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Letter to the Editor

Levetiracetam effects on hippocampal blood flow and symptoms in medication-free individuals with nonaffective first episode psychosis (letter)

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Hippocampal hyperactivity, demonstrated by MRI with gadolinium measurement of blood volume, or by cerebral blood flow (CBF) measured by arterial spin labeling (ASL), has been associated with early psychosis, has predicted hippocampal volume loss, and has differentiated individuals with schizophrenia from healthy controls (Allen et al., 2016; McHugo et al., 2019; Schobel et al., 2013). However, therapeutic approaches based on this model not been developed.

Levetiracetam is an antiepileptic agent that acts primarily as an antagonist at synaptic vesicle glycoprotein 2A to reduce neurotransmitter release under conditions of sustained high activation (Meehan et al., 2011; Rossi et al., 2022). In patients with mild cognitive impairment, levetiracetam normalized hippocampal hyperactivity and improved performance on a pattern separation task (Bakker et al., 2015). Concerns about aggressive behavior have limited levetiracetam's use in psychiatric patients (Hansen et al., 2018).

We report results of a placebo-controlled single-dose pilot trial of levetiracetam 185 mg and 500 mg in medication-free first episode nonaffective psychosis patients conducted to provide evidence of target engagement, tolerability, and acute symptom response. A levetiracetam dose of 185 mg was selected to achieve blood levels estimated to fall within the range of steady state blood levels that were effective in a previous study of elderly patients with MCI (Bakker et al., 2015) and a 500 mg dose was selected as a standard starting dose for the treatment of epilepsy.

This study was conducted at NYU Langone Medical Center between August 2017 and November 2021. The protocol was approved by the NYU Grossman School of Medicine IRB and was registered at clinicaltrials.gov NCT03129360. All participants provided written informed consent. Participating patients were antipsychotic-free for at least 4 weeks, ages 16–30, with a first episode of nonaffective psychosis defined by a score of 4 or greater on at least one psychosis item of the Brief Psychiatric Rating Scale (BPRS) in the absence of substance use or other potential organic etiologies (including epilepsy), or major mood disorder and a duration of illness less than 3 years. Healthy controls met the same exclusionary criteria and were group-matched by age and sex.

A diagnostic assessment was performed by a research psychiatrist using the SCID-IV. Patients completed the Systematic Assessment for Treatment Emergent Side Effects (SAFTEE) and the BPRS followed by ASL imaging. Patients were then administered levetiracetam 185 mg, 500 mg or placebo orally in identical capsules, randomized in a 1:1:1 ratio in blocks of random size (3 or 6), stratified by diagnosis. The ASL imaging, BPRS, and SAFTEE were repeated 2 h after administration of study drug. Healthy controls had a single session of ASL imaging and did not receive study drug.

Blood flow was measured in the hippocampus and in the cortex with a Siemens 3 T Prisma MRI with a 64 channel head coil using a pulsed arterial spin labelling sequence with excellent spatial resolution, sensitivity and test-retest reliability (ICC = 0.90) (Rusinek et al., 2011). See supplement for ASL methods.

Descriptive statistics were computed to describe characteristics of the study population. Fisher's exact test for binary and categorical variables and the Kruskal-Wallis rank sum test for continuous variables were used to evaluate differences across treatment groups. Linear regression models with non-parametric bootstrap standard errors, percentile confidence intervals, and bootstrap *p*-values were used to evaluate hypotheses. A two-sided p-value threshold of 0.05 was used for tests of significance without correction for multiple comparisons.

Twenty-five early psychosis patients and 10 healthy controls were enrolled (Supplemental Table 1). Eight patients (33 %) were medication-naïve; one patient received one injection of haloperidol 10 days prior to enrollment. One healthy control was excluded from data analysis due to an abnormal MRI; three early psychosis patients were excluded from all analyses because they did not meet entry criteria. In addition, the ASL scan from one patient was excluded from analysis due to head movement, leaving a total of 9 healthy controls and 21 early psychosis patients for analysis of blood flow and 22 early psychosis patients for analysis of symptom response. Patients and healthy controls did not differ in any demographic variable; nor did patients assigned to the three treatment arms differ significantly in demographic or clinical variables.

At baseline, neither hippocampal or cortical blood flow differed between patients and healthy controls (Table 1). Hippocampal blood

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Table 1
Levetiracetam blood levels and change from baseline in blood flow and BPRS total score.

