8TH INTERNATIONAL CONGRESS
53ª JORNADAS NACIONALES
SEVILLA 15/17 OCTUBRE 2026
SOCIDROGALCOHOL
Sociedad Científica Española de Estudios sobre el Alcohol, el Alcoholismo y las otras Toxicomanías

# PHARMACOLOGICAL POTENTIATION OF BDNF SIGNALLING AS A POSSIBLE STRATEGY TO REDUCE ALCOHOL BRAIN DAMAGE

Instituto de Estudios de las Adicciones
Universidad CEU San Pablo

CEU Universidad San Pablo

**Celia Ruiz-González[1]; Alba García-Guerra[1]; Elisa Rivera-Illades[1]; Héctor Cañeque-Rufo[1,2]; Teresa Fontán-Baselga[1]; José María Zapico[2]; Claire Coderch[2]; Beatriz De Pascual-Teresa[2]; Gonzalo Herradón[1,3,4]; Esther Gramage[1,3,4]**

[1] Departamento de Ciencias Farmacéuticas y de la Salud, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Urbanización Montepríncipe, 28660 Boadilla del Monte, Spain
[2] Departamento de Química y Bioquímica, Facultad de Farmacia, Universidad San Pablo-CEU, CEU Universities, Urbanización Montepríncipe, 28660 Boadilla del Monte, Spain
[3] Red de Investigación en Atención Primaria de Adicciones, Instituto de Salud Carlos III, MICINN y FEDER, Madrid, Spain
[4] Instituto Universitario de Estudios de las Adicciones, Universidad San Pablo-CEU, CEU Universities, Madrid, Spain

NEUROFAN

## BACKGROUND

Alcohol consumption during **adolescence** can lead to addiction and cognitive deficits associated with neurodegeneration. Neuroprotective factors have been shown to mitigate the harmful effects of drugs of abuse. In particular, **brain-derived neurotrophic factor (BDNF)** binds to the TrkB tyrosine kinase receptor, triggering receptor dimerization and autophosphorylation. This process activates multiple signaling pathways that promote neuroprotection, enhancing neuronal survival and modulating the addictive properties of alcohol[1]. The **tyrosine phosphatases SHP-1 and SHP-2** interact with the TrkB receptor and negatively regulate BDNF signaling by inhibiting TrkB autophosphorylation and activation. Therefore, **pharmacological inhibition of SHP-1 and SHP-2 may potentiate the BDNF signaling cascade** and amplify its neuroprotective effects. A rational drug design strategy led to the identification of FM45, a selective dual inhibitor with improved potency, favorable drug-like properties, and demonstrated blood–brain barrier penetration following oral administration in mice.

**FM45:** Small dual inhibitor of SHP-1 and SHP-2

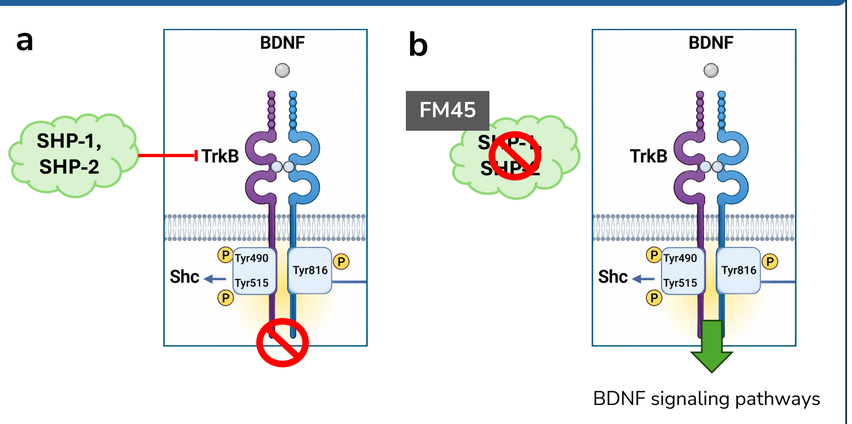


**Figure 1.** Schematic diagram of the activation of BNDF signaling pathways through the inhibition of SHP-1 and SHP-2 phosphatases.

