



Zuranolone, a positive allosteric modulator of the GABAA receptor and a neuroactive steroid: hypothesized mechanism of action in depression

J. Payne, Jodi Pawluski, A. Althaus, S. Gee, T. Vera, N. d'Alberto, S. Kyaga, M. Kotecha, M. Pollack, R. McIntyre, et al.

► To cite this version:

J. Payne, Jodi Pawluski, A. Althaus, S. Gee, T. Vera, et al.. Zuranolone, a positive allosteric modulator of the GABAA receptor and a neuroactive steroid: hypothesized mechanism of action in depression. 36th ECNP Congress 2023, Oct 2023, Barcelona, Spain. pp.103521, 10.1016/j.nsa.2023.103521 . hal-04387403

HAL Id: hal-04387403

<https://hal.science/hal-04387403>

Submitted on 30 May 2024

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NEUROSCIENCE APPLIED 2 (2023) 102442 103520

NEUTROPHIL/LYMPHOCYTE RATIO AND PLATELET/LYMPHOCYTE RATIO IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND CONCOMITANT MOOD DISORDERS

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Introduction: Systemic lupus erythematosus (SLE) is a prototypical chronic autoimmune disease, characterized by systemic involvement. Clinical presentation comprises a wide range of symptoms, including neuropsychiatric disorders [1]. In this regard, several studies have shown a connection between increased disease activity in SLE and a higher risk of depression [1]. This connection underscores the central role that the immune and inflammatory systems play in the development of mood disorders [2]. Studies have also reported an increase in proinflammatory cytokines in the blood and central nervous system of people with depression [3]. Simple, repeatable indicators of inflammation like the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are cost-effective and commonly used in clinical practice [4]. This study aims to evaluate the NLR and PLR in a group of SLE patients with and without mood disorders, compared to those with major depressive disorder and healthy volunteers.

Methods: The sample included four groups: 72 SLE patients and 14 SLE patients with comorbid mood disorders (SLE-MD) on active follow-up at the Autoimmune Disease Unit of the Cruces University Hospital (Spain). Additionally, 26 patients with major depressive disorder (MDD) and 27 healthy controls were included. Sociodemographic and clinical data were collected, and relationships between clinical and biological variables were assessed. Laboratory data of lymphocytes and neutrophils were obtained from study inclusion. Molecular analyses for proinflammatory cytokines (including IL6 and IFN- γ), anti-inflammatory cytokine IL-10, and the inflammatory marker CRP (C-reactive protein) were performed using commercial ELISA and particle-enhanced immuno-turbidimetric assay kits. The Kruskal-Wallis test and Dunn's multiple comparison test were used for statistical analysis, and clinical correlations were assessed using the Pearson correlation coefficient.

Results: Overall, increased levels of NLR and PLR were found in the SLE and SLE-MD compared to the healthy control group. In this regard, patients with SLE with and without concomitant mood disorders, presented higher levels of NLR compared to controls (SLE 2.27 ± 1.05 ; SLE-MD 2.97 ± 1.21 and healthy controls 1.35 ± 0.53 ; $p < 0.0001$). Additionally, significant differences were also observed between the SLE-MD and the MDD groups, with the SLE-MD group showing higher NLR values ($U = 74.500$; $p < 0.001$). Regarding PLR values, similar results were obtained. Patients with SLE and SLE-MD presented higher PLR levels compared to controls (SLE 141.3 ± 55.59 , SLE-MD 224.3 ± 121 and controls 116.4 ± 29.10 ; $p = 0.0001$). Specifically, for the PLR, a significant association was found between SLE and SLE-MD group [$U = 359.5$; $p = 0.018$]. Additionally, significant correlations were observed between NLR and IFN- γ [$R^2 = 0.189$; $p = 0.023$], PLR and IFN- γ [$R^2 = 0.317$; $p = 1.004 \times 10^{-4}$] and, NLR and PCR [$R^2 = 0.259$; $p = 0.002$].

Conclusion: Our study highlights an association between systemic lupus erythematosus and increased levels of NLR and PLR. More specifically, patients with SLE and mood disorders (SLE-MD) showed increased levels of NLR and PLR compared to other groups, but this was not observed in the depressed group (MDD). Therefore, our findings suggest that the increased NLR and PLR are associated with the SLE disorder rather than with depressive status itself. In this sense, the use of NLR in clinical practice may be a valuable tool to identify this inflammatory imbalance.

