et al. (2017)	Colorado	Registry 2009/2015.	Review of pediatric emergencies for accidental cannabis ingestion before and after legalization in Colorado (increased after legalization).	

5. Repercussions of legalization on psychiatric emergencies

Research in Colorado shows that cannabis legalization has seen significant increases in cases of psychosis, suicide, and other substance abuse (Roberts, 2019). In this state, ED presentations for mental illness with a cannabis-related code increased five times faster than visits for mental illnesses without such a code between 2012 and 2014 (Wang et al., 2017). The largest increases involved persons diagnosed with schizophrenia and other psychotic disorders, suicide, intentional self-harm, and mood disorders (Hall et al., 2018). Thus, in 10 of the 13 prospective longitudinal studies carried out, it was found that users of cannabis have a significantly higher risk of psychosis compared to those who do not (Murray & Hall, 2020).

Regarding anxiety disorder, in USA states where cannabis has been legalized, use has increased among adults in general, but this increase was disproportionate among the population diagnosed with anxiety (Weinberger et al., 2020). There does not appear to be an association between higher anxiety and patterns of cannabis use in USA states with legalized medical marijuana, with cannabis use being more frequent in these states (McBain et al., 2020).

6. Repercussions of legalization on traffic accidents

With regard to traffic accidents, the deleterious effects of cannabis on the brain include reduced complex decision-making capacity, which may not be reversible with abstinence and which could be linked to an increase in accident rates and road traffic mortality and, therefore, to increased hospital emergency service activity. Such increases in emergencies due to motor vehicle collisions have been documented after legalization (Roberts, 2019). In the USA, a slight increase in fatal traffic accidents was seen in states where recreational cannabis is legal (Lane & Hall, 2019). THC positivity among driver deaths has increased since legalization in various USA states, at a three times higher rate from 1993-2000 to 2001-2015. THC-positive traffic fatalities were more frequent among young people and more likely in single-vehicle crashes, night-time crashes and speeding; moreover, victims were less likely to have worn a seat belt or helmet (Steinemann et al., 2018). The state of Colorado recorded an increase in the trend of all fatal accidents after recreational cannabis legalization and the start of over-the-counter sales. While traffic fatalities increased, deaths of pedestrians being hit by cars did not, however (Calvert & Erickson, 2020).

At the same time, in the year following the implementation of recreational cannabis sales, traffic fatalities increased by an average of one additional death per million residents in states where recreational cannabis had been legalized, i.e., Colorado, Washington and Oregon and its neighbouring jurisdictions (Lane & Hall, 2019).

In Uruguay, 2013 legislation legalizing recreational cannabis use may be associated with an increase in fatal

Table 11
Impact on traffic accidents

Author (year)	Place	Method	Results	Comments
Calvert and Erickson (2020)	Colorado (2012)	Longitudinal. Registry of histories.	Increasing trend in all fatal crashes after recreational cannabis legalization. No link to pedestrian deaths.	
Eichelberger (2019)	Washington	Self-reported longitudinal study of 2,355 drivers (2014/2015).	The proportion daytime drivers with positive THC increased from 8% before retail sales to 23% 6 months after retail sales; no change in the proportion among night drivers (19% and 20%).	
Goodman et al. (2020)	Canada and USA	Cross-sectional survey.	In legal states, high-THC products were significantly more likely to be used than in illegal USA states or Canada, and users were more likely to drive after cannabis use than users in Canada ($p < .001$ for all).	
Keric et al. (2018)	USA	Longitudinal study (2008-2017). Survey of 127 participating trauma surgeons.	Variation between states studied in prevalence of cannabis and alcohol. The impact of marijuana decriminalization did not appear to affect the incidence of driving while high on marijuana.	
Lane and Hall (2019)	Colorado Washington and Oregon	Registry. 2009-2016.	Slight increase (+ 1/million inhabitants) in fatal traffic accidents in legal states.	
Nazif-Muñoz et al. (2020)	Uruguay	Uninterrupted time series analysis. January 1, 2012 to December 31, 2017.	Increase in traffic accidents (light vehicles) in Uruguay after legalization.	
Salomonsen-Sautel et al. (2014)	Colorado	Comparativa 1994-2009 y periodo post-legalización 2009-2011.	Increased proportion of THC-positive drivers in fatal Colorado traffic accidents pre vs post legalization, although period of time after legalization was short.	

motor vehicle crashes, particularly involving drivers of light vehicles and urban settings (Nazif-Muñoz et al., 2020).

7. Impact on the legal system: Violence and crime

Another aspect to consider regarding legalization is the possible reduction in the number of legal cases and everything crime related, including violence. Studies show that in the states where marijuana was legalized during 2010 and 2014, there were no statistically significant differences in the rates of property crime, but violent crime, murder, aggravated assault, robbery, and theft appeared to be higher in states where marijuana was completely banned (Maier, Mannes & Koppenhofer, 2017).

Research by Dragone, Prarolo, Vanin, and Zanella (2019) provides evidence that legalization of the cannabis market in USA states has led to a drop in crime. Thus, in Washington, burglaries fell by approximately 15% to 30%, crimes by between 10% and 20%, and robberies by between 13% and 22%. Nor was an increase in crime noted in Denver or Colorado when cannabis also became available recreationally in neighbourhoods with the highest density of therapeutic cannabis dispensaries (Freisthler, Gaidus, Tam, Ponicki & Gruenewald, 2017). It is still unknown whether the legalization of recreational cannabis has affected the variations detected in crimes, and if so, how. It will still take some time for data that may clarify these issues to become available, although the most recent studies have not found any associations between changes in legalization and the increase or decrease in crime (Maier et al., 2017). However, certain meta-analyses have shown that cannabis use is linked to violence in high-risk populations and those with severe mental problems, so measures should be taken to mitigate the risks (Dellazizzo, Potvin, Athanassiou & Dumais, 2020).

Rates of cannabis-related arrests among African American and white adults decreased significantly with the legalization of possession and remained at a lower rate after the retail marijuana market opened. However, relative disparities in marijuana arrest rates for African Americans increased among older adults and were unchanged for younger adults (Firth, Maher, Dilley, Darnell & Lovrich, 2019).

Minor criminal justice offenses in Washington State fell substantially after legalization, but disproportionate enforcement among racial/ethnic minorities continues (Jensen & Roussell, 2016). At the same time, it can be seen that while legalization has not reduced arrests of young people for possession, it does seem to have done so among adults (Plunk, Peglow, Harrell & Grucza, 2019).

Discussion

There is considerable heterogeneity in the legislative measures adopted by the different countries where the recreational use of cannabis has been legalized. Thus, Uruguay introduced a model with strict control by the state, without advertisements promoting cannabis use, but this less commercial model, with potentially less risk to public health, has not yet been fully implemented. To date, the measures introduced have not succeeded in completely suppressing the illicit market for this substance in the country, which is possibly due to a reluctance on the part of users to register. Conversely, the business model

Table 12
Impact on the legal system

Author (year)	Place	Method	Results	Comments
Dragone et al. (2019)	USA	Quasi-experimental design, data from US Uniform Crime Reporting for the years 2010 to 2014.	Crime fell in states with legalized recreational use, and more in neighbourhoods with more dispensaries, with disruption of the illegal market being the most plausible explanation.	Four possible causes of this decrease in crime are established.
Dellazizzo et al. (2020)	Various countries	Meta-analysis.	Evidence-based research from meta-analyses has shown that cannabis use is associated with violence; measures must be taken to mitigate risks.	
Firth et al. (2019)	Washington	Longitudinal registry study. National Reporting System Based on Incidents 2012-2015.	Arrest rates among African American (2.5) and white (5) adults fell after legalization and remained at a lower rate after the market opened.	However, the relative disparities in cannabis arrest rates for African Americans increased for those of legal age. No changes in younger adults.
Jensen y Roussell (2016)	Washington	Longitudinal registry	Minor cannabis-related offenses with criminal justice system involvement were substantially reduced, but disproportionate enforcement of racial/ ethnic minorities continues.	
Maier et al. (2017)	USA	Uniform Crime Report (UCR) from 2010-2014 comparing 50 US states with and without legalization.	Results indicated the trend for violent and property crime rates was rising in states where cannabis was still illegal; the difference was not significant.	Even when controlling for factors that can lead to crime, the legal status of cannabis in the states failed to predict property or violent crime rates in 2014.
Plunk et al. (2019)	USA (2008/2017)	Record of arrests: January 1, 2000 to December 31, 2016.	Legalization led to reduced arrests for possession in adults but not in young people.	

