Micronized/ultramicronized palmitoylethanolamide improves depression and fatigue in coronavirus disease 2019 (COVID-19) survivors

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Coronavirus disease 2019 (COVID-19) may lead to neuropsychiatric sequelae. Palmitoylethanolamide (PEA) is an anti-inflammatory and neuroprotective amide used in depressive syndromes. Here we investigate whether micronized/ultramicronized (m/um) PEA improves neuropsychiatric sequelae in COVID-19 survivors. Patients evaluated at our post-COVID-19 outpatient clinic between February and August 2021 and presenting neuropsychiatric manifestations ($n = 98$) were offered treatment with m/umPEA 600 mg twice daily for 3 months. Those accepting m/umPEA therapy ($n = 57$) were compared with those who did not ($n = 41$), in terms of depression, fatigue, chronic pain and subjective well-being, through validated scales administered pre- and posttreatment. The two groups did not differ in terms of demographics, comorbidities, psychiatric history, antidepressant therapy, acute COVID-19 severity and baseline neuropsychiatric status. Patients receiving m/umPEA showed a greater improvement in depression and fatigue (both $P < 0.05$). Conversely, no association was found with changes in chronic pain or subjective well-being. At multivariable logistic regression, m/umPEA predicted neuropsychiatric improvement independently of age, sex and baseline neuropsychiatric status. Worse pretreatment fatigue and subjective well-being identified those who most likely benefited from treatment. In conclusion, despite its retrospective nature, our study suggests that m/umPEA may improve depression and fatigue in COVID-19 survivors, justifying future research in this setting. *Int Clin Psychopharmacol* **XXX: XXXX–XXXX**

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Introduction

Coronavirus disease 2019 (COVID-19) has been threatening human health and public safety since late 2019. Besides respiratory implications, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can lead to neurological consequences, mostly caused by viral-induced immune activation and inflammation within the central nervous system (CNS) (Mazza *et al.*, 2021). Increased levels of neurofilament light chain, a marker of neuro-axonal damage, were found in the plasma of COVID-19 patients during acute disease (De Lorenzo *et al.*, 2021a), supporting the potential neurotoxicity of SARS-CoV-2-induced immune activation (Ding *et al.*, 2004; Seiden, 2004; Wheeler *et al.*, 2017; Wu *et al.*, 2020). Such evidence may also disclose potential pathogenic clues underlying the neuropsychiatric long-term sequelae of COVID-19 (De Lorenzo *et al.*, 2020; Mazza *et al.*, 2020). Indeed, a significant proportion of COVID-19 survivors develop chronic pain, fatigue and subjective decrease of well-being following recovery, commonly referred to as 'long COVID' (De Lorenzo *et al.*, 2020; Mazza *et al.*, 2020; Benedetti *et al.*, 2021). Neuropsychiatric complaints are a major feature of long-COVID and may range from cognitive dysfunction,

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attention and concentration deficit and memory issues to mood disorders, anxiety, and depression. Potential underlying mechanisms encompass neuroinflammation, vascular impairment induced by coagulopathy and endothelial dysfunction and neuronal injury (Mazza *et al.*, 2022a; Davis *et al.*, 2023). The exact pathophysiology, however, remains elusive. Likely owing to the limited knowledge of their molecular mechanisms, effective therapeutic strategies for COVID-19 neuropsychiatric sequelae have not yet been clearly identified. Some preliminary reports suggested a rapid response to selective serotonin reuptake inhibitors in post-COVID depression as well as a significant effect of cognitive remediation therapy on post-COVID persistent cognitive impairments (Mazza *et al.*, 2022b; Palladini *et al.*, 2022). However, notwithstanding these sparse proof of concept studies, the treatment of post-COVID neuropsychiatric complaints still represents an important unmet clinical need given the remarkably high prevalence of these manifestations.