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No conflict of interest

doi: <https://doi.org/10.1016/j.nsa.2023.103520>

P.1156

NEUROSCIENCE APPLIED 2 (2023) 102442 103521

ZURANOLONE, A POSITIVE ALLOSTERIC MODULATOR OF THE GABAA RECEPTOR AND A NEUROACTIVE STEROID: HYPOTHESIZED MECHANISM OF ACTION IN DEPRESSION

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Major depressive disorder (MDD) and postpartum depression (PPD) are serious mental health disorders characterized by depressed mood and/or loss of interest or pleasure in activities, among other symptoms, that can lead to impaired functioning and diminished quality of life. Depressive symptoms are associated with dysregulated activity of brain networks involved in mood, sleep, and cognition, including deficits in γ -aminobutyric acid (GABA) signaling and altered neuroplasticity. Many antidepressant medications are hypothesized to improve depressive symptoms by restoring excitatory-inhibitory balance in neuronal signaling and improving neuroplasticity.[1]

GABA is the primary inhibitory neurotransmitter in the Central Nervous System (CNS) and has a critical role in maintaining balance in brain network activity. Amplifying GABA signaling may restore balance in brain networks dysregulated in depression. GABA binds to two types of GABAA receptors (GABAARs): the γ subunit-containing synaptic GABAARs and the δ subunit-containing extrasynaptic GABAARs, leading to phasic and tonic inhibition, respectively. Levels of allopregnanolone, an endogenous neuroactive steroid and positive allosteric modulator (PAM) of GABAARs, increase considerably during pregnancy and drop precipitously post parturition. Disruption in the ability of the GABA system to adapt to changes in allopregnanolone levels during the peripartum period may underlie the pathogenesis of PPD.

Zuranolone is an investigational positive allosteric modulator of GABAARs and neuroactive steroid in clinical development as an oral, once-daily, 14-day treatment course for adults with MDD or PPD.[2] Zuranolone is designed for greater selectivity at GABAARs, improved oral bioavailability, and once-daily dosing.[3] In several double-blind, placebo-controlled clinical studies, adults with MDD or PPD treated with zuranolone once daily for 14 days showed rapid improvements in depressive symptoms, starting as early as Day 3, that were sustained at measured timepoints beyond the 14-day treatment period.[2]

It should be noted that although both zuranolone and benzodiazepines act on GABAARs, their putative mechanisms of action are distinct and result in different CNS effects. Zuranolone binds to both synaptic and extrasynaptic GABAARs and upregulates GABAAR expression, whereas benzodiazepines act only on synaptic GABAARs and are associated with a downregulation of GABAARs.[3] Zuranolone and benzodiazepines may also affect brain network oscillations differently, as measured by cortical electroencephalogram (EEG) recordings. While both benzodiazepines and neuroactive steroid GABAAR PAMs, including zuranolone, led to increased beta-band power in rat EEG studies, they modulated theta-band EEG power differentially.[4,5] A benzodiazepine (diazepam), a non-benzodiazepine (alpidem), and a benzodiazepine receptor partial agonist (imepitoin) exhibited minimal theta-band modulation, whereas neuroactive steroid GABAAR PAMs

(zuranolone, SGE-516 and SGE-872) robustly increased theta-band power in rats.[4,5] These distinct effects of zuranolone and benzodiazepines reflect the differential pharmacological modulation of GABAAR subpopulations and potentially their differential effects on depressive symptoms.

In conclusion, zuranolone is hypothesized to increase neuroplasticity and restore excitatory-inhibitory balance via upregulation of GABAAR expression and increased phasic and tonic inhibitory GABAergic signaling, thus allowing the brain to respond appropriately to internal and external stimuli. Via these mechanisms, treatment with zuranolone may result in rapid and sustained restoration of balance in brain networks involved in depression.

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Conflict of interest:

Disclosure statement, Jodi Pawluski reports no disclosures.

Jennifer L. Payne consults for Sage Therapeutics, Biogen, Bria Biologics, Merck, Pure Tech, Flo Health, and the Women's Tennis Association. She holds founders' stock in and provides unpaid consulting for Dionysus Health. Dr. Payne is the current president for Marce of North America and the International Marce Perinatal Mental Health Societies. Dr. Payne receives royalties from UpToDate and Elsevier has received payments from CMETOGO and has delivered lectures to Karuna Therapeutics and for Field Trip, GLC Healthcare, Medscape, and Peer-view. Dr. Payne holds patent number 13851897.2-1403 PCT/US2013068241 and filed patent application serial no.: 63/373,151 filed August 22, 2022.

Ali Althaus, Steven Gee, Theresa Vera, and Mark Pollack are employees of Sage Therapeutics, Inc., and may hold stock and/or stock options.

Nicholas D'Albarto, Simon Kyaga, and Mona Kotecha are employees of Biogen Inc. and may hold stock.

Roger S. McIntyre served as a consultant to Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular Therapies, and NewBridge Pharmaceuticals. He is the CEO of Braxia Scientific Corp, has received research grant support from CIHR/GACD/National Natural Science Foundation of China (NSFC), and has served on speakers bureaus for Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular Therapies, NewBridge Pharmaceuticals, Abbvie, and Atai Life Sciences. Dr McIntyre has provided expert testimony for Lundbeck, Janssen, Alkermes, Neumora Therapeutics, Boehringer Ingelheim, Sage, Biogen, Mitsubishi Tanabe, Purdue, Pfizer, Otsuka, Takeda, Neurocrine, Sunovion, Bausch Health, Axsome, Novo Nordisk, Kris, Sanofi, Eisai, Intra-Cellular Therapies, NewBridge Pharmaceuticals, Abbvie, and Atai Life Sciences.