## MATERIALS AND METHODS

### Acute Ethanol Intoxication

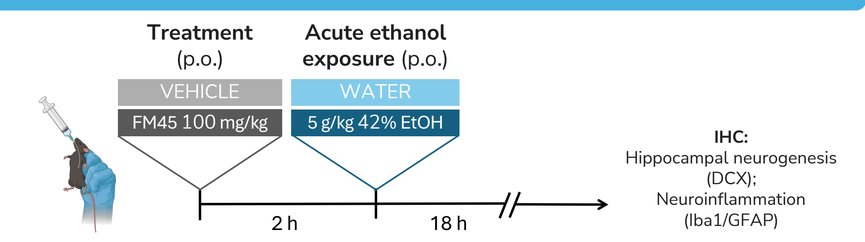


**Figure 2. Acute Ethanol Intoxication in adolescent mice[2].** Mice were administered with FM45 (100 mg/kg) or its vehicle by oral gavage 2 h before acute ethanol intoxication (5 g/kg, 42% v/v)[3] or water (control) (n = 5-6/group/sex).

### Binge-like ethanol drinking: Drinking in the Dark (DID)

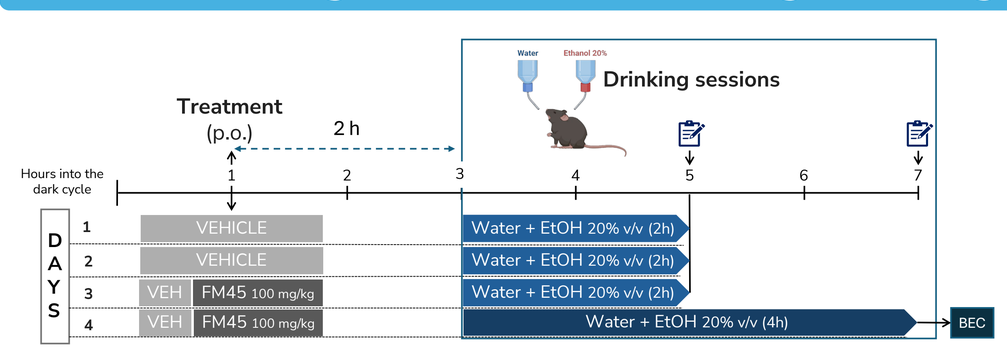


**Figure 3. Model of binge-like ethanol drinking: Drinking in the Dark (DID) procedure in adolescent mice[4].** Mice had access to ethanol and water for 2 h on days 1–3 and for 4 h on day 4. Vehicle (VEH) was administered on days 1–2, whereas FM45 (100 mg/kg) or vehicle were administered by oral gavage 2 h before the drinking session on days 3–4 (n = 12-15/group/sex). BEC: blood ethanol concentration.