Palmitoylethanolamide (PEA) is a natural amide of ethanolamine and palmitic acid and is part of the *N*-acylethanolamine family of bioactive lipids (Calignano *et al.*, 2001). PEA is naturally present in the CNS and has antinociceptive properties in several animal models (Lambert *et al.*, 2002; D'Agostino *et al.*, 2012; Crupi *et al.*, 2013; Coppola and Mondola, 2014). It also prevents neurotoxicity and neurodegeneration (D'Agostino *et al.*, 2012; Esposito *et al.*, 2012) and inhibits peripheral inflammation (Lo Verme *et al.*, 2005; Esposito *et al.*, 2011). PEA solubility is limited when used in its naïve form. For this reason, PEA for oral administration is micronized (mPEA) and/or ultramicronized (umPEA) to increase its bioavailability (Impellizzeri *et al.*, 2014). The micronization process, by reducing particle size, improves PEA absorption and distribution, increasing its biological efficacy, making it a promising candidate for clinical use (Impellizzeri *et al.*, 2014; Petrosino and di Marzo, 2017; Petrosino *et al.*, 2018). m/umPEA has been successfully used in the clinical setting for the treatment of chronic pain and depression syndromes poorly responsive to standard therapies (Cobellis *et al.*, 2011; Truini *et al.*, 2011; Gatti *et al.*, 2012). Given its immunomodulatory, antiinflammatory, neuroprotective and pain-relieving properties (Paladini *et al.*, 2016) and in light of its multifaceted therapeutic profile that may share molecular targets with COVID-19-associated neuronal damage, the use of m/umPEA in patients experiencing neuropsychiatric sequelae following COVID-19 seems reasonable. However, data on the effects of PEA in patients recovered from COVID-19 are scarce (Raciti *et al.*, 2022). In the post-COVID-19 outpatient clinic of our institution, m/umPEA has been empirically prescribed by physicians to patients presenting with chronic pain, depression or fatigue at 3 months after hospital discharge. This study addresses the hypothesis that m/umPEA may improve neuropsychiatric sequelae in COVID-19 survivors. Here we report our experience and compare neuropsychiatric clinical outcomes of patients who received m/umPEA for at least 3 months with those who did not take PEA.

Experimental procedures

Design and study population

This retrospective observational study is a substudy of the more extensive COVID-BioB study, implemented at San Raffaele University Hospital in Milan, Italy (Ciceri *et al.*, 2020). Adult patients previously hospitalized for COVID-19 at San Raffaele University Hospital were enrolled in the COVID-BioB study and evaluated at the post-COVID-19 outpatient clinic of the same institution at 1, 3 and 6 months postdischarge (Rovere Querini *et al.*, 2020). Inclusion criteria for the present study were: (1) having been evaluated at the clinic during the study period (i.e. between 15 February and 31 August 2021) and (2) having been proposed therapy with m/umPEA (Normast MPS, Epitech Group SpA, Milan, Italy) by the examining physician at the 3-month visit. PEA treatment was suggested by the visiting physician to patients presenting with an altered neuropsychiatric status including depression traits, fatigue or chronic pain refractory to standard therapy. One capsule to be taken orally, containing 600 mg of m/umPEA, twice a day was the recommended dose to be continued for 3 months, specifically from the 3-month postdischarge visit to the following 6-month visit. Patients who chose to receive the proposed treatment were compared to those who did not, thereby constituting the control group. Both groups were reevaluated at the 6-month visit and included in the present analysis. No preexisting chronic therapy was discontinued during PEA treatment. Specifically, all patients took PEA in addition to ongoing therapy, including psychopharmacological drugs. All patients signed written informed consent. The COVID-BioB study protocol conforms to the declaration of Helsinki, was approved by the Hospital Ethics Committee, namely Comitato Etico Ospedale San Raffaele (CE-OSR, protocol no. 34/int/2020) and registered on ClinicalTrials.gov (NCT04318366).