implemented in many USA states has given rise to strong commercial interests and aggressive marketing strategies that may contribute to greater cannabis use and lower risk perception. Despite this, these models have not managed to eliminate the black market either, but rather to reduce prices because of stronger competition and thus greater availability. Canada, with stronger advertising limits, represents an intermediate level of control regarding the sale of cannabis compared to the other two countries, yet similarly, it is recognized that the illicit market still plays an important role. The aim of suppressing this market and protecting the most vulnerable, such as adolescents, have therefore not been achieved to date.

The legalization of cannabis markets has substantially reduced the price of cannabis and increased its potency, and prices are likely to continue declining if legalization becomes federal policy in the USA, especially if imports and home delivery are permitted (Kilmer & Neel, 2020). As for the prices of illicit cannabis in both Canada and the United States, these are lower than for cannabis sold in official dispensaries, which is why many users, especially minors continue to resort to the illicit market for their supplies (Rehm & Manthey, 2020).

Regarding the relationship between price and potency, governments of states authorizing the retail sale of cannabis have not taxed cannabis products based on their potency, as is the case with alcohol (Hall & Lynskey, 2020). Currently, no USA jurisdiction has raised cannabis taxes high enough to prevent falling prices after legalization, with tax rates ranging from 10% in states like Colorado or Nevada to 37% in Washington (Davis, Hill & Phillips, 2019). It should be noted that in both the USA and Canada, the dispensing of products with high concentrations of THC at low prices puts consumers at greater risk of developing both CUD and psychotic disorders. Although only a minority develop a psychotic disorder, those consuming cannabis with over 10% THC daily are five times more likely to develop a psychotic disorder than those who have never used it (Di Forti, 2020). In the USA, this increase in THC content in legalized states has not been matched by greater access to accurate information about the potency of products accessible to consumers; the opposite has rather been the case as the industry tends to avoid contemplation of the drawbacks and risks of cannabis with high concentrations of THC and low CBD (Cash et al., 2020; Chandra et al., 2019). In both the USA states that have legalized cannabis and in Canada and Uruguay, there is an inherent tension between the political goals of minimizing taxes to reduce the illicit market for cannabis and imposing high taxes to discourage excessive use (Hall et al., 2019).

On the other hand, legalization has also generated new forms of cannabis use, highlighting products made with "hash oil" such as "dabs" and edibles, which have been associated with a higher risk of adverse effects (Grewal & Loh, 2020), the main cause being the large amount of THC that these products contain. The risk of addiction is 20-30% higher in people who use cannabis 100 times or more, and could be higher in those who use high-potency products (Chandra et al., 2019). To address these drawbacks, Matheson and Le Foll (2020) propose three approaches to minimize these harms: Early restriction of cannabis edibles and high potency products; clear and consistent labelling stating dose/serving size and health risks; and the implementation of robust data collection frameworks to monitor harms, disaggregated by type of cannabis product (e.g., dose, potency, route of administration) and consumer characteristics (e.g., age, sex, gender, ethnicity).

Furthermore, it was to be expected that the legalization of "recreational" use would have an impact on the levels of cannabis consumption due to the effects on price, accessibility, acceptance and promotion of use. While there is evidence of a moderate increase among adults, although not adolescents, this has possibly not been higher due to the slow processes in the introduction of legislative changes and greater accessibility to the product. The importance of the accessibility factor is shown by the higher consumption evident in regions with greater proximity to dispensaries (Everson et al., 2019). According to Hall and Lynskey (2020), these moderate effects on the increase in use among adults and the smaller effect among young people may be due to the shortage of sales dispensaries in many towns and cities and the limitations in marketing due to the federal prohibition in the USA. Increases in use could be due to rises in the quantity and frequency of use among previous users or the appearance of new users.

Increasing use by pregnant women has also been detected in the three countries, as well as a decrease in risk perception regarding the effects of cannabis on the foetus (Gnofam, Allshouse, Stickrath & Metz, 2020; Lee et al., 2020). Some epidemiological studies have suggested that cannabis use during pregnancy was associated with an increased risk of being small for gestational age, preterm delivery, low birth weight, and admission to a neonatal intensive care unit (Bailey, Wood & Shah, 2020; Kharbanda et al., 2020). Despite this, in countries where cannabis has been legalized, pregnant women justify its use to treat nausea, vomiting, pain, and other symptoms (Postonogova, Xu & Moore, 2020; Takakuwa & Schears, 2019). There is a growing public health concern in the USA regarding this issue and several authors argue that pregnant women do not receive enough cannabis-related testing and counselling from health professionals (Mark & Terplan, 2017; Polen, Whitlock, Wisdom, Nygren & Bougatsos, 2010).

The effect of cannabis legalization on road traffic fatalities is another growing public health concern (Kilmer, 2017). There is increasing evidence that cannabis impairs driving ability by reducing attention, perception of speed, and motor coordination (Sewell, Poling & Sofuoglu, 2009).

Thus, in the USA states where it has been legalized, Canada and Uruguay, results suggest that legalizing the sale of cannabis for recreational use may lead to an increase in deaths from traffic accidents (Lane & Hall, 2019).

There are no conclusive data on the psychopathological repercussions of recreational cannabis legalization, partly due to the as yet short period of observation, but given the relationship between increased use and potency of cannabis and problems such as psychosis and other mental disorders, it is expected that this effect may be observed in the future.

The new models of regulation focus on creating a market economy for legal cannabis, with the purported diversion of profits from illicit markets and the reduction of prohibition-related costs. However, to reduce the risks associated with the legalization of cannabis, an approach that specifically focuses on the health and safety rights of the individual should be considered. Such an approach should promote and protect individual and social health and safety, establish strict quality control of legal cannabis products regulated on the basis of THC and CBD content, and eliminate all kinds of incentives to use, thus providing a more comprehensive, coherent, sustainable and ethical framework for legalizing the use of non-medicinal cannabis.

Trivializing language and increased use of "recreational cannabis" in public spaces can lead to a widespread underestimation of the risks of cannabis use.

Thus far, the alleged advantages of the legalization and regularization of cannabis have not produced the results expected globally since consequences in various areas continue to persist and have in some cases worsened, such as in emergency hospital admissions, traffic accidents, pediatric consequences, use during pregnancy and appearance or worsening of psychiatric conditions. However, it is considered that the ultimate consequences of legalizing recreational cannabis use cannot be fully assessed until a decade or more has passed.

Conflict of interests

The authors declare no conflict of interest with regard to the implementation of this study.

References

Alcocer, J. J. (2020). Exploring the effect of Colorado's recreational marijuana policy on opioid overdose rates. *Public Health, 185*, 8-14. doi:10.1016/j.puhe.2020.04.007.

Alley, Z. M., Kerr, D. C. & Bae, H. (2020). Trends in college students' alcohol, nicotine, prescription opioid and other drug use after recreational marijuana legalization: 2008–2018. *Addictive Behaviors, 102*, 106212. doi:10.1016/j.addbeh.2019.106212.