## RESULTS

### Effects of SHP-1/SHP-2 inhibition with FM45 on hippocampal neurogenesis and neuroinflammation

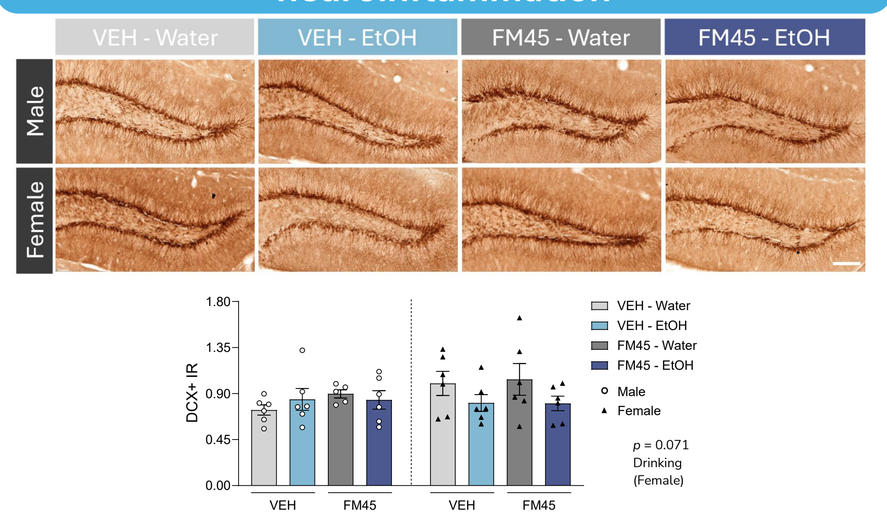


**Figure 4. Effects of FM45 on ethanol-induced effects on neural progenitor cells in the adolescent hippocampus.** Photomicrographs show doublecortin (DCX)-immunostained hippocampal sections, with quantification of the DCX immunoreactivity index (DCX+ IR area relative to the total SGZ area) in the dentate gyrus (n = 5–6/group) . Scale bar = 200 µm.