Evaluation of neuropsychiatric sequelae

A comprehensive evaluation of physical, neurological, cognitive and mental health was performed by a multidisciplinary team consisting of internists, neurologists and psychiatrists, as described elsewhere (De Lorenzo *et al.*, 2020; Rovere Querini *et al.*, 2020; De Lorenzo *et al.*, 2021b). At both 3- and 6-month visits, patients were evaluated through validated self-report scales: a 0–10 visual analog scale (VAS) for chronic pain (VAS-pain), a 0–100 VAS scale for subjective well-being (VAS-general), the Zung Self-Rating Depression Scale (ZSDS) for depression and the Fatigue Severity Scale (FSS) and the

Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls questionnaire (SARC-F) for fatigue (Zung *et al.*, 1965; Krupp *et al.*, 1989; Malmstrom *et al.*, 2016; De Lorenzo *et al.*, 2021a; Mazza *et al.*, 2022c).

For VAS-pain 0 means no pain and 10 means worst imaginable pain, while for VAS-general, 0 means worst imaginable health status and 100 means best imaginable health status.

ZSDS consists of a 20-item scale assessing the full spectrum of depressive symptoms, where the examinee rates the frequency of each symptom using a scale of descriptors, specifically none or a little of the time/some of the time/good part of the time/most of the time (scored respectively from 1 to 4) (Hunter and Murphy, 2011). A cutoff index of ≥30 was chosen to indicate the presence of psychopathology, where higher scores indicate worse depression.

SARC-F consists of five components, namely strength, walking, rising from a chair, climbing stairs and falls. Each component is assigned a score ranging from 0 to 2, reflecting the level of difficulty or inability in performing each activity (0 indicating no difficulty and 2 indicating a lot of difficulty or inability) and the number of falls (ranging from no falls to four or more). Consequently, the overall scale score ranges from 0 to 10, with 0 representing the 'best' status and higher scores indicating a worse condition. (ZUNG, 1965)

FSS questionnaire includes nine statements designed to assess the severity of fatigue symptoms by asking patients to choose for each item a number from 1 to 7, according to which best reflects their experience. We applied the standard cutoff of ≥4 to identify clinically significant fatigue, higher scores corresponding to worse status.

Variables

Demographical data (i.e. age, sex), comorbidities [i.e. hypertension (HTN), coronary artery disease (CAD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), active cancer, psychiatric disorders], preexisting antidepressant drugs, as well as length of hospital stay (LoS), and transfer to the ICU were extracted for all patients at the first visit. At both the 3- and 6-month visits, scores obtained at the VAS-pain scale, VAS-general scale, ZSDS, FSS and SARC-F were collected. Prior to analysis, data were cross-checked with medical charts and verified by data managers and clinicians for accuracy.

Outcomes

To assess changes in all scales from the 3- to the 6-month visit both in patients who took PEA and those who did not, scores at 6 months were subtracted with scores at 3 months in a pairwise manner, obtaining a delta (Δ) score for each scale ($\Delta\text{score} = \text{score}_{6\text{ months}} - \text{score}_{3\text{ months}}$). Accordingly, for ZSDS, SARC-F, FSS and VAS-pain positive values indicated worsening while negative values indicated *improvement*. On the other hand, for VAS-general, positive values indicated *improvement* while negative values indicated worsening. Improvement in each domain (i.e. depression, fatigue, perception of general health status and chronic pain) was identified as a decrease of at least one unit for ZSDS, SARC-F, FSS and VAS-pain, and as an increase of at least one unit for VAS-general. For the purpose of the analysis, improvement of the neuropsychiatric status or global improvement was defined as an improvement in at least three scales (i.e. VAS-general, ZSDS, FSS, VAS-pain or SARC-F).