Al-Zouabi, I., Stogner, J. M., Miller, B. L. & Lane, E. S. (2018). Butane hash oil and dabbing: Insights into use, amateur production techniques, and potential harm mitigation. *Substance Abuse and Rehabilitation, 9*, 91. doi:10.2147/SAR.S135252.

Amroussia, N., Watanabe, M. & Pearson, J. (2020). Seeking safety: A focus group study of young adults' cannabis-related attitudes, and behavior in a state with legalized recreational cannabis. *Harm Reduction Journal, 17*, 1-7. doi:10.1186/s12954-020-00442-8.

Anderson, D. & Rees, D. (2014). The legalization of recreational marijuana: How likely is the worst-case scenario? *Journal of Policy Analysis and Management*, 33, 221-232. https://www.jstor.org/stable/pdf/24033304.pdf refreqid=excelsior%3A37f192bddf91ff79 f95a82f216981566.

Anderson, D., Hansen, B., Rees, D. & Sabia, J. (2019). Association of marijuana laws with teen marijuana use: New estimates from the youth risk behavior surveys. *JAMA Pediatrics*, *173*, 879-881. doi:10.1001/jamapediatrics.2019.1720.

Auger, N., Luu, T. M., Ayoub, A., Bilodeau-Bertrand, M., Lo, E. & Low, N. (2020). Cannabis-related hospitalizations among youth in Canada before and after cannabis legalization. *Journal of Addiction Medicine, 15*, 245-247. doi:10.1097/adm.0000000000000747.

Bae, H. & Kerr, D. (2020). Marijuana use trends among college students in states with and without legalization of recreational use: Initial and longer-term changes from 2008 to 2018. *Addiction*, *115*, 1115-1124. doi:10.1111/add.14939.

Bailey, B. A., Wood, D. & Shah, D. (2020). The role of in utero exposure to drugs beyond opioids in the development and severity of neonatal opioid withdrawal syndrome (NOWS). https://dc.etsu.edu/etsu-works/7673.

Barbosa-Leiker, C., Burduli, E., Smith, C. L., Brooks, O., Orr, M. & Gartstein, M. (2020). Daily cannabis use during pregnancy and postpartum in a state with legalized recreational cannabis. *Journal of Addiction Medicine, 14*, 467. doi:10.1097/ADM.0000000000000625.

Borodovsky, J. T., Crosier, B. S., Lee, D. C., Sargent, J. D. & Budney, A. J. (2016). Smoking, vaping, eating: Is legalization impacting the way people use cannabis? *International Journal of Drug Policy, 36*, 141-147. doi:10.1016/j.drugpo.2016.02.022.

Borodovsky, J. T. & Budney, A. J. (2017). Legal cannabis laws, home cultivation, and use of edible cannabis products: A growing relationship? *International Journal of Drug Policy, 50*, 102-110. doi:10.1016/j.drugpo.2017.09.014.

Borodovsky, J. T., Lee, D. C., Crosier, B. S., Gabrielli, J. L., Sargent, J. D. & Budney, A. J. (2017). US cannabis legalization and use of vaping and edible products among youth. *Drug and Alcohol Dependence, 177*, 299-306. doi:10.1016/j.drugalcdep.2017.02.017.

Borodovsky, J. T., Cavazos-Rehg, P. A., Bierut, L. J. & Grucza, R. A. (2020). Cannabis vaping and health: Regulatory considerations. *Addiction, 115*, 587-588. doi:10.1111/add.14855.

Brooks-Russell, A., Ma, M., Levinson, A. H., Kattari, L., Kirchner, T., Goodell, E. M. A. & Johnson, R. M. (2019). Adolescent marijuana use, marijuana-related perceptions, and use of other substances before and after initiation of retail marijuana sales in Colorado (2013–2015). *Prevention Science, 20*, 185-193. doi:10.1007/s11121-018-0933-2.

Budney, A. J. & Borodovsky, J. T. (2017). The potential impact of cannabis legalization on the development of cannabis use disorders. *Preventive Medicine, 104*, 31-36. doi:10.1016/j.ypmed.2017.06.034.

Calvert, C. & Erickson, D. (2020). An examination of relationships between cannabis legalization and fatal motor vehicle and pedestrian-involved crashes. *Traffic Injury Prevention, 21*, 521-526. doi:10.1080/15389588.2020.1810246.

Cash, M. C., Cunnane, K., Fan, C. & Romero-Sandoval, E. A. (2020). Mapping cannabis potency in medical and recreational programs in the United States. *PloS One, 15*. doi:10.1371/journal.pone.0230167.

Castro, M. M., Pinto, F., Pereiras, C., Castells, A. F., Agoglia, C. V., Duarte, V.,… González, G. (2020). Autodeclaración del consumo de marihuana, tabaco, alcohol y derivados de cocaína en embarazadas en 2013 y 2016, Montevideo, Uruguay. *Adicciones, 32*, 173-180. doi:10.20882/adicciones.1107.

Cavazos-Rehg, P. A., Krauss, M. J., Cahn, E., Lee, K. E., Ferguson, E., Rajbhandari, B.,... Bierut, L. J. (2019). Marijuana promotion online: An investigation of dispensary practices. *Prevention Science, 20*, 280-290. doi:10.1007/s11121-018-0889-2.

Cerdá, M., Wall, M., Keyes, K. M., Galea, S. & Hasin, D. (2012). Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug and Alcohol Dependence, 120*, 22-27. doi:10.1016/j.drugalcdep.2011.06.011.

Cerdá, M. & Kilmer, B. (2017). Uruguay's middle-ground approach to cannabis legalization. *The International Journal on Drug Policy, 42*, 118. doi:10.1016/j.drugpo.2017.02.007.

Cerdá, M., Mauro, C., Hamilton, A., Levy, N., Santaella-Tenorio, J., Hasin, D.,... Martins, S. (2020). Association between recreational marijuana legalization in the United States and changes in marijuana use and cannabis use disorder from 2008 to 2016. *JAMA Psychiatry*, *77*, 165-171. doi:10.1001/jamapsychiatry.2019.3254.

Chandra, S., Radwan, M. M., Majumdar, C. G., Church, J. C., Freeman, T. P. & ElSohly, M. A. (2019). New trends in cannabis potency in USA and Europe during the last decade (2008–2017). *European Archives of Psychiatry and Clinical Neuroscience, 269*, 5-15. doi:10.1007/s00406-019-00983-5.

Chihuri, S. & Li, G. (2019). State marijuana laws and opioid overdose mortality. *Injury Epidemiology, 6*, 1-12. doi:10.1186/s40621-019-0213-z.

Choo, E. K., Benz, M., Zaller, N., Warren, O., Rising, K. L. & McConnell, K. J. (2014). The impact of state medical marijuana legislation on adolescent marijuana use. *Journal of Adolescent Health, 55*, 160-166. doi:10.1016/j.jadohealth.2014.02.018.

Chung, C., Salottolo, K., Tanner, A., Carrick, M. M., Madayag, R., Berg, G.,… Bar-Or, D. (2019). The impact of recreational marijuana commercialization on traumatic injury. *Injury Epidemiology, 6*, 1-8. doi:10.1186/s40621-019-0180-4.

Clarke, P., Dodge, T. & Stock, M. L. (2018). The impact of recreational marijuana legislation in Washington, DC on marijuana use cognitions. *Substance Use and Misuse, 53*, 2165-2173. doi:10.1080/10826084.2018.1461226.

Crume, T. L., Juhl, A., Brooks-Russell, A., Hall, K., Wymore, E. & Borgelt, L. (2018). Cannabis use during the perinatal period in a state with legalized recreational and medical marijuana: The association between maternal characteristics, breastfeeding patterns, and neonatal outcomes. *The Journal of Pediatrics*, *197*, 90-96. doi:10.1016/j.jpeds.2018.02.005.