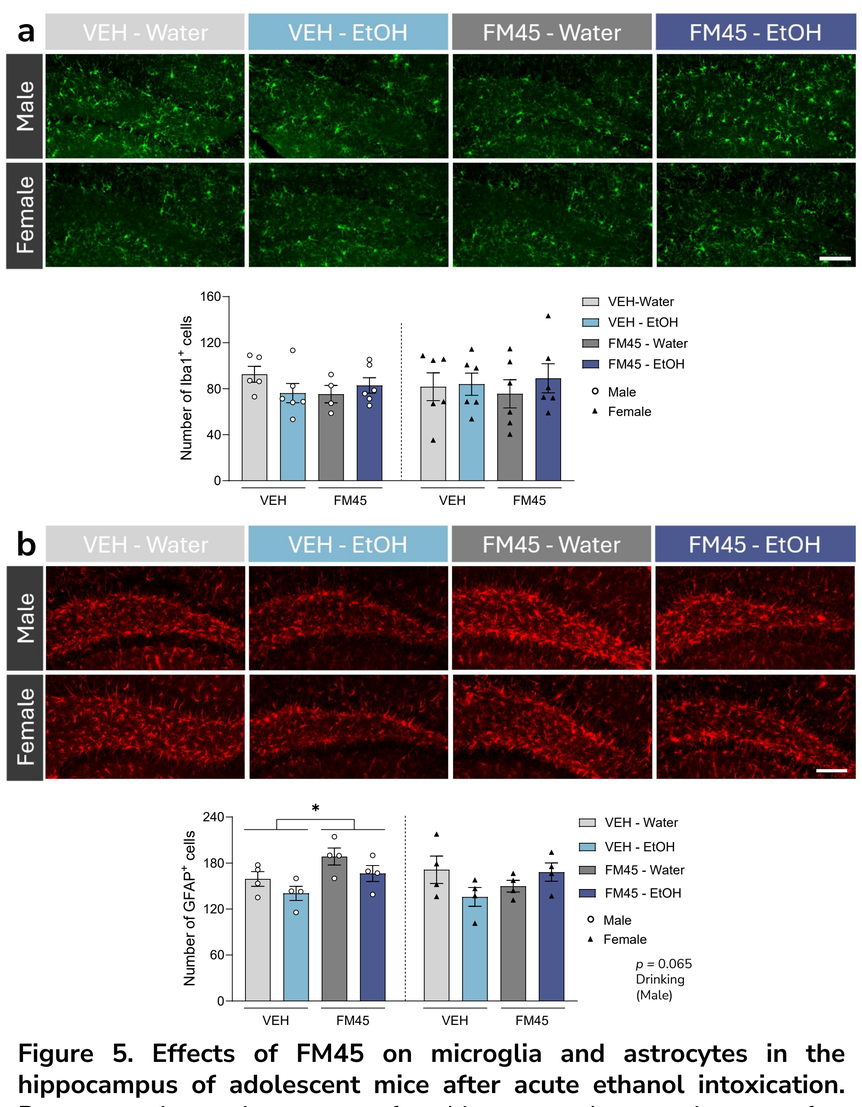


**Figure 5. Effects of FM45 on microglia and astrocytes in the hippocampus of adolescent mice after acute ethanol intoxication.** Representative images of hippocampal sections after immunofluorescence for (a) ionized calcium-binding adaptor molecule 1 (Iba1), a microglial marker (n = 5–6/group) and (b) glial fibrillary acidic protein (GFAP), an astrocytic marker (n = 4/group, preliminary data). Graphs show the quantification of Iba1- and GFAP-positive cells in the dentate gyrus of the hippocampus. Data are depicted as mean ± S.E.M. * $p < 0.05$ for treatment differences. Scale bar = 100 µm.

