

LETTER TO THE EDITOR

Impact of substance use on intestinal permeability in patients with schizophrenia

Impacto del consumo de sustancias sobre la permeabilidad intestinal en pacientes con esquizofrenia

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There is increasing evidence of a bidirectional relationship between the intestinal microbiota and the brain, known as the microbiome-gut-brain axis (Salavrakos et al., 2021). Patients with severe mental disorders such as schizophrenia commonly present alterations in the gastrointestinal microbiome (Borkent et al., 2022). Many factors, including substance use, can alter intestinal permeability and affect the inflammatory system, which is in turn related to the central nervous system (Wiedlocha et al., 2021). The effects of smoking, for example, can cause changes in the microbiota, increases in mucosal permeability, and poor immune responses at this level (Gui et al., 2021). However, in some diseases, such as ulcerative colitis, nicotine has been described as potentially acting as a protective factor, reducing inflammation and improving permeability (McGilligan et al., 2007), while cannabis has been shown

to play a regulatory role in inflammation and permeability of the mucosa of the gastrointestinal tract (Kienzl et al., 2020). On the other hand, alcohol use can contribute to the deterioration of the mucosa and increase the permeability of the barrier (Simeonova et al., 2018). In patients with schizophrenia, however, the impact of toxin consumption on the gut-brain axis has barely been investigated. This study therefore aimed to analyze the impact that the consumption of toxins (tobacco, cannabis and alcohol) has on intestinal permeability in patients with schizophrenia.

A cross-sectional study was performed of outpatients from Health Area IV (Oviedo) diagnosed with schizophrenia (DSM-5). Assessment was carried out through an ad hoc questionnaire (demographic and clinical information), the Positive and Negative Schizophrenia Syndrome Scale (PANSS), the Calgary Depression Scale (CDS), the CGI-S, the International Physical Activity Questionnaire

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(IPAQ), adherence to Mediterranean diet, and the Bristol Scale for assessment of constipation. Indirect markers of bacterial translocation and plasma inflammation were analyzed: soluble CD14 (sCD14), lipopolysaccharide-binding protein (LBP) and C-reactive protein (CRP). Non-normal distribution of these markers was checked using the Kolmogorov-Smirnov test, statistical correlations were analyzed using Spearman, Mann-Whitney U tests, and linear and logistic regressions were performed. The study was approved by the local research ethics committee.

Of the total sample of 98 patients [mean age (SD) = 41.97 (12.29) years; men: 60.2%], 36.7% reported being smokers [mean daily cigarette consumption (SD) = 16.31 (8.06)], 20.4% drank alcohol (≥ 1 SDU/week) [mean consumption (SD) = 0.81 (2.30)] and 14.3% reported having used cannabis in the previous month. Regarding the analytical parameters, the following mean (SD) values were obtained: sCD14 [(2.40 (0.68) $\mu\text{g}/\text{dl}$], LBP [(15.00 (5.40) $\mu\text{g}/\text{dl}$)] and CRP [(0.60) (1.10) mg/dl].

Significant correlations were found between sCD14 and LBP ($r = 0.283$; $p = 0.005$) and CRP ($r = 0.310$; $p = 0.002$) and between LBP and CRP ($r = 0.576$; $p < 0.001$). As for the relationship between permeability markers and sociodemographic variables, there were no differences by sex, nor correlation with age ($p > 0.05$). Furthermore, no significant relationships were identified with age at diagnosis, years of disease evolution, body mass index, metabolic syndrome, antipsychotic treatment, nor with psychometric scales, including questionnaires on adherence to the Mediterranean diet and physical activity. Constipation was associated with a lower concentration of sCD14 ($U = 579$; $p = 0.031$).

In terms of substance use, differences close to statistical significance were only found between cannabis users and non-cannabis users in sCD14 (mean (SD) = 2.77 (0.84) vs 2.34 (0.63); $U = 388$; $p = 0.054$), but not in LBP or CRP.

Nor were differences identified in any of these markers on the basis of tobacco or alcohol use.

The linear regression with sCD14 as a dependent variable, and age, smoking, and the statistically significant variables (LBP, CRP, constipation, cannabis use) as independent variables yielded a predictive model which explained 12.1% of the variance ($F = 6.248$; $p = 0.003$). Cannabis use and the LBP marker, but not CRP, were the only variables associated with sCD14 levels in the model (Table 1).

A logistic regression was subsequently performed with cannabis use as the dependent variable, and sex, age, and statistically significant variables (adherence to the Mediterranean diet, constipation, tobacco, sCD14) as independent variables. In this case, smoking, sCD14 concentration, and weaker dietary adherence were associated with cannabis use in patients with schizophrenia (Table 1).

As conclusions of the study, our findings do not allow tobacco and alcohol use to be associated with an impact on the degree of intestinal permeability in patients with schizophrenia. Nevertheless, patients who habitually use cannabis may present greater alterations of their intestinal mucosa, identified by increased concentrations of the bacterial translocation marker sCD14, regardless of the degree of systemic inflammation.

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Table 1
Variables included in the regression models

Factors associated with sCD14								
	B	Standard error	Beta	t	p	Lower bound	Upper bound	
Cannabis use	0.538	0.186	0.289	2.899	0.005	0.169	0.907	
LBP	0.031	0.012	0.247	2.479	0.015	0.006	0.055	
Factors associated with cannabis use								
	B	Standard error	Wald	gl	p	Exp (B)	Lower bound	Upper bound
Mediterranean diet adherence questionnaire	-0.349	0.157	4.935	1	0.026	0.705	0.518	0.960
Tobacco	2.978	0.905	10.832	1	0.001	19.654	3.336	115.808
sCD14	1.330	0.507	6.889	1	0.009	3.780	1.400	10.203

Note. sCD14 = soluble CD14; LBP = lipopolysaccharide-binding protein.

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Conflict of interests

On behalf of all authors, the first signatory of the manuscript declares no conflict of interest in relation to this article.

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