Cunningham, J. A. (2020). Beliefs about cannabis at the time of legalization in Canada: Results from a general population survey. *Harm Reduction Journal, 17*, 1-4. doi:10.1186/s12954-019-0353-z.

D'Amico, E. J., Miles, J. N. & Tucker, J. S. (2015). Gateway to curiosity: Medical marijuana ads and intention and use during middle school. *Psychology of Addictive Behaviors, 29*, 613–619. doi:10.1037/adb0000094.

Davis, C., Hill, M. E. & Phillips, R. (2019). *Taxing cannabis.* Washington State: Institute on Taxation and Economic Policy Washington, https://itep.org/taxing-cannabis/.

Degenhardt, L., Whiteford, H. A., Ferrari, A. J., Baxter, A. J., Charlson, F. J., Hall, W. D.,… Engell, R. E. (2013). Global burden of disease attributable to illicit drug use and dependence: Findings from the global burden of disease study 2010. *The Lancet, 382*, 1564-1574. doi:10.1016/S0140-6736(13)61530-5.

Dellazizzo, L., Potvin, S., Athanassiou, M. & Dumais, A. (2020). Violence and cannabis use: A focused review of a forgotten aspect in the era of liberalizing cannabis. *Frontiers in Psychiatry, 11*, 971. doi:10.3389/fpsyt.2020.567887.

Department of Revenue Colorado. (2019). *2019 annual report. Marihuana enforcement division* (Colorado Department of Revenue ed.). Colorado. https://spl.cde.state.co.us/artemis/revserials/rev11internet/rev112019internet.pdf.

Di Forti, M. (2020). To legalize or not to legalize cannabis, that is the question! *World Psychiatry, 19*, 188. doi:10.1002/wps.20737.

Dilley, J. A., Richardson, S. M., Kilmer, B., Pacula, R. L., Segawa, M. B. & Cerdá, M. (2019). Prevalence of cannabis use in youths after legalization in Washington State. *JAMA Pediatrics, 173*, 192-193. doi:10.1001/jamapediatrics.2018.4458.

Doran, N., Strong, D., Myers, M. G., Correa, J. B. & Tully, L. (2021). Post-legalization changes in marijuana use in a sample of young California adults. *Addictive Behaviors, 115*, 106782. doi:10.1016/j.addbeh.2020.106782.

Dragone, D., Prarolo, G., Vanin, P. & Zanella, G. (2019). Crime and the legalization of recreational marijuana. *Journal of Economic Behavior & Organization*, 159, 488-501. doi:10.1016/j.jebo.2018.02.005.

Drug Enforcement Administration. (2020). *Domestic cannabis suppression / eradication program*. United States Drug Enforcement Administration. https://www.dea.gov/domestic-cannabis-suppression-eradication-program.

Eichelberger, A. H. (2019). Marijuana use and driving in Washington State: Risk perceptions and behaviors before and after implementation of retail sales. *Traffic injury prevention*, *20*, 23-29. doi:10.1080/15389588.2018.1530769.

ElSohly, M. A., Chandra, S., Radwan, M., Gon, C. & Church, J. C. (2021). A comprehensive review of cannabis potency in the USA in the last decade. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 6,* 603-606. doi:10.1016/j.bpsc.2020.12.016.

Estoup, A., Moise-Campbell, C., Varma, M. & Stewart, D. G. (2016). The impact of marijuana legalization on adolescent use, consequences, and perceived risk. *Substance Use & Misuse*, *51*, 1881-1887. doi:10.1080/10826084.2016.1200623.

Everson, E. M., Dilley, J. A., Maher, J. E. & Mack, C. E. (2019). Post-legalization opening of retail cannabis stores and adult cannabis use in Washington State, 2009–2016. *American Journal of Public Health, 109*, 1294-1301. doi:10.2105/AJPH.2019.305191.

Felson, J., Adamczyk, A. & Thomas, C. (2019). How and why have attitudes about cannabis legalization changed so much? *Social Science Research, 78,* 12-27. doi:10.1016/j.ssresearch.2018.12.011.

Firth, C. L., Maher, J. E., Dilley, J. A., Darnell, A. & Lovrich, N. P. (2019). Did marijuana legalization in Washington State reduce racial disparities in adult marijuana arrests? *Substance Use and Misuse, 54*, 1582-1587. doi:10.1080/10826084.2019.1593007.

Fleming, C. B., Guttmannova, K., Cambron, C., Rhew, I. C. & Oesterle, S. (2016). Examination of the divergence in trends for adolescent marijuana use and marijuana-specific risk factors in Washington State. *Journal of Adolescent Health, 59*, 269-275. doi:10.1016/j.jadohealth.2016.05.008.

Freisthler, B., Gaidus, A., Tam, C., Ponicki, W. R. & Gruenewald, P. J. (2017). From medical to recreational marijuana sales: Marijuana outlets and crime in an era of changing marijuana legislation. *The Journal of Primary Prevention*, *38*, 249-263. doi:10.1007/s10935-017-0472-9.

Ghinai, I., Pray, I. W., Navon, L., O'Laughlin, K., Saathoff-Huber, L., Hoots, B.,… Layer, M. (2019). E-cigarette product use, or vaping, among persons with associated lung injury—Illinois and Wisconsin, April–September 2019. *Morbidity and Mortality Weekly Report, 68*, 865. doi:10.15585/mmwr.mm6839e2.

Ghosh, T. S., Vigil, D. I., Maffey, A., Tolliver, R., Van Dyke, M., Kattari, L.,… Wolk, L. (2017). Lessons learned after three years of legalized, recreational marijuana: The Colorado experience. *Preventive Medicine, 104*, 4-6. doi:10.1016/j.ypmed.2017.02.021.

Gnofam, M., Allshouse, A. A., Stickrath, E. H. & Metz, T. D. (2020). Impact of marijuana legalization on prevalence of maternal marijuana use and perinatal outcomes. *American Journal of Perinatology, 37*, 059-065. doi:10.1055/s-0039-1696719.

Goodman, S., Wadsworth, E., Leos-Toro, C. & Hammond, D. (2020). Prevalence and forms of cannabis use in legal vs. illegal recreational cannabis markets. *International Journal of Drug Policy, 76*, 102658. doi:10.1016/j.drugpo.2019.102658.

Goodwin, R. D., Kim, J., Cheslack-Postava, K., Weinberger, A., Wu, M., Wyka, K. & Kattan, M. (2021). Trends in cannabis use among adults with children in the home in the United States, 2004–2017: Impact of state-level legalization for recreational and medical use. *Addiction*, *116*, 2770-2778. doi:10.1111/add.15472.

Gourdet, C., Giombi, K. C., Kosa, K., Wiley, J. & Cates, S. (2017). How four US states are regulating recreational marijuana edibles. *International Journal of Drug Policy, 43*, 83-90. doi:10.1016/j.drugpo.2017.01.018.

Government of Canada. (2018). Canadian cannabis survey 2018 summary. https://www.canada.ca/en/services/health/publications/drugs-health-products/canadian-cannabis-survey-2018-summary.html.

Government of Canada. (2020). Cannabis act (S.C. 2018, c. 16) an act respecting cannabis and to amend the controlled drugs and substances act, the criminal code and other acts 17 October 2018. Ottawa: Department of Justice. https://laws-lois.justice.gc.ca/PDF/C-24.5.pdf.

Government of Canada. (2021). *Canadian cannabis survey 2020: Summary.* https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/canadian-cannabis-survey-2020-summary.html#a2.

Graves, J., Whitehill, J. M., Miller, M., Brooks-Russell, A., Richardson, S. M. & Dilley, J. (2019). Employment and

marijuana use among Washington State adolescents before and after legalization of retail marijuana. *Journal of Adolescent Health, 65*, 39-45. doi:10.1016/j.jadohealth.2018.12.027.