Statistical analysis

Descriptive statistics were performed for all variables. Continuously coded variables were expressed as medians and interquartile ranges (IQRs), while categorical variables as absolute counts and proportions (%). The Mann–Whitney *U* test and the χ^2 tests were used to compare medians and proportions, respectively. Patients who did not take PEA treatment were used as controls. Δscores were compared between patients who took PEA and those who did not using Mann–Whitney *U* test, while improvement in each scale through χ^2 tests. Multivariable logistic regression analyses were performed to investigate whether PEA treatment has an independent impact on *global improvement*, thereby adjusting for confounders. To reduce model overfitting while determining the predictive ability of PEA on neuropsychiatric improvement irrespectively of each other variable, several multiple logistic regressions (one for each covariate) were performed on the entire cohort. Logistic regression analyses were also used to identify potential predictors of improvement in each scale within the group of patients who received m/umPEA treatment, among demographic features, comorbidities, length of stay, transfer to ICU and scores at neuropsychiatric evaluations at 3 months (i.e. VAS-general, ZSDS, FSS, VAS-pain and SARC-F). Missing data were not imputed. All statistical tests were performed using the R statistical package v.4.0.0 (R Foundation for Statistical Computing, Vienna, Austria, www.r-project.org). All tests were two sided, with a significance level set at $P < 0.05$.

Results

General patient characteristics

A total of 98 patients were proposed m/umPEA treatment at the 3-month postdischarge visit between 15 February and 31 August 2021 and were included in the study. Of these, 57 accepted to receive treatment with m/umPEA for at least 3 months (PEA patients), while 41 patients refused treatment (non-PEA patients). All patients had been previously hospitalized for COVID-19 and discharged between 5 November 2020 and 27 May 2021. Table 1 reports the general characteristics (demographics, past medical history, chronic antidepressive therapy, LoS and transfer to ICU) of the cohort. Patients had a median (IQR) age of 70.2 (59.6–75.6),

no statistically significant difference being detected between PEA and non-PEA patients. Male sex (56 patients, 57.1%) was predominant in both groups ($P > 0.05$). The two cohorts did not differ in terms of preexisting comorbidities (i.e. HTN, CAD, DM, COPD, CKD, active cancer or psychiatric disorders). Also, no difference was found in the proportion of patients under preexisting antidepressant drugs ($P > 0.05$). Median (IQR) LoS was 17 (9.2-31) days in the whole sample and was similar in the two groups ($P > 0.05$). Likewise, no difference was found in the proportion of patients who had been transferred to the ICU during hospital stay between PEA patients (14.6%) and non-PEA patients (15.8%), suggesting a comparable severity of acute disease. Therefore, the two cohorts did not differ in terms of demographics, preexisting health status and severity of acute COVID-19.

Three-month (baseline) evaluation

At the 3-month visit, all patients underwent neuropsychiatric assessment through validated scales (see *Evaluation of neuropsychiatric sequelae*). Median scores at ZSDS and at SARC-F and FSS scales in the entire cohort were all in the pathological range for depression and fatigue, respectively (ref). Median VAS-general score was below 80, while median VAS-pain was 3 in the entire cohort, suggesting suboptimal quality of life and the wide presence of chronic pain within the population.

No differences in all scales (i.e. VAS-general, ZSDS, VAS-pain, SARC-F and FSS) were found prior to PEA initiation between patients who then received therapy with PEA and those who did not (Table 2). Therefore, patients who accepted to take PEA had a similar neuropsychiatric status at 3 months compared with those who refused, indicating that the two groups were comparable for baseline characteristics.

Neuropsychiatric changes between 3- and 6-month evaluations

The changes in all scales between the 3- and 6-month evaluations were measured as the pairwise difference (Δ) in each score obtained at the two time points. As detailed in *Evaluation of neuropsychiatric sequelae*, positive Δscores indicated worsening for ZSDS, SARC-F, FSS and VAS-pain, while they indicated improvement for VAS-general. In the overall population, global improvement (i.e. an improvement in at least three scales among VAS-general, ZSDS, FSS, VAS-pain or SARC-F) was reached in 17 (17.3%) patients, of whom 14 (24.6%) in the PEA cohort and 3 (7.3%) in the non-PEA cohort, this difference being statistically significant ($P < 0.05$, Fig. 1).

