Lamotrigine Reduces Stress Symptoms of Chronic Anxiety in the Times of the Covid-19 Natural Catastrophe-A Case Report

Thuylinh L. Pham 1, George P. Chrousos 2,3, Andreas Merkenschlager 4, Katja Petrowski 5 and Enrico Ullmann 1,3,6*

1 Department of Child and Adolescent Psychiatry, Psychotherapy, and Psychosomatics, University of Leipzig, Leipzig, Germany, 2 University Research Institute of Maternal and Child Health and Precision Medicine, National and Kapodistrian University of Athens, Athens, Greece, 3 School of Medical Biology, South Ural State University, Chelyabinsk, Russia, 4 Department of Neuropediatrics, University of Leipzig, Leipzig, Germany, 5 Department of Medical Psychology and Medical Sociology, Clinic and Polyclinic for Psychosomatic Medicine and Psychotherapy, University Medicine Mainz, Mainz, Germany, 6 Department of Internal Medicine, Technical University of Dresden, Dresden, Germany

OPEN ACCESS

Edited by:
Rafael Christophe Freire, Queen’s University, Canada

Reviewed by:
Maira Benatti, University of São Paulo, Brazil
Flavio Veras, University of São Paulo, Brazil

*Correspondence:
Enrico Ullmann
enrico.ullmann@uniklinikum-dresden.de

Specialty section:
This article was submitted to Mood and Anxiety Disorders, a section of the journal Frontiers in Psychiatry

Received: 18 January 2021
Accepted: 27 May 2021
Published: 21 June 2021

Citation:
Pham TL, Chrousos GP, Merkenschlager A, Petrowski K and Ullmann E (2021) Lamotrigine Reduces Stress Symptoms of Chronic Anxiety in the Times of the Covid-19 Natural Catastrophe-A Case Report. Front. Psychiatry 12:655079. doi: 10.3389/fpsyt.2021.655079

The SARS-CoV-2 pandemic has been a worldwide chronic, stress-inducing natural catastrophe associated with increased emotional challenging. Patients with Post-traumatic stress disorder (PTSD), self-injury behavior, and obesity are predisposed to aggravation of their symptoms at this time, requiring new therapeutic approaches to balance their disrupted neuro-hormonal stress axis. Here we present our observations of an off-label treatment with lamotrigine in an adolescent girl with PTSD, self-injury behavior, and obesity. Lamotrigine was an efficacious pharmaceutical intervention that helped the patient deal with chronic stress and associated anxiety. The results are discussed based on our previous basic research outcomes in animals and humans that focused on the glutamate-cortisol circuits within the limbic brain.

Keywords: Post-traumatic stress disorder, lamotrigine, inflammation, self-harm behavior, obesity

INTRODUCTION

During the current war between humanity and SARS-CoV-2, new treatment options are needed to confront its adverse psychological consequences in patients with chronic stress-related disorders. Especially Post-traumatic stress disorder (PTSD) seems to be serious in the Covid-19 natural catastrophe (1). “Stress” is a state of disturbed homeostasis or “dyshomeostasis,” when stressors are poorly confronted by our adaptation mechanisms. Here we refer to the concepts of “cacostasis,” when disturbed homeostasis allows survival at the expense of good health, and “hyperstasis” (2), when homeostasis is associated with increased psychosomatic resilience to stressors. Generally, cacostasis is associated with a hyperactivation of the Limbic-Hypothalamic-Pituitary-Adrenal (LHPA) axis and un-needed and damaging systemic inflammation (“para-inflammation”), while hyperstasis is linked to decreased set-points of reactivity to stressors, and restrained activation of the LHPA axis and the inflammatory reaction (3).

We have shown that obese humans, labeled as low cortisol reactors, consume less food, and that more active and “offensive” rats have low levels of anxiety and increased glutamate+glutamine levels in the striatum and inversely related glutamate levels in the amygdala (3–5). These pathophysiological limbic circuit changes are present not only in patients with obesity and/or less...
physical activity, but also in patients with PTSD (6). The novel
diagnosis of “complex PTSD” (CPTSD) was introduced in the
new WHO diagnostic nomenclature (ICD-11), referring to a
distinct subgroup of PTSD patients, who have experienced
multiple and sustained traumas and have greater functional
impairment than those with classic PTSD, mainly manifesting
chronic anxiety (7). CPTSD includes disruptions in eating as well
as non-suicidal self-injury behavior (8).

First-line interventions focusing specific symptoms included
emotion regulation strategies, narration of trauma memory,
cognitive restructuring, anxiety and stress management, and
interpersonal skills. Meditation and mindfulness interventions
were shown as an effective second-line approach for emotional,
attentional, and behavioral (e.g., aggression) disturbances (9). To
date no pharmaceutical interventions are available to treat PTSD
adequately. Glutamate seems to be an important moderator in
PTSD, while lamotrigine (LTG), a glutamate release-inhibitor,
has been proposed as a new treatment option in PTSD (10). LTG
is a member of the class of 1,2,4-triazines, in which the triazine
skeleton has substitutions by amino groups at positions 3 and
5, and by a 2,3-dichlorophenyl group at position 6. LTG use is
allowed in children and youths (> 12 years of age) only in epilepsy
therapy, and in adults in epilepsy-, myoclonus-, bipolar disorder-,
and recurrent depression therapies. In adults, PTSD symptom
reduction of around 50% occurred with LTG treatment compared
to 25% reduction in the placebo group, while a significant
weight reduction took place in obese patients taking LTG (11,
12). Based on our basic research results, we hypothesized that
adolescents with PTSD and/or obesity, LTG will decrease CPTSD
symptomatology and circulating inflammation markers, and
will reduce self-injury behavior, as well as their Body Mass
Index (BMI).