Grewal, J. K. & Loh, L. C. (2020). Health considerations of the legalization of cannabis edibles. *Canadian Medical Association Journal, 192*, 1-2. doi:10.1503/cmaj.191217.

Grigsby, T. M., Hoffmann, L. M. & Moss, M. J. (2020). Marijuana use and potential implications of marijuana legalization. *Pediatrics in Review, 41*, 61-72. doi:10.1542/pir.2018-0347.

Guttmannova, K., Lee, C. M., Kilmer, J. R., Fleming, C. B., Rhew, I. C., Kosterman, R. & Larimer, M. E. (2016). Impacts of changing marijuana policies on alcohol use in the United States. *Alcoholism: Clinical and Experimental Research, 40*, 33-46. doi:10.1111/acer.12942.

Hall, K., Monte, A., Chang, T., Fox, J., Brevik, C., Vigil, D. I. & Van Dyke, M. (2018). Mental health–related emergency department visits associated with cannabis in Colorado. *Academic Emergency Medicine, 25*, 526-537. doi:10.1111/acem.13393.

Hall, W., Stjepanović, D., Caulkins, J., Lynskey, M., Leung, J., Campbell, G. & Degenhardt, L. (2019). Public health implications of legalising the production and sale of cannabis for medicinal and recreational use. *The Lancet, 394*, 1580-1590. doi:10.1016/S0140-6736(19)31789-1.

Hall, W. & Lynskey, M. (2020). Assessing the public health impacts of legalizing recreational cannabis use: The US experience. *World Psychiatry, 19*, 179-186. doi:10.1002/wps.20735.

Hammond, C., Chaney, A., Hendrickson, B. & Sharma, P. (2020). Cannabis use among US adolescents in the era of marijuana legalization: A review of changing use patterns, comorbidity, and health correlates. *International Review of Psychiatry, 32*, 221-234. doi:10.1080/09540261.2020.1713056.

Hammond, D., Wadsworth, E., Reid, J. & Burkhalter, R. (2021). Prevalence and modes of cannabis use among youth in Canada, England, and the US, 2017 to 2019. *Drug and Alcohol Dependence, 219*, 108505. doi:10.1016/j.drugalcdep.2020.108505.

Harper, S., Strumpf, E. C. & Kaufman, J. S. (2012). Do medical marijuana laws increase marijuana use? Replication study and extension. *Annals of Epidemiology, 22*, 207-212. doi:10.1016/j.annepidem.2011.12.002.

Harpin, S. B., Brooks-Russell, A., Ma, M., James, K. A. & Levinson, A. (2018). Adolescent marijuana use and perceived ease of access before and after recreational marijuana implementation in Colorado. *Substance Use & Misuse, 53*, 451-456. doi:10.1080/10826084.2017.1334069.

Hasin, D. S., Sarvet, A. L., Cerdá, M., Keyes, K. M., Stohl, M., Galea, S. & Wall, M. M. (2017). US adult illicit cannabis use, cannabis use disorder, and medical marijuana laws: 1991-1992 to 2012-2013. *JAMA Psychiatry, 74*, 579-588. doi:10.1001/jamapsychiatry.2017.0724.

Hawley, P., Gobbo, M. & Afghari, N. (2020). The impact of legalization of access to recreational cannabis on Canadian medical users with cancer. *BMC Health Services Research, 20*, 1-12. doi:10.1186/s12913-020-05756-8.

Heinrich, M. (2018). *The national cannabis economy.* Joint Economic Committee Democrats Report. https://www.jec.senate.gov/public/index.cfm/democrats/2018/12/jec-dems-report-the-national-cannabis-economy.

Huestis, M. A. (2007). Human cannabinoid pharmacokinetics. *Chemistry and Biodiversity, 4*, 1770. doi:10.1002/cbdv.200790152.

Hunt, P. & Pacula, R. L. (2017). Early impacts of marijuana legalization: An evaluation of prices in Colorado and Washington. *The Journal of Primary Prevention, 38*, 221-248. doi:10.1007/s10935-017-0471-x.

Instituto de regulación y control del cannabis. (2021). Nuevo precio del cannabis dispensado en farmacias a partir del 1 de febrero de 2021. https://www.ircca.gub.uy/nuevo-precio-del-cannabis-dispensado-en-farmacias-a-partir-del-1-de-febrero-de-2021-2/.

Isorna, M. (2017). Legalización del cannabis: Dos perspectivas. In Universidad de Vigo (Ed.), *Cannabis: Efectos, riesgos y beneficios terapéuticos* (pp. 177-216). Vigo: Universidad de Vigo: Servicio de publicaciones.

Jensen, E. & Roussell, A. (2016). Field observations of the developing legal recreational cannabis economy in Washington State. *International Journal of Drug Policy*, *33*, 96-101. doi:10.1016/j.drugpo.2016.02.023.

Jones, J., Jones, K. & Peil, J. (2018). The impact of the legalization of recreational marijuana on college students. *Addictive Behaviors*, 77, 255-259. doi:10.1016/j.addbeh.2017.08.015.

Keric, N., Hofmann, L. J., Babbitt-Jonas, R., Michalek, J., Dolich, M., Khoury, L.,... Cohn, S. M. (2018). The impact of marijuana legalization on vehicular trauma. *Cureus*, *10*. doi:10.7759/cureus.3671.

Kerr, D. C., Bae, H., Phibbs, S. & Kern, A. C. (2017). Changes in undergraduates' marijuana, heavy alcohol, and cigarette use following legalization of recreational marijuana use in Oregon. *Addiction, 112*, 1992-2001. doi:10.1111/add.13906.

Kerr, D. C., Bae, H. & Koval, A. L. (2018). Oregon recreational marijuana legalization: Changes in undergraduates' marijuana use rates from 2008 to 2016. *Psychology of Addictive Behaviors, 32*, 670. doi:10.1037/adb0000385.

Kharbanda, E. O., Vazquez-Benitez, G., Kunin-Batson, A., Nordin, J. D., Olsen, A. & Romitti, P. A. (2020). Birth and early developmental screening outcomes associated with cannabis exposure during pregnancy. *Journal of Perinatology, 40*, 473-480. doi:10.1038/s41372-019-0576-6.

Kilmer, B. (2017). Recreational cannabis minimizing the health risks from legalization. *New England Journal of Medicine, 376*, 705-707. doi:10.1056/NEJMp1614783.

Kilmer, B. & Neel, E. (2020). Being thoughtful about cannabis legalization and social equity. *World Psychiatry*, *19*, 194. doi:10.1002/wps.20741.

Krauss, M. J., Sowles, S. J., Sehi, A., Spitznagel, E. L., Berg, C. J., Bierut, L. J. & Cavazos-Rehg, P. A. (2017). Marijuana advertising exposure among current marijuana users in the U.S. *Drug and Alcohol Dependence, 174*, 192–200. doi:10.1016/j.drugalcdep.2017.01.017.

Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S.,… Yu, B. (2021). PubChem in 2021: New data content and improved web interfaces. *Nucleic Acids Research, 49*, 1388-1395. doi:10.1093/nar/gkaa971.

Kosterman, R., Bailey, J., Guttmannova, K., Jones, T., Eisenberg, N., Hill, K. & Hawkins, J. (2016). Marijuana legalization and parents' attitudes, use, and parenting in Washington State. *Journal of Adolescent Health, 59*, 450-456. doi:10.1016/j.jadohealth.2016.07.004.

Kropp, A. K., Nichols, S. D., Chung, D. Y., Kaufman, D. E., McCall, K. L. & Piper, B. J. (2020). Prescription opioid distribution after the legalization of recreational marijuana in Colorado. *International Journal of Environmental Research and Public Health, 17*, 3251. doi:10.3390/ijerph17093251.