While no difference between PEA patients and non-PEA patients was found in VAS-general, VAS-pain and SARC-F, depression and fatigue improved selectively in the PEA group (Table 3). Specifically, ZSDS and FSS scores decreased in patients who took PEA, while they

Table 1 General characteristics of the cohort

Variable	Entire cohort, $n = 98$	No PEA treatment, $n = 41$	PEA treatment, $n = 57$	P value
Age (years)	70.2 (59.6–75.6)	67.6 (58.7–74.5)	72.7 (59.9–77.9)	0.21
Male sex	56 (57.1)	34 (59.6)	22 (53.7)	0.7
Comorbidities				
HTN	56 (57.1)	23 (56.1)	33 (57.9)	1.00
CAD	14 (14.3)	7 (17.1)	7 (12.3)	0.71
DM	16 (16.3)	6 (14.6)	10 (17.5)	0.91
COPD	14 (14.3)	4 (9.8)	10 (17.5)	0.42
CKD	7 (7.1)	3 (7.3)	4 (7)	0.99
Active cancer	3 (3.1)	2 (4.9)	1 (1.8)	0.77
Psychiatric disorders	16 (16.3)	9 (22)	7 (12.3)	0.32
Chronic antidepressive therapy	19 (19.4)	9 (22.0)	10 (17.5)	0.78
Length of stay	17 (9.2–31)	18 (11–33)	15 (9–27)	0.5
Transfer to ICU	15 (15.3%)	9 (15.8%)	6 (14.6%)	1.00

Continuous variables were expressed as median (interquartile range), while categorical variables as count (percentage). Mann–Whitney U test was used to compare continuous variables between the two groups, while χ^2 or Fisher test, as appropriate, was employed for categorical variables.
CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HTN, arterial hypertension; PEA, palmitoylethanolamide.

Table 2 Three-month postdischarge neuropsychiatric evaluations

Variable	Entire cohort, $n = 98$	No PEA treatment, $n = 41$	PEA treatment, $n = 57$	P value
VAS	75 (65–80)	75 (67.5–77.5)	75 (66.2–80)	0.63
ZSDS	49 (42.5–58.8)	48.1(41.2–55)	51.2 (45–60)	0.15
VAS-pain	3 (1–5)	3 (0–5)	3 (1.1–5)	0.58
SARC-F	1 (1–2.2)	1 (0–2.2)	2 (1–2.2)	0.20
FSS	37 (26–46)	35 (23.5–46)	38 (27.2–46)	0.55

Variables were expressed as median (interquartile range). Mann–Whitney U test was used to compare variables between the two groups.
FSS, Fatigue Severity Scale; PEA, palmitoylethanolamide; SARC-F, Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls; VAS, visual analog scale; ZSDS, Zung Self-Rating Depression scale.

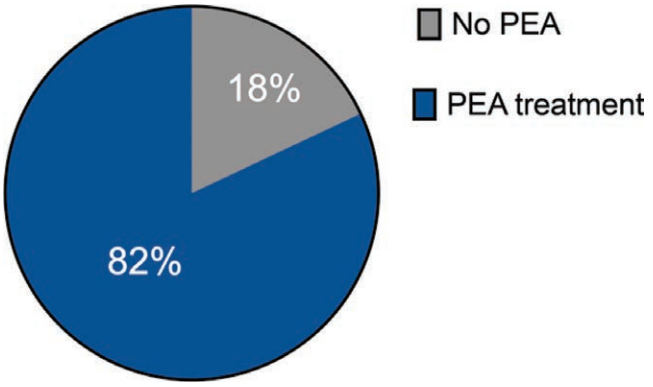
increased in those who refused therapy (both $P < 0.05$, Fig. 2). Accordingly, the proportions of patients experiencing improvement in depression (ZSDS) and fatigue (FSS) were significantly higher among PEA patients (both $P < 0.05$, Table 3).

To confirm the observed association between m/umPEA treatment and improvement in neuropsychiatric status, multivariable logistic regression analyses predicting global improvement were employed. Multiple multivariable analyses, one for each covariate, were performed to minimize model overfitting. m/umPEA treatment emerged as being a significant predictor of global improvement independently of age, sex and neuropsychiatric status prior to therapy (Table 4).

