some of these problems were tackled with changes in the new training program starting from 2014, it seems that there is still a high level of dissatisfaction with academic opportunities.

Migration tendencies of junior psychiatrists in Croatia present a worrying trend that could negatively impact the performance of the healthcare system in Croatia. Taking into account the overall decline of recruitment of psychiatry trainees and positive migration trend towards high income countries, it seems necessary to implement strategies to prevent brain drain, such as improvement of educational and professional opportunities followed with adequate financial income (Andlauer et al. 2012, Nawka et al. 2015). As seen in the recent COVID-19 pandemic, stable and functioning medical system is of utmost importance. Our study provides important data which could be used by medical stakeholders to retain junior doctors in order to sustain quality of medical service in Croatia. Existing shortage of healthcare personnel, accompanied by increasing emigration tendencies of the junior doctors who were to be the system's backbone in the future, might lead to insufficient service capabilities. Psychiatric patients are already considered as a group with unmet service needs whose unfavorable position could further decline with the rise of the new global mental health challenges associated with the COVID-19 pandemics (Moreno et al. 2020).

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DULOXETINE DOES NOT AFFECT VASCULAR ENDOTHELIAL GROWTH FACTOR PLASMA LEVELS IN PATIENTS WITH FIRST-EPISODE, DRUG-NAÏVE MAJOR DEPRESSION

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Dear editor,

According to the neurotrophic hypothesis of major depression (MD), impairment in growth factor signaling may be associated with the pathology of this disorder. Current evidence demonstrates that impaired neuroplasticity induced by alterations in neurotrophic growth factors and related signaling pathways may be underlying to the pathophysiology of MD (Boku et al. 2018). Stress induces alterations in the neuroplastic pathways in the emotional and cognitive processing areas of the brain, leading to reduced neurogenesis and hippocampal volume, and predisposing an individual to depression.

A key factor in the neuroplastic pathways is the vascular endothelial growth factor (VEGF), which is known to possess strong neurogenic effects. VEGF was first presented as an inducer of vascular permeability, but the understanding of its actions has broadened to include stimulation of angiogenesis and acetogenesis, and promotion of neurogenesis and neuroprotective mechanisms (Storkebaum et al. 2004). Novel VEGF-related associations identified by MD genome-wide association studies (GWAS) suggest a role for this molecule in MD development. This could help to promote personalized medicine (Xie et al. 2017). We previously reported a genotype-diagnosis interaction for GWAS single nucleotide polymorphism (SNP) rs6921438 (G/G versus GA/AA genotype) in the subiculum of the left hippocampus, but not for rs4416670, rs6993770, or rs10738760 (Nguyen et al. 2019).

Recent reports show that VEGF plays a crucial role in the pathogenesis of MD by increasing blood-brain barrier (BBB) permeability, indicating that VEGF inhibition is a potential therapeutic strategy for the MD subtype associated with BBB dysfunction (Matsumoto et al. 2022). Our previous research demonstrated that neither paroxetine, a selective serotonin reuptake inhibitor (SSRI), nor milnacipran, a serotonin and noradrenaline reuptake inhibitor (SNRI), changed plasma VEGF levels in patients with MD (Yoshimura et al. 2022). The present study aimed to investigate the effect of duloxetine on plasma VEGF levels in patients with first-episode, drug-naïve MD.

Twenty-eight patients who met MD criteria according to the Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) (American Psychiatric Association, 2013) were enrolled in this study (age 47.5±13.1 years; male/female 14/14). Additionally, 20 age-, and sex-matched healthy control (HC) patients

Table 1. Difference of plasma VEGF between R- and NR- group

	R	NR	p-value	Adjusted p-value
Plasma VEGF (W4-W0) pg/ml	-0.01±1.71	0.44 ±1.49	0.46	0.65

(age 42.3±10.0 years; male/female 12/8) were enrolled. Patients were treated for four weeks using SNRI duloxetine. The maximum dose of duloxetine at week 4 was 43.5±14.1 mg/day. Depressive symptoms were evaluated pre- and post-treatment using the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960). Blood was drawn at 9:00 a.m.

Plasma VEGF levels were measured using a Quantikine® HS Human IL-6 Immunoassay kit (R&D Systems, Minneapolis, USA). Plasma levels were analyzed in duplicate, and mean values were calculated for each data point. Plasma level differences were determined for i) MD versus HC groups at baseline, ii) MD patients at baseline versus at week 4, and iii) responder (RG; 50% or greater decrease in HAM-D score) versus non-responder (NR) groups.

This study was approved by the ethics committee of the University of Occupational and Environmental Health, and written informed consent was obtained from all the participants.

HAM-D scores significantly decreased in the MD group after duloxetine treatment (week 0, 25.4±3.0; week 4, 13.2±4.6; p<0.001, paired t-test). No difference was found in baseline plasma VEGF levels between the MD and HC groups (MD, 18.3±3.1 pg/ml, HC, 18.3±2.7 pg/ml, p=0.89, multiple regression analysis). In the MD group, VEGF plasma levels were not significantly altered four weeks after duloxetine treatment (week 0, 18.3±3.1 pg/ml; week 4, 18.6±3.5 pg/ml; p=0.41, paired t-test). Furthermore, no correlation was found between plasma VEGF levels and HAM-D score changes (rho = -0.06, p=0.74, Spearman rank correlation coefficient). Table 1 shows the analysis of R group and NR groups. No difference was found in plasma VEGF levels between these two groups.

The results of the present study showed that treatment with duloxetine for four weeks did not change plasma VEGF levels and that plasma VEGF levels were not associated with the clinical response to duloxetine. Fornaro et al. (2013) reported no significant difference in VEGF plasma levels compared to those in health controls, whereas VEGF levels significantly increased with clinical response to duloxetine in early responders at week 6.

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