Lane, T. J. & Hall, W. (2019). Traffic fatalities within US states that have legalized recreational cannabis sales and their neighbours. *Addiction, 114*, 847-856. doi:10.1111/add.14536.

Laqueur, H., Rivera-Aguirre, A., Shev, A., Castillo-Carniglia, A., Rudolph, K. E., Ramirez, J.,... Cerdá, M. (2020). The impact of cannabis legalization in Uruguay on adolescent cannabis use. *International Journal of Drug Policy, 80,* 102748. doi:10.1016/j.drugpo.2020.102748.

Lee, E., Pluym, I. D., Wong, D., Kwan, L., Varma, V. & Rao, R. (2020). The impact of state legalization on rates of marijuana uses in pregnancy in a universal drug screening population. *The Journal of Maternal-Fetal & Neonatal Medicine*, 1-8. doi:10.1080/14767058.2020.1765157.

Leos-Toro, C., Fong, G. T., Meyer, S. B. & Hammond, D. (2020). Cannabis health knowledge and risk perceptions among Canadian youth and young adults. *Harm Reduction Journal, 17*, 1-13. doi:10.1186/s12954-020-00397-w.

Mahamad, S. & Hammond, D. (2019). Retail price and availability of illicit cannabis in canada. *Addictive Behaviors, 90*, 402-408. doi:10.1016/j.addbeh.2018.12.001.

Mahamad, S., Wadsworth, E., Rynard, V., Goodman, S. & Hammond, D. (2020). Availability, retail price and potency of legal and illegal cannabis in Canada after recreational cannabis legalisation. *Drug and Alcohol Review, 39*, 337-346. doi:10.1111/dar.13069.

Maier, S. L., Mannes, S. & Koppenhofer, E. L. (2017). The implications of marijuana decriminalization and legalization on crime in the United States. *Contemporary Drug Problems*, 44, 125-146. doi:10.1177/0091450917708790.

Mair, C., Sumetsky, N., Kranich, C. & Freisthler, B. (2021). Availability of medical cannabis dispensaries and cannabis abuse/dependence-related hospitalizations in California. *Addiction*, *116*, 1908-1913. doi:10.1111/add.15420.

Mark, K. & Terplan, M. (2017). Cannabis and pregnancy: Maternal child health implications during a period of drug policy liberalization. *Preventive Medicine*, 104, 46-49. doi:10.1016/j.ypmed.2017.05.012.

Mason, W., Fleming, C., Ringle, J., Hanson, K., Gross, T. & Haggerty, K. (2016). Prevalence of marijuana and other substance use before and after Washington State's change from legal medical marijuana to legal medical and nonmedical marijuana: Cohort comparisons in a sample of adolescents. *Substance Abuse*, *37*, 330-335. doi:10.1080/08897077.2015.1071723.

Matheson, J. & Le Foll, B. (2020). Cannabis legalization and acute harm from high potency cannabis products: A narrative review and recommendations for public health. *Frontiers in Psychiatry, 11*, 1017. doi:10.3389/fpsyt.2020.591979.

Mauro, P. M., Santaella-Tenorio, J., Perlmutter, A. S., Hasin, D. S., Mauro, C. M. & Martins, S. S. (2019). Correct knowledge of medical cannabis legal status in one's own state: Differences between adolescents and adults in the United States, 2004–2013. *Addictive Behaviors, 88*, 23-28. doi:10.1016/j.addbeh.2018.07.021.

McBain, R. K., Wong, E. C., Breslau, J., Shearer, A. L., Cefalu, M. S., Roth, E.,… Collins, R. L. (2020). State medical marijuana laws, cannabis use and cannabis use disorder among adults with elevated psychological distress. *Drug and Alcohol Dependence, 215*, 108191. doi:10.1016/j.drugalcdep.2020.108191.

Melchior, M., Nakamura, A., Bolze, C., Hausfater, F., El Khoury, F., Mary-Krause, M. & Da Silva, M. A. (2019). Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis. *BMJ Open, 9*. doi:10.1136/bmjopen-2018-025880.

Mennis, J. & Stahler, G. J. (2020). Adolescent treatment admissions for marijuana following recreational legalization in Colorado and Washington. *Drug and Alcohol Dependence, 210*. doi:10.1016/j.drugalcdep.2020.107960.

Midgette, G. & Reuter, P. (2020). Has cannabis use among youth increased after changes in its legal status? A commentary on use of monitoring the future for analyses of changes in state cannabis laws. *Prevention Science, 21*, 137-145. doi:10.1007/s11121-019-01068-4.

Miller, A. M., Rosenman, R. & Cowan, B. W. (2017). Recreational marijuana legalization and college student

use: Early evidence. *SSM-Population Health*, *3*, 649-657. doi:10.1016/j.ssmph.2017.08.001.

Murray, R. M. & Hall, W. (2020). Will legalization and commercialization of cannabis use increase the incidence and prevalence of psychosis? *JAMA Psychiatry, 77*, 777-778. doi:10.1001/jamapsychiatry.2020.0339.

National Academies of Sciences, Engineering, and Medicine (2017). *The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research*. Washington: National Academies Press. doi:10.17226/24625.

Nazif-Muñoz, J. I., Oulhote, Y. & Ouimet, M. C. (2020). The association between legalization of cannabis use and traffic deaths in Uruguay. *Addiction, 115*, 1697-1706. doi:10.1111/add.14994.

Ng, J. H., Rice, K. K., Ananth, C. V. & Brandt, J. S. (2020). Attitudes about marijuana use, potential risks, and legalization: A single-center survey of pregnant women. *The Journal of Maternal-Fetal and Neonatal Medicine,* 1-9. doi:10.1080/14767058.2020.1858279.

Nicksic, N., Do, E. & Barnes, A. (2020). Cannabis legalization, tobacco prevention policies, and cannabis use in e-cigarettes among youth. *Drug and Alcohol Dependence*, *206*. doi:10.1016/j.drugalcdep.2019.107730.

Observatorio Español de las Drogas y las Adicciones. (2020). *Informe 2020. Alcohol, tabaco y drogas ilegales en España.* Madrid. https://pnsd.sanidad.gob.es/profesionales/sistemasInformacion/informesEstadisticas/pdf/2020OEDA-INFORME.pdf.

Observatorio Uruguayo de Drogas. (2019). *VII encuesta nacional sobre consumo de drogas en población general. informe de investigación año 2019*. Uruguay: Junta Nacional de Drogas (JND) - Uruguay. https://www.gub.uy/junta-nacional-drogas/sites/junta-nacional-drogas/files/documentos/publicaciones/VII_encuesta_nacional_drogas_poblacion_general_2019.pdf.

Okaneku, J., Vearrier, D., McKeever, R. G., LaSala, G. S. & Greenberg, M. I. (2015). Change in perceived risk associated with marijuana use in the United States from 2002 to 2012. *Clinical Toxicology, 53*, 151-155. doi:10.3109/15563650.2015.1004581.

Orens, A., Light, M., Lewandowski, B., Rowberry, J. & Saloga, C. (2018). Market size and demand for marijuana in Colorado 2017 market update. *Colorado Department of Revenue. Marijuana Enforcement Division,* 1-46. https://www.colorado.gov/pacific/sites/default/files/MED%20Demand%20and%20Market%20%20Study%20%20082018.pdf.

Palamar, J. J., Ompad, D. C. & Petkova, E. (2014). Correlates of intentions to use cannabis among US high school seniors in the case of cannabis legalization. *International Journal of Drug Policy, 25*, 424-435. doi:10.1016/j.drugpo.2014.01.017.