Factors predicting PEA efficacy in PEA patients

We performed logistic regression analyses to identify potential predictors of PEA efficacy within the group of patients who received m/umPEA treatment, among demographic features, comorbidities, LoS, transfer to ICU and scores at neuropsychiatric evaluations at 3 months (i.e. VAS-general, ZSDS, FSS, VAS-pain and SARC-F). For the purpose of this analysis, we used the improvement in each neuropsychiatric scale as a measure of PEA efficacy. Therefore, separate analyses were performed, one for each scale. No variable emerged as significant predictor of improvement of VAS-general, ZSDS or VAS-pain (not shown). On the other hand, lower baseline scores of SARC-F significantly predicted improvement in SARC-F [odds ratio, OR, (95% confidence interval, CI) 1.87 (1.11–3.83), $P = 0.046$] and FSS [OR (95% CI) 2.91 (1.33–8.66), $P = 0.025$]. Moreover, lower baseline FSS scores [OR (95% CI) 1.081 (1.028–1.16), $P = 0.0080$] and VAS-general [OR (95% CI) 0.88 (0.78–0.97), $P = 0.025$] scores were significant predictors of improvement in FSS.

Fig. 1



Global improvement in patients taking PEA and those not taking PEA. The proportions (percentage) of patients who experienced global improvement are shown. PEA, palmitoylethanolamide.

Discussion

Here we investigated the impact of 3-month m/umPEA treatment on neuropsychiatric sequelae in COVID-19 survivors evaluated at the post-COVID-19 outpatient clinic of our institution at 3 and 6 months after discharge. m/umPEA emerged as being effective in reducing depression and fatigue, while no significant benefit was observed in terms of chronic pain and subjective perception of health status. Moreover, m/umPEA treatment was a significant predictor of global neuropsychiatric improvement independently of age, sex and degree of neuropsychiatric impairment prior to therapy. Interestingly, patients with worse baseline neuropsychiatric status were more likely to benefit from m/umPEA treatment.

Our observations in the clinical setting may reflect events occurring at the molecular level. The development of psychiatric sequelae in COVID-19 is mediated, at least in part, by aberrant immune system activation and systemic inflammation (Mazza *et al.*, 2020). Similarly, an unsynchronized and exaggerated production of inflammatory mediators including interleukin (IL)-1, IL-6 and tumor necrosis factor α is involved in the pathogenesis of major depression (Pariante, 2017; Müller, 2013). Such shared pathogenetic mechanisms may underly common

Table 3 Differences in neuropsychiatric status between 3 and 6 months postdischarge

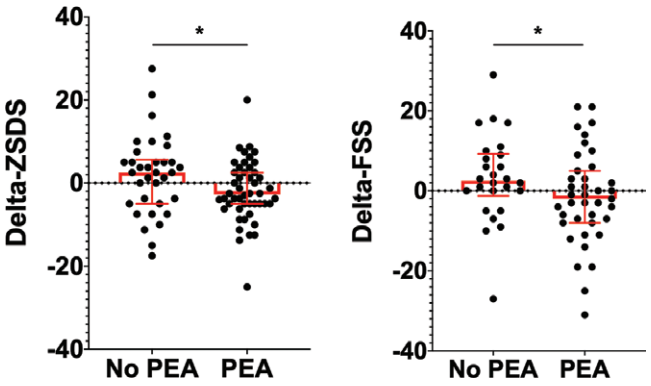
Variable	Entire cohort, $n = 98$	No PEA treatment, $n = 41$	PEA treatment, $n = 57$	*P* value
ΔVAS	−5 (−10 to 0)	−5 (−10 to 0)	0 (−10 to 5)	0.43
ΔZSDS	0 (−5 to 5)	2.5 (−4.7 to 5)	−2.8 (−5 to 2.5)	0.040
ΔVAS pain	0 (−1 to 1)	0 (0 to 1.5)	0 (−1 to 1)	0.31
ΔSARC-F	0 (−1 to 1)	0 (0 to 0.5)	0 (−1 to 1)	0.27
ΔFSS	0 (−6 to 6)	2.5 (0 to 8.8)	−2 (−7.5 to 4)	0.049
VAS improvement	36 (36.7)	18 (43.9)	18 (31.6)	0.25
ZSDS improvement	40 (40.8)	11 (26.8)	29 (50.9)	0.020
VAS-pain improvement	17 (17.3)	4 (9.8)	13 (22.8)	0.23
SARC-F improvement	24 (24.5)	7 (17.1)	17 (29.8)	0.13
FSS improvement	28 (28.6)	6 (14.6)	22 (38.6)	0.020

