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CE - LETTER TO THE EDITOR

COVID-19 and related symptoms in patients under disulfiram for alcohol use disorder

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Dear Editor,

COVID-19, a severe acute respiratory syndrome (SARS) due to a new SARS coronavirus (SARS-CoV-2) infection, caused a global pandemic with > 58 million cases and nearly 1.4 million deaths so far.

There is no established treatment for SARS-CoV-2. Disulfiram, a hepatic aldehyde dehydrogenase inhibitor approved for alcohol aversion therapy, may inhibit the SARS coronavirus proteases [1], but clinical evidence on SARS-CoV-2 is lacking [2].

We explored whether patients under disulfiram for alcohol use disorder (AUD) had reduced COVID-19 and related symptoms.

This is a multicenter observational telephone interview on patients aged > 18 with AUD living in Northern Italy (Lombardy, Veneto, Emilia Romagna, Piedmont, and Liguria regions), where the first COVID-19 peak was more severe in spring 2020.

Patients were asked on laboratory-confirmed COVID-19 (SARS-CoV-2 positivity by polymerase chain reaction, PCR; primary outcome), hospitalization related to COVID-19, pneumonia, and symptoms compatible with COVID-19 (fever, dyspnea; secondary outcomes) [3] from February 21st to May 31st, 2020, demographic and clinical covariates, disulfiram treatment and dosage.

Fisher's exact test was applied to categorical variables. For continuous variables, Student's *t* test and Mann–Whitney *U* test were applied. Multivariate logistic regression backward models explored the effect of disulfiram and the covariates, which significantly differed between groups at baseline (i.e., age, liver disease, and opioid abuse), on symptoms compatible with COVID-19 (fever, dyspnea, either fever, or dyspnea; binary dependent variable). $P < 0.05$ (two-tailed) was the significance threshold.

We included 1297 patients (age 50.1 ± 10.3, range 21–79; 881 men, 418 women), of whom 752 under disulfiram (dosage 241.7 ± 112.3, median 200, range 100–800 mg; disulfiram treatment duration 14.0 ± 9.3, median 10, range 3–120 months) and 545 not taking disulfiram (control group). Among baseline demographic and clinical covariates, age, liver disease, and opioid abuse significantly differed between groups (Table 1).

Laboratory-confirmed COVID-19 ($N = 10$, 0.77%), hospitalization due to confirmed COVID-19, and pneumonia were less, but not significantly, common in disulfiram group. Symptoms compatible with COVID-19 were significantly less common in disulfiram group (Table 1).

The multivariate logistic regression model showed significantly reduced risk of fever (unadjusted odds ratio, OR 0.39 [95% CI 0.18–0.81]; adjusted OR: 0.37 [95% CI 0.18–0.77], $p = 0.007$), dyspnea (unadjusted OR 0.50 [95% CI 0.31–0.82]; adjusted OR 0.53 [95% CI 0.32–0.85], $p = 0.009$), either fever or dyspnea (unadjusted OR 0.44 [95% CI 0.28–0.72]; adjusted OR 0.45 [95% CI 0.29–0.70], $p < 0.001$) for disulfiram group, while the covariates that

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Table 1 Demographic and clinical characteristics of the participants and outcome measures

Variables	Disulfiram ($N=752$)	Control ($N=545$)	p value
Baseline—demographic			
Gender—M/W (%)	501/251 (66.6/33.4%)	380/165 (69.7/30.3%)	0.25
Age (years)[a]	49.5 ± 10.3, 50	50.8 ± 10.3, 51	0.03*
BMI (Kg/m^2)[a]	25.1 ± 4.1, 24.6	25.0 ± 4.1, 24.5	0.6
Baseline—clinical—no. (%)			
Diabetes	28 (3.7%)	29 (5.3%)	0.17
Hypertension	108 (14.4%)	68 (12.5%)	0.37
COPD	18 (2.4%)	19 (3.5%)	0.31
Liver disease	43 (5.7%)	71 (13.0%)	< 0.001*
Heart disease	25 (3.3%)	28 (5.1%)	0.12
Smoke	390 (51.9%)	266 (48.8%)	0.29
Opioid abuse	19 (2.5%)	28 (5.1%)	0.016*
Outcome—no. (%)			
Laboratory-confirmed COVID-19	5 (0.66%)	5 (0.92%)	0.75
Hospitalization due to confirmed COVID-19[b]	4 (0.53%)	4 (0.73%)	0.73
Pneumonia	4 (0.53%)	8 (1.47%)	0.14
Symptoms compatible with COVID-19			
Fever	11 (1.46%)	22 (4.04%)	0.006*
Dyspnea	30 (3.99%)	40 (7.34%)	0.0012*
Either fever or dyspnea	34 (4.52%)	52 (9.54%)	< 0.001*

BMI body mass index, *COPD* chronic obstructive pulmonary disease

[a]Mean ± SD, median

[b]All patients who were hospitalized due to confirmed COVID-19 were also reported as laboratory-confirmed COVID-19 cases

*Significant between-group comparison

differed at baseline (age, liver disease, opioid abuse) were not significant.

Among liver disease patients ($N=114$), none in disulfiram group reported laboratory-confirmed COVID-19 or related hospitalization (control: $N=1$), pneumonia (control: $N=4$), and symptoms compatible with COVID-19 (control: fever, $N=6$; dyspnea, $N=4$), but the difference was not significant.

We found no significant difference for laboratory-confirmed COVID-19, related hospitalization, or pneumonia, but symptoms compatible with COVID-19 were significantly less common in disulfiram group. Multivariate model confirmed disulfiram to carry significantly reduced risk of symptoms compatible with COVID-19.

We found 0.77% of the cohort to have laboratory-confirmed COVID-19 positivity, in line with Northern Italy prevalence at the time of the study (i.e., around 0.9%) [4], suggesting our patients to be representative of the general population. Our sample had slightly higher mean age and prevalence of men than the general population, but the risk of symptomatic SARS-CoV-2 infection is similar among adults, regardless of age [3].

The study failed the primary outcome, but laboratory-confirmed COVID-19 percentage was smaller in disulfiram group. The reduced PCR availability during the first COVID-19 peak might have contributed to this finding. In accordance with estimates of Italian population infected by SARS-CoV-2 [5], symptoms compatible with COVID-19 were 10 times more common than laboratory-confirmed positivity in controls, suggesting this secondary outcome may represent a good proxy of COVID-19 cases [3]. Non-SARS-CoV-2 viral infections should not be a bias, being equally distributed between groups [3].

None of the liver disease patients under disulfiram had laboratory-confirmed COVID-19 and symptoms compatible with COVID-19, but the small size prevented a robust statistical analysis. These data might be of interest, because altered liver function tests were reported to be highly prevalent in COVID-19 patients and associated with worse outcome [6].

The study strengths are the large sample size, similar baseline characteristics, no influence of covariates that differed between groups. The limitations are the retrospective observational design, the small number of PCR-confirmed cases that might have resulted in missing mild/asymptomatic SARS-CoV-2 infections [3], and not having considered other symptoms (i.e., myalgia, arthralgia, fatigue, and headache) as compatible with COVID-19.

Because of the discrepancy between patients with and without laboratory confirmed COVID-19, our data should be considered preliminary and should be confirmed in further studies. Disulfiram might be considered in patients with AUD and high risk of COVID-19 severe course. Future phase II/III randomized controlled trials should explore disulfiram efficacy on COVID-19 in the general population, since this drug may represent a cost-effective option for people with limited access to vaccines and specific antiviral drugs.

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Compliance with ethical standards

Conflict of interest No conflict declared.

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