Stephen M. Stahl served as a consultant to Acadia, Adamas, Alkermes, Allergan, AbbVie, Arbor Pharmaceuticals, Assertio Therapeutics, AstraZeneca, Avanir, Axovant, Axsome, Biogen, BioMarin, Biopharma, Celgene, Concert, ClearView, EMD Serono, Eisai Pharmaceuticals, EuroLink, Ferring, Forest, Genomind, Innovative Science Solutions, Impel, Karuna, NeuroPharma, Intra-Cellular Therapies, Ironshore Pharmaceuticals, Janssen, Jazz, Karuna, Lilly, Lundbeck, Merck, Neos, Neurocrine, Novartis, Noveida, Otsuka, Perrigo, Pfizer, Pierre Fabre, Proxym, Relmada, Reviva, Sage, Servier, Shire, Sprout, Sunovion, TMS NeuroHealth, Takeda, Talia, Teva, Tonix, Tris Pharma, Trius, Vanda, Vertex and ViforPharma. He holds options in Genomind, Lipid, and Delix. He has been a board member of RCT Logic and Genomind. He has served on speakers bureaus for Acadia,

Genentech, Janssen, Lundbeck, Merck, Otsuka, Servier, Sunovion, Takeda, and Teva, and has received research and/or grant support from Acadia, Alkermes, Allergan/AbbVie, AssureX, Astra Zeneca, Arbor Pharmaceuticals, Avanir, Axovant, Biogen, Braeburn Pharmaceuticals, Bristol Myers Squibb, Celgene, CeNeRx, Cephalon, Dey, Eisai, Eli Lilly, Forest, Genomind, Glaxo Smith Kline, Harmony Biosciences, Indivior, Intra-Cellular Therapies, Ironshore, ISSWSH, Janssen, JayMac, Jazz, Lundbeck, Merck, Neurocrine, Neuronetics, Novartis, Otsuka, Pear Therapeutics, Pfizer, Reviva, Roche, Sage, Servier, Shire, Sprout, Sunovion, Supernus, TMS NeuroHealth Centers, Takeda, Teva, Tonix, Torrent, and Vanda.

Funding

This work was funded by Sage Therapeutics, Inc. and Biogen Inc. Medical writing and editorial support were provided by Meditech Media, Ltd., and funded by Sage Therapeutics, Inc. and Biogen Inc.

doi: <https://doi.org/10.1016/j.nsa.2023.103521>

P.1158

NEUROSCIENCE APPLIED 2 (2023) 102442 103522

A BAYESIAN APPROACH TO EXAMINING SUBCORTICAL STRUCTURES IN MAJOR DEPRESSIVE DISORDER USING 7T MRI

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Background: Despite notable advances in recent years, our understanding of neuropathological mechanisms underlying major depressive disorder (MDD) remains limited, resulting in a significant delay in developing effective treatments. Animal and theoretical models of affective psychopathology suggest the involvement of specific subcortical regions and their subnuclei [1]; however, the current neuroimaging techniques lack the necessary precision to investigate the structural integrity of these areas thoroughly. As a result, our understanding of these subcortical brain systems in the context of MDD is constrained, significantly impeding the practical application and translation of research findings in this field. Nevertheless, introducing ultra-high resolution MRI protocols, particularly those acquiring data at 7 Tesla (7T), holds significant potential in addressing these limitations and facilitating a more comprehensive understanding of the neurobiological foundations of MDD [2]. In line with this objective, we conducted a cutting-edge 7T imaging study to unravel the pathophysiology of MDD by investigating subcortical structures.

Methods: We acquired T1-weighted MP2RAGE images and T2-weighted quantitative images at 7T MRI from a cohort of 71 individuals, including 57 MDD patients and 14 healthy controls. The segmentation of subcortical regions was performed using Nighres, a novel open-source parcellation algorithm designed for processing high-resolution neuroimaging data [3]. Thirty-one subcortical structures were sampled onto each subject's volumetric space, and the T1-/T2*-data corresponding to these structures were processed using Nighres' profile sampling module. Statistical analysis included Bayesian ANCOVA and correlation analysis implemented in JASP, aiming to elucidate effects observed across groups and within the MDD patient group. Segmentations of subcortical regions, lateral ventricles, and total volume were compared between patients and controls using Bayesian ANCOVA controlling for age and sex. We also explored the effects of symptom severity, medication (antidepressants/psychotropics), childhood trauma, and comorbid anxiety using a between-patients dimensional approach. **Results:** Both Bayesian ANCOVA and regression analysis yielded anecdotal to moderate evidence in favor of the absence of a group effect of MDD across all thirty-one subcortical regions. Bayesian ANCOVA demonstrated anecdotal to moderate evidence for the effects of medication, childhood trauma, and comorbid anxiety on MDD across all thirty-one subcortical subnuclei. Bayesian regression identified no association between the symptom severity of MDD and subcortical brain volumes. Additionally, sample characteristics such as mean age, gender, and medication use did not moderate the alterations in subcortical volumes.

Conclusions: Our study represents one of the few novel research endeavors investigating subcortical nuclei in depression using ultra-high field imaging. Although the Bayesian framework provided weak to moderate evidence for identifying depression biomarkers in our study, ultra-high field imaging remains a promising method to unravel the neuropathology of MDD. Further research on