Continuous variables were expressed as median (interquartile range), while categorical variables as count (percentage). Mann–Whitney *U* test was used to compare continuous variables between the two groups, while χ^2 or Fisher test, as appropriate, was employed for categorical variables. $\Delta\text{score} = \text{score}_{6\text{ months}} - \text{score}_{3\text{ months}}$.
FSS, Fatigue Severity Scale; PEA, palmitoylethanolamide; SARC-F, Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls; VAS, visual analog scale; ZSDS, Zung Self-Rating Depression scale.

responses to treatment with PEA, in line with the recognized anti-inflammatory and neuroprotective properties of PEA (Esposito *et al.*, 2012; Skaper and Facci, 2012). The effects of PEA are mediated by the activation of the peroxisome proliferator-activated receptor α and cannabinoid-type G-coupled receptors (Conti *et al.*, 2002; D'Agostino *et al.*, 2007; Guida *et al.*, 2017). The endocannabinoid system is specifically implicated in the pathogenesis of depression (Smaga *et al.*, 2014). Furthermore, PEA has been suggested as being an endogenous protective mediator in *N*-methyl-D-aspartate receptor-induced neuronal death and to regulate glutamate transmission in depressive disorders (Sanacora *et al.*, 2012; Richter *et al.*, 2016). These considerations suggest a molecular rationale behind the beneficial effects of m/umPEA on depression observed in our cohort.

Growing evidence suggests an association between persistent fatigue following COVID-19 and systemic inflammation (Ceban *et al.*, 2022), making it tempting to speculate that the observed beneficial effects of PEA on fatigue might at least in part be explained by its known anti-inflammatory properties. Moreover, depression after COVID-19 was recently found to predict persistent fatigue independent of acute COVID-19 severity (Mazza *et al.*, 2022c), suggesting that the PEA-associated improvements in depression and fatigue may be pathogenetically interrelated. Although the exact mechanisms underlying PEA effects on post-COVID-19 fatigue remain unclear, considering the very high prevalence of fatigue among patients recovered from COVID-19 and the implications of this condition on overall health status and quality of life (Mazza *et al.*, 2022c), clinical evidence might itself justify the use of m/umPEA in COVID-19 survivors, pending clinical trials to validate results.

Fig. 2



Changes (delta) in ZSDS (depression) and FSS (fatigue) between 3- and 6-month visits in patients taking PEA and those who did not receive PEA treatment. For each patient subgroup (patients taking PEA and those not taking PEA), median and interquartile ranges are shown. *$P < 0.05$. FSS, Fatigue Severity Scale; PEA, palmitoylethanolamide; ZSDS, Zung Self-Rating Depression Scale.

The lack of association between m/umPEA treatment and changes in chronic pain during convalescence after COVID-19 may reflect the likely multifactorial etiology of chronic pain in survivors. Prolonged immobilization due to hospitalization causing alterations in nerve, bone and joint function, together with potential corticosteroids-associated mechanisms of pain perpetuation might contribute to chronic pain besides COVID-19-associated inflammatory and neurotoxicity (Baumbach *et al.*, 2016; Parisien *et al.*, 2022).