### FM45 decreases binge-like ethanol drinking (DID) in adolescent mice

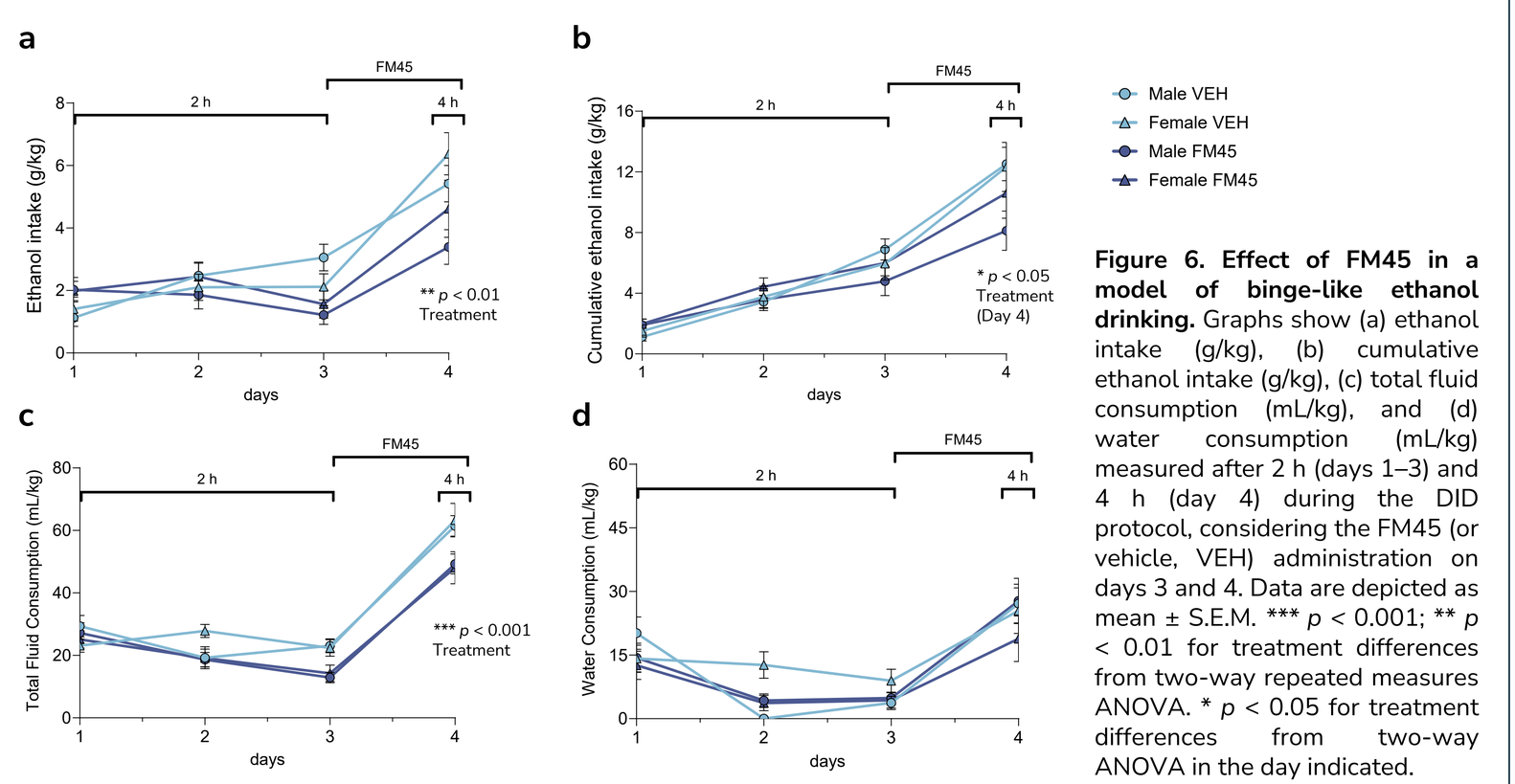


**Figure 6. Effect of FM45 in a model of binge-like ethanol drinking.** Graphs show (a) ethanol intake (g/kg), (b) cumulative ethanol intake (g/kg), (c) total fluid consumption (mL/kg), and (d) water consumption (mL/kg) measured after 2 h (days 1–3) and 4 h (day 4) during the DID protocol, considering the FM45 (or vehicle, VEH) administration on days 3 and 4. Data are depicted as mean ± S.E.M. *** $p < 0.001$; ** $p < 0.01$ for treatment differences from two-way repeated measures ANOVA. * $p < 0.05$ for treatment differences from two-way ANOVA in the day indicated.