Parnes, J. E., Smith, J. & Conner, B. (2018). Reefer madness or much ado about nothing? Cannabis legalization outcomes among young adults in the United States. *International Journal of Drug Policy*, *56*, 116-120. doi:10.1016/j.drugpo.2018.03.011.

Pergam, S. A., Woodfield, M. C., Lee, C. M., Cheng, G., Baker, K. K., Marquis, S. R. & Fann, J. R. (2017). Cannabis use among patients at a comprehensive cancer center in a state with legalized medicinal and recreational use. *Cancer, 123*, 4488-4497. doi:10.1002/cncr.30879.

Plunk, A. D., Peglow, S. L., Harrell, P. T. & Grucza, R. A. (2019). Youth and adult arrests for cannabis possession after decriminalization and legalization of cannabis. *JAMA Pediatrics, 173*, 763-769. doi:10.1001/jamapediatrics.2019.1539.

Polen, M. R., Whitlock, E. P., Wisdom, J. P., Nygren, P. & Bougatsos, C. (2010). *Screening in primary care settings for illicit drug use: Staged systematic review for the United States Preventive Services Task Force.* https://www.ncbi.nlm.nih.gov/books/NBK33960/pdf/Bookshelf_NBK33960.pdf.

Postonogova, T., Xu, C. & Moore, A. (2020). Marijuana during labour: A survey of maternal opinions. *Journal of Obstetrics and Gynaecology Canada, 42*, 774-778. doi:10.1016/j.jogc.2019.10.030.

Public Safety Canada. (2017). *The price of cannabis in Canada*. Ottawa. Ontario. https://www.publicsafety.gc.ca/cnt/rsrcs/pblctns/2017-r005/index-en.aspx.

Rehm, J. & Manthey, J. (2020). Cannabis and public health: A global experiment without control. *World Psychiatry, 19*, 192. doi:10.1002/wps.20740.

República de la Presidencia Oriental de Uruguay. (2014). Decreto reglamentario CM/847, (2014). https://medios.presidencia.gub.uy/jm_portal/2014/noticias/NO_M908/decreto.pdf.

Rylander, M., Valdez, C. & Nussbaum, A. M. (2014). Does the legalization of medical marijuana increase completed suicide? *The American journal of drug and alcohol abuse*, *40*, 269-273. doi:10.3109/00952990.2014.910520.

Roberts, B. A. (2019). Legalized cannabis in Colorado emergency departments: A cautionary review of negative health and safety effects. *Western Journal of Emergency Medicine, 20*, 557. doi:10.5811/westjem.2019.4.39935.

Rotermann, M. (2019). Analysis of trends in the prevalence of cannabis use and related metrics in Canada. *Health reports*, *30*, 3-13. doi:10.25318/82-003-x201900600001-eng.

Rotermann, M. (2020). What has changed since cannabis was legalized. *Health Rep*, *31*, 11-20. http://fileserver.idpc.net/library/00002-eng.pdf.

Rusby, J. C., Westling, E., Crowley, R. & Light, J. M. (2018). Legalization of recreational marijuana and community

sales policy in Oregon: Impact on adolescent willingness and intent to use, parent use, and adolescent use. *Psychology of Addictive Behaviors, 32*, 84. doi:10.1037/adb0000327.

Russell, C., Rueda, S., Room, R., Tyndall, M. & Fischer, B. (2018). Routes of administration for cannabis use-basic prevalence and related health outcomes: A scoping review and synthesis. International *Journal of Drug Policy, 52*, 87-96. doi:10.1016/j.drugpo.2017.11.008.

Sahlem, G. L., Tomko, R. L., Sherman, B. J., Gray, K. M. & McRae-Clark, A. L. (2018). Impact of cannabis legalization on treatment and research priorities for cannabis use disorder. *International Review of Psychiatry, 30*, 216-225. doi:10.1080/09540261.2018.1465398.

Salomonsen-Sautel, S., Min, S. J., Sakai, J. T., Thurstone, C. & Hopfer, C. (2014). Trends in fatal motor vehicle crashes before and after marijuana commercialization in Colorado. *Drug and Alcohol Dependence*, *140*, 137-144. doi:10.1016/j.drugalcdep.2014.04.008.

Sandhu, H. S., Anderson, L. N. & Busse, J. W. (2019). Characteristics of Canadians likely to try or increase cannabis use following legalization for nonmedical purposes: A cross-sectional study. *Canadian Medical Association Journal Open, 7*, 399. doi:10.9778/cmajo.20190008.

Sarvet, A., Wall, M., Fink, D., Greene, E., Le, A., Boustead, A.,... Hasin, D. (2018). Medical marijuana laws and adolescent marijuana use in the United States: A systematic review and meta-analysis. *Addiction, 113*, 1003-1016. doi:10.1111/add.14136.

Sewell, R. A., Poling, J. & Sofuoglu, M. (2009). The effect of cannabis compared with alcohol on driving. *American Journal on Addictions, 18*, 185-193. doi:10.1080/10550490902786934.

Shi, Y., Cao, Y., Shang, C. & Pacula, R. L. (2019). The impacts of potency, warning messages, and price on preferences for cannabis flower products. *International Journal of Drug Policy, 74*, 1-10. doi:10.1016/j.drugpo.2019.07.037.

Shi, Y. & Liang, D. (2020). The association between recreational cannabis commercialization and cannabis exposures reported to the US national poison data system. *Addiction, 115*, 1890-1899. doi:10.1111/add.15019.

Sikorski, C., Leos-Toro, C. & Hammond, D. (2021). Cannabis consumption, purchasing and sources among young Canadians: The cannabis purchase and consumption tool (CPCT). *Substance Use and Misuse*, 1-9. doi:10.1080/10826084.2021.1879142.

Skelton, K. R., Hecht, A. A. & Benjamin-Neelon, S. E. (2020). Recreational cannabis legalization in the US and maternal use during the preconception, prenatal, and postpartum periods. *International Journal of Environmental Research and Public Health, 17*, 909. doi:10.3390/ijerph17030909.

Smart, R., Caulkins, J. P., Kilmer, B., Davenport, S. & Midgette, G. (2017). Variation in cannabis potency and prices in a newly legal market: Evidence from 30 million cannabis sales in Washington State. *Addiction, 112*, 2167-2177. doi:10.1111/add.13886.

Smart, R. & Pacula, R. L. (2019). Early evidence of the impact of cannabis legalization on cannabis use, cannabis use disorder, and the use of other substances: Findings from state policy evaluations. *The American Journal of Drug and Alcohol Abuse, 45*, 644-663. doi:10.1080/00952990.2019.1669626.

Sokoya, M., Eagles, J., Okland, T., Coughlin, D., Dauber, H., Greenlee, C. & Winkler, A. (2018). Patterns of facial trauma before and after legalization of marijuana in Denver, Colorado: A joint study between two Denver hospitals. *The American Journal of Emergency Medicine*, *36*, 780-783. doi:10.1016/j.ajem.2017.10.014.

Spindle, T. R., Bonn-Miller, M. O. & Vandrey, R. (2019). Changing landscape of cannabis: Novel products, formulations, and methods of administration. *Current Opinion in Psychology, 30*, 98-102. doi:10.1016/j.copsyc.2019.04.002.

Standeven, L. R., Scialli, A., Chisolm, M. S. & Terplan, M. (2020). Trends in cannabis treatment admissions in adolescents/young adults: Analysis of TEDS-A 1992 to 2016. *Journal of Addiction Medicine, 14*, 29-36. doi:10.1097/ADM.0000000000000586.

Statistics Canada. (2018). *Cannabis prices in Canada (cannabis for medical and non-medical purposes, per gram).* Goverment of Canada. https://surveys-enquetes.statcan.gc.ca/cannabis/.