Our results are in line with previous reports proposing beneficial effects of m/umPEA in COVID-19 (Noce *et al.*, 2021). PEA has also been studied in combination with other anti-inflammatory molecules such as α-lipoic acid, emerging as being able to counteract the cytokine storm following SARS-CoV-2 infection and act as a powerful antioxidant (Uberti *et al.*, 2021). Furthermore, in patients with persistent olfactory dysfunction following acute COVID-19, PEA comicronized with luteolin showed to boost recovery (D'Ascanio *et al.*, 2021). Analogously to our cohort, a previous retrospective study reported a beneficial effect of umPEA on functional status as evaluated with the Post-COVID-19 Functional Status (PCFS) scale in patients with long-COVID (Raciti *et al.*, 2022).

Our study has limitations. First, its retrospective, observational nature might jeopardize the generalizability of results. However, patients taking m/umPEA and those

Table 4 Multivariable logistic regression analyses predicting global improvement from 3-month to 6-month evaluation

Covariates	Odds ratio (95% CI) of covariate	*P* value of covariate	Odds ratio (95% CI) of PEA treatment	*P* value of PEA treatment
Age (years)	0.98 (0.93–1.02)	0.34	4.11 (1.22–18.99)	0.037
Female sex	1.01 (0.34–3.12)	0.98	4.12 (1.23–18.90)	0.036
SARC-F at 3 months	0.99 (0.73–1.30)	0.99	4.53 (1.33–21.04)	0.027
FSS at 3 months	0.99 (0.96–1.04)	0.85	3.65 (1.06–16.90)	0.059
VAS-general at 3 months	0.99 (0.96–1.03)	0.61	4.19 (1.23–19.4)	0.036
VAS-pain at 3 months	0.92 (0.71–1.17)	0.49	4.31 (1.22–20.50)	0.036
ZSDS at 3 months	1.01 (0.95–1.06)	0.80	3.94 (1.17–18.10)	0.043

Each raw reports results of one multivariable logistic regression analysis using PEA treatment and each other variable as covariate. Odds ratio (95% confidence interval, CI) and *P* value for each covariate and for PEA treatment are reported for each multivariable analysis.
FSS, Fatigue Severity Scale; PEA, palmitoylethanolamide; SARC-F, Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls; VAS, visual analog scale; ZSDS, Zung Self-Rating Depression scale.

who did not were comparable in terms of demographics, past medical history and severity of acute COVID-19, minimizing the effects of confounders. Second, patients refusing treatment served as controls, which might have led to selection bias. Nevertheless, these patients showed a similar baseline neuropsychiatric status compared with patients taking m/umPEA, indicating that the two groups were suitable for comparison analyses in terms of neuropsychiatric benefits. Third, the limited sample size of the cohort might have underpowered some statistical analyses. Also, the duration of m/umPEA treatment was arbitrarily established and may not be enough to unveil variations in all evaluated outcomes.

Despite these limitations, our results provide support for utilizing m/umPEA in treating neuropsychiatric symptoms in COVID-19 survivors. Tailored and more effective treatment plans targeting neuropsychiatric sequelae are needed for the care of long-COVID patients. The use of m/umPEA may be relevant in this context, encouraging the exploration of novel molecules with similar applications.

In conclusion, the results of our study provide evidence that 3-month treatment with m/umPEA ameliorates depression and fatigue in COVID-19 survivors. Given the current dearth of effective therapeutic strategies for patients with long-COVID, the positive outcomes observed in our study warrant continued investigation into m/umPEA as a viable treatment option for managing the neuropsychiatric sequelae of COVID-19.

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R.D.L., S.D., F.B. and P.R.Q. designed the study and wrote the protocol. R.D.L., A.M., G.P., S.C., M.P., S.D., G.V., V.C., M.C., S.M., E.F., M.F., J.C., G.P., C.M., A.F. and M.M. managed the data curation. R.D.L., A.M. and G.P. undertook the statistical analysis and wrote the first draft of the manuscript. F.B. and P.R.Q. managed study supervision. All authors contributed to and have approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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