	Mean (SD)			
	Delta HBF (***n*** = 21)	Delta CBF (n = 21)	Delta BPRS (***n*** = 22)	Levetiracetam Blood Level[e] (n = 21)
Placebo	−1.29 (1.66)	0.457 (1.94)	−9.00 (8.04)	0.00 (0.00)
Levetiracetam 185 mg	−2.21 (3.20)	0.194 (2.70)	**−17.00**[b] **(8.08)**	**2.38**[c] **(0.74)**
Levetiracetam 500 mg	**−3.83**[a] **(2.29)**	−0.983 (2.54)	−12.20 (8.89)	**7.67**[d] **(2.42)**

Values in bold are statistically significant at the 0.05 level.

[a] Coefficient from the linear regression model comparing change in Levetiracetam 500 mg vs Placebo was statistically significant at the 0.05 level (−2.548, 95 % Bootstrap percentile confidence interval [−4.759, −0.254]).

[b] Coefficient from the linear regression model comparing change in Levetiracetam 185 mg vs Placebo was statistically significant at the 0.05 level (−8.000, 95 % Bootstrap percentile confidence interval [−16.133, 0.267]).

[c] Coefficient from the linear regression model comparing change in Levetiracetam 185 mg vs Placebo was statistically significant at the 0.05 level (2.375, 95 % Bootstrap percentile confidence interval [1.912, 2.800]).

[d] Coefficient from the linear regression model comparing change in Levetiracetam 500 mg vs Placebo was statistically significant at the 0.05 level (7.667, 95 % Bootstrap percentile confidence interval [6.126, 9.500]).

[e] Levetiracetam blood level was correlated with Delta HCBF - Coefficient from the linear regression model was statistically significant at the 0.05 level (−0.295, 95 % Bootstrap percentile confidence interval [−0.656,-0.093]) – the more the blood level increased the more change in Delta HCBF.

flow (HBF) was significantly reduced from baseline in the levetiracetam 500 mg group compared to placebo but not in the 185 mg group (Table 1). Change in cortical blood flow did not differ between groups. The change in hippocampal blood flow was significantly associated with levetiracetam serum concentrations (Supplemental Fig. 1). The reduction in BPRS total score was greater in the levetiracetam 185 mg group compared to placebo and did not differ significantly from placebo in the high dose group (Table 1). Psychosis items that significantly decreased with levetiracetam 185 mg compared to placebo included conceptual disorganization and hallucinations (Supplemental Table 2). Hallucinations also significantly decreased with levetiracetam 500 mg. Mild sedation and dizziness were reported in 3 patients who received levetiracetam; one patient reported an episode of hostility the day following levetiracetam 500 mg administration.

We found significant reduction of hippocampal blood flow following a single dose of levetiracetam 500 mg compared to placebo and a significant correlation between the reduction of hippocampal blood flow and levetiracetam blood concentrations across treatment groups. This effect appeared to be relatively specific for hippocampal blood flow, as we found no effect of levetiracetam on cortical blood flow. Of note, the lower dose of levetiracetam improved the BPRS total score, including hallucinations and conceptual disorganization, whereas the higher dose of levetiracetam improved hallucinations only. These findings require further study in a larger sample.

While our findings suggest that levetiracetam decreased hippocampal blood flow and decreased psychosis, we can't conclude that levetiracetam "normalized" hippocampal activity since patients did not differ from controls at baseline. Levetiracetam was well tolerated in this small, single dose study. Larger studies utilizing repeated dosing are needed to assess the potential risk of aggressive behavior. In summary, these results provide preliminary support for levetiracetam as a treatment to reduce hippocampal activity and psychosis in early-stage schizophrenia and suggest that larger clinical trials employing repeated dosing are warranted.

CRediT authorship contribution statement

DCG designed the study, obtained funding, supervised research staff and prepared the manuscript. MS provided statistical support. GC, FA and KH assisted with participant recruitment, data collection, and data management. AC and HR provided training and technical support for imaging data acquisition and analysis. All authors contributed to editing of the paper and have approved the current manuscript.

Declaration of competing interest

Dr. Goff has received no research funding or honoraria from commercial entities over the past three years. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.08.018.

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Donald C. Goff[a,d,*], Michele Santacatterina[b], Gillian Capichioni[a], Fumika Ando[a], Kamber Hart[a], Antonio Convit[a,c,d], Henry Rusinek[c]

[a] *Department of Psychiatry, NYU Grossman School of Medicine, New York, NY, United States of America*

[b] *Department of Population Health, NYU Grossman School of Medicine, New York, NY, United States of America*

[c] *Department of Radiology, NYU Grossman School of Medicine, New York, NY, United States of America*

[d] *Nathan Kline Institute for Psychiatric Research, Orangeburg, NY, United States of America*

* Corresponding author at: Department of Psychiatry, NYU Grossman School of Medicine, One Park Ave, Rm 8-212, New York, NY 10116, United States of America.

E-mail address: Donald.Goff@nyulangone.org (D.C. Goff).