Steigerwald, S., Cohen, B. E., Vali, M., Hasin, D., Cerda, M. & Keyhani, S. (2020). Differences in opinions about marijuana use and prevalence of use by state legalization status. *Journal of Addiction Medicine, 14*, 337. doi:10.1097/ADM.0000000000000593.

Steinemann, S., Galanis, D., Nguyen, T. & Biffl, W. (2018). Motor vehicle crash fatalities and undercompensated care associated with legalization of marijuana. *Journal of Trauma and Acute Care Surgery, 85*, 566-571. doi:10.1097/TA.0000000000001983.

Subbaraman, M. S. & Kerr, W. C. (2020). Subgroup trends in alcohol and cannabis co-use and related harms during the rollout of recreational cannabis legalization in Washington State. *International Journal of Drug Policy, 75*. doi:10.1016/j.drugpo.2019.07.003.

Takakuwa, K. M. & Schears, R. M. (2019). Why pregnant women may justifiably choose to use cannabis. *JAMA Internal Medicine, 179*, 120-120. doi:10.1001/jamainternmed.2018.6890.

The NORML Foundation. (2021). A voice for responsible marijuana consumers. https://norml.org/about-norml/.

United States Census Bureau. (2021). *State population totals and components of change: 2010-2019. Measuring America's*

People, Places, and Economy. https://www.census.gov/data/tables/time-series/demo/popest/2010s-state-total.html.

Veligati, S., Howdeshell, S., Beeler-Stinn, S., Lingam, D., Allen, P. C., Chen, L. & Grucza, R. A. (2020). Changes in alcohol and cigarette consumption in response to medical and recreational cannabis legalization: Evidence from US state tax receipt data. *International Journal of Drug Policy, 75*. doi:10.1016/j.drugpo.2019.10.011.

Wang, J. B., Ramo, D. E., Lisha, N. E. & Cataldo, J. K. (2016a). Medical marijuana legalization and cigarette and marijuana co-use in adolescents and adults. *Drug and Alcohol Dependence*, 166, 32-38. doi:10.1016/j.drugalcdep.2016.06.016.

Wang, G. S., Le Lait, M., Deakyne, S. J., Bronstein, A. C., Bajaj, L. & Roosevelt, G. (2016b). Unintentional pediatric exposures to marijuana in Colorado, 2009-2015. *JAMA Pediatrics, 170*. doi:10.1001/jamapediatrics.2016.0971.

Wang, G. S., Hall, K., Vigil, D., Banerji, S., Monte, A. & VanDyke, M. (2017). Marijuana and acute health care contacts in Colorado. *Preventive Medicine, 104*, 24-30. doi:10.1016/j.ypmed.2017.03.022.

Wang, G., Davies, S., Halmo, L., Sass, A. & Mistry, R. (2018). Impact of marijuana legalization in Colorado on adolescent emergency and urgent care visits. *Journal of Adolescent Health, 63*, 239-241. doi:10.1016/j.jadohealth.2017.12.010.

Weinberger, A. H., Zhu, J., Levin, J., Barrington-Trimis, J., Copeland, J., Wyka, K.,... Goodwin, R. D. (2020). Cannabis use among US adults with anxiety from 2008 to 2017: The role of state-level cannabis legalization. *Drug and Alcohol Dependence*, *214*. doi:10.1016/j.drugalcdep.2020.108163.

Wendelboe, A. M., Mathew, R., Chongsuwat, T., Rainwater, E., Wendelboe, M. A., Wickersham, E. & Chou, A. F. (2019). Is there less opioid abuse in states where marijuana has been decriminalized, either for medicinal or recreational use? A clin-IQ. *Journal of Patient-Centered Research and Reviews, 6*, 267. doi:10.17294/2330-0698.1704.

Whitehill, J. M., Harrington, C., Lang, C. J., Chary, M., Bhutta, W. A. & Burns, M. M. (2019). Incidence of pediatric cannabis exposure among children and teenagers aged 0 to 19 years before and after medical marijuana legalization in Massachusetts. *JAMA Network Open, 2*. doi:10.1001/jamanetworkopen.2019.9456.

Wilson, J., Freeman, T. P. & Mackie, C. J. (2019). Effects of increasing cannabis potency on adolescent health. *The Lancet Child and Adolescent Health, 3*, 121-128. doi:10.1016/S2352-4642(18)30342-0.

Wolf, L. A., Perhats, C., Clark, P. R., Frankenberger, W. D. & Moon, M. D. (2020). The perceived impact of legalized cannabis on nursing workload in adult and pediatric emergency department visits: A qualitative exploratory study. *Public Health Nursing, 37*, 5-15. doi:10.1111/phn.12653.

Yeung, M. E., Weaver, C. G., Janz, K., Haines-Saah, R. & Lang, E. (2020). Clearing the air: A study of cannabis-related presentations to urban Alberta emergency departments following legalization. *Canadian Journal of Emergency Medicine, 22*, 776-783. doi:10.1017/cem.2020

AUTHOR GUIDELINES

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Introduction

This section should be relatively brief, but provide the necessary and introductory explanation so that readers can understand the state of the issue prior to the research, and so that they can see the need for such research and how it was approached. This section should not include tables or figures, unless they are essential to the understanding of the text. It should include a final paragraph setting out clearly the objective(s) of the work.

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This section should clearly describe the methodology employed (selection of the sample, collection of data, data-collection or assessment instruments, timeframe, etc.). It should also identify the methods, assessment instruments, treatments, drugs used, apparatus, assessment system, statistical methods where they are new, new types of method, and so on. The author should specify the type of study (descriptive, epidemiological, experimental, clinical trial, etc.), system of assignment of participants to groups, randomization, etc. All submissions should indicate the reference of the Ethics Committee or Research Office which has approved the adequacy of this research to the corresponding ethical and legal framework. It is important that experimental studies and clinical trials are registered and the registration number is indicated in the trials database (e.g., Clinicaltrials.gov). Authors should state the type of statistical analysis used, describe it where it is new or little known, and indicate the statistics package employed. It is strongly recommended to indicate, when possible, the exact significance data obtained in the results (as opposed to formulas such as $p < .05$ or $p < .01$) as well as to include, also when possible, effect size statistics.

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Randomized clinical trials should follow the CONSORT guidelines (www.consort-statement.org) and studies with non-experimental designs should follow international guidelines (e.g.,STROBE https://www.strobe-statement.org/), to provide greater clarity for readers and reviewers. Likewise, effect size statistics will be presented.

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It is necessary to start with the general objective of the study. This section will emphasize the novel and important aspects of the study and the conclusions deriving from it. It should not repeat in detail the results presented in either the previous section or the introduction. The discussion should highlight the most important and controversial aspects and relate them to other relevant studies on the matter. Do not make assumptions if they are not supported by the data. Where appropriate, this section can include recommendations. Indicate the implications of the study's findings and its limitations (these will preferably be contained in a paragraph at the end of the article).

Acknowledgements

This section will be situated after the end of the article proper, and just before the Conflicts of interest. Where considered necessary, it will include the names of persons, institutions or bodies that have collaborated with or supported the research. It may include mention of those people who have helped in the preparation of the article, but not with the intensity required for being considered as authors. Sources of funding should also be indicated here.

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References

These will follow strictly the norms of the American Psychological Association [American Psychological Association (2020). *Publication Manual of the American Psychological Association* (7th ed.). Washington, DC. **http://www.apastyle.org**

Tables and Figures

These will appear at the end of the text, numbered, and each one on a different page. The place where they should be placed should be indicated in the text of the manuscript.

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- A copy of the revised manuscript.
- Another document setting out in detail the principal modifications made, together with authors' own comments on the main aspects of the review.

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4. A final document or galley proof will be generated, which the authors must also review.
5. A DOI will be assigned to the work and it will be published in advance online, until pages are assigned within a specific volume in which the manuscripts will finally be published.

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EDITORIAL

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