### Sex differences in the effects of FM45 on sucrose consumption in adolescent mice.

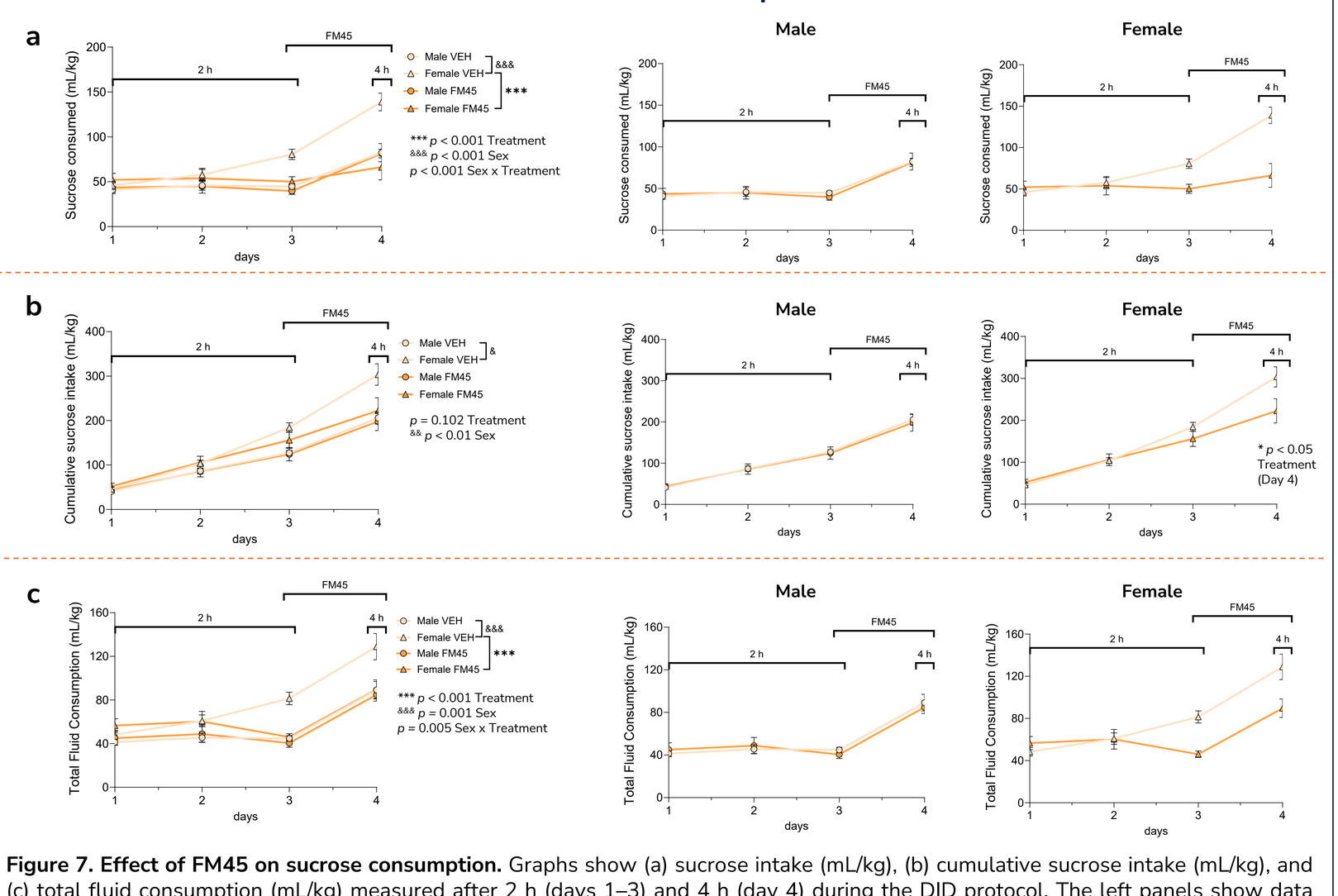


**Figure 7. Effect of FM45 on sucrose consumption.** Graphs show (a) sucrose intake (mL/kg), (b) cumulative sucrose intake (mL/kg), and (c) total fluid consumption (mL/kg) measured after 2 h (days 1–3) and 4 h (day 4) during the DID protocol. The left panels show data from both sexes combined, whereas the right panels show the data separated by sex. Data are depicted as mean ± S.E.M. *** $p \leq 0.001$ for treatment differences; &&& $p \leq 0.001$; && $p < 0.01$ for sex differences from two-way repeated measures ANOVA. Significance from post hoc analysis is indicated in the group legends when applicable. * $p < 0.05$ for treatment differences from one-way ANOVA in the day indicated (right panel).

## CONCLUSION

- Pretreating adolescent mice with FM45 prior to acute ethanol intoxication does not alter the status of neuronal progenitor cells in the hippocampal dentate gyrus.
- FM45 treatment significantly increases the number of GFAP+ cells in the hippocampus of male mice, without affecting the number of microglia in either sex.
- FM45 treatment reduces ethanol intake in a DID procedure for ethanol binge-drinking, in both male and female mice. This suggests that pharmacological inhibition of SHP-1 and SHP-2 phosphatases may be an effective strategy to reduce alcohol consumption.
- The data show important sex differences in the impact of FM45 on sucrose consumption, highlighting the need for additional research to better characterize the effect of this dual inhibitor of SHP-1 and SHP-2 on reward and consumption.

## REFERENCES

1. Cutuli, D., & Sampedro-Piquero, P. (2022). *Current neuropharmacology*, 20(11), 2202–2220. 2. Galan-Llario et al. (2023). *Neurotoxicology*, 94, 98–107. 3. Bishir, M. et al. [Poster presentation number T021]. *Alcohol: Clinical and Experimental Research*, 49(Suppl. 1), 339. 4. Fernández-Calle et al. (2018). *Neuropharmacology*, 137, 86-95.

## ACKNOWLEDGEMENTS

This work was supported by National Plan on Drug abuse, Ministerio de Sanidad of Spain (grant 2024I044 to. E.G.) and by ISCIII Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS), Red de Investigación en Atención Primaria de Adicciones (RIAPAd; grant RD24/0003/0011 to G.H.). Celia Ruiz González is supported by a CEU scholarship.

MINISTERIO DE SANIDAD · SECRETARÍA GENERAL DE SANIDAD · DELEGACIÓN DEL GOBIERNO PARA EL PLAN NACIONAL SOBRE DROGAS
RIAPAd Atención Primaria en Adicciones
Instituto de Salud Carlos III
CEU