**CASE DESCRIPTION**

Our patient was a 17-year-old girl, living in a children’s home
far from her parents. She initially presented in Child and
Adolescent Psychiatry in 2015, with self-injury behavior and
suicidal thoughts. She reported that she was bullied at school,
had anxiety, and had to change school. She was started on
psychotherapy, which was continued for 2 years. Since 2018,
shortly after she moved out from her mother’s home to a
children’s facility, the patient received in- and out-patient
care at the Departments of Child and Adolescent Psychiatry
and Psychotherapy at Merseburg and the University of Leipzig
(Germany, Table 1). After several crisis interventions in both
departments and a suicide attempt by paracetamol uptake on
the 18th of January 2020, we intensified the clinical diagnostics
during her in-patient care from 22nd to the 26th of January
2020 and diagnosed complex PTSD presenting with self-injury
behavior, suicidal ideation, recurrent depressive episodes, and
overweight/obesity (BMI: 29.7 kg/m²). Furthermore, we found
increased inflammation markers (circulating C-reactive protein
and tumor necrosis factor-alpha, without an increase of interleukin 6, Table 2), which we interpreted as a result of chronic
stress (13).

Due to recurrent psychiatric crises leading to longer
episodes of in-patient care within our department of Child
and Adolescent psychiatry, we used several treatment options
(emotion regulation strategies, narration of trauma memory,
cognitive restructuring, anxiety and stress management, and
interpersonal skills). These therapeutic approaches, based on the
consensus strategy of the International Society for Traumatic
Stress Studies Complex Trauma Task Force (ISTSS), were not
sufficiently effective (9).

Thus, we decided to start a new off-label treatment option with
lamotrigine (LTG) based on evidence in adult subjects. Using the
glutamate-moderating effects of lamotrigine, we hypothesized a
beneficial role in improving PTSD symptomatology, including
self-aggressive (externalizing) and depressive (internalizing)
behavior, and a potential reduction of the inflammation markers
and BMI. After about 8 months of treatment with LTG, the
patient herself decided to stop taking this medication, so we
began tapering lamotrigine on the 14th October 2020.

The dosage schedule of lamotrigine was as follows starting at
19th February 2020:

- Week 1, 2: 0-0-25 mg
- Week 3, 4: 0-0-50 mg
- Week 5, 6: 50mg-0-50 mg
- Week 7, 8: 50mg-0-100 mg
- Week 9, 10: 100mg-0-100 mg
  (After week 34: 50-mg-0-50 mg)

**Diagnostic Assessment and Statistical Analysis**

Besides a continuous evaluation by a consultant in child
and adolescent psychiatry and psychotherapy, we used our
psychometric diagnostic trauma inventory (Table 2) focusing on
specific PTSD symptoms: Lifetime incidence of traumatic events
was assessed using the LEC-5 (1-4), a 17-item self-report screening

---

**TABLE 1 | Timeline of in- and out-patient care with the related diagnoses.**

| Time range of in-patient stay | Clinic | Diagnoses |
|------------------------------|-------|-----------|
| May-August 2018 | Clinic Merseburg | F33.2 Major depressive disorder, recurrent severe without psychic features |
| | | F44.9 Dissociative and conversion disorder, unspecified |
| December 2018 | University Clinic Leipzig | F32.1 Major depressive disorder, single episode, moderate |
| | | X84 Intentional self-harm by unspecified means |
| November 2019 | University Clinic Leipzig | F33.2 Major depressive disorder, recurrent severe without psychic features |
| | | X84 Intentional self-harm by unspecified means |
| January 2020 | Clinic St. Georg Leipzig | F39.1 Unspecified mood [affective] disorder |
| | | F21 Schizotypal disorder |
| January-February 2020 | University Clinic Leipzig | F43.1 Post-traumatic stress disorder |
TABLE 2 | Chronic stress measurement via psychometric and biological markers.

| Method of chronic stress measurement | 28th January 2020 | 26th February 2020 | 27th April 2020 | 6th October 2020 | 2nd December 2020 |
|-------------------------------------|-------------------|-------------------|----------------|----------------|------------------|
| SDQ                                 | 20                | 16                | 8              | 8              | 15               |
| SSS-8                               | 13                | 10                | 3              | 3              | 12               |
| PHQ-9                               | 21                | 8                 | 6              | 4              | 21               |
| GAD-7                               | 15                | 4                 | 4              | 5              | 14               |
| PCL-5                               | 42                | 22                | 14             | 11             | 41               |
| B-criteria for PTSD                 | 11                | 8                 | 4              | 4              | 6                |
| C-criteria for PTSD                 | 4                 | 3                 | 1              | 1              | 5                |
| D-criteria for PTSD                 | 17                | 4                 | 3              | 2              | 17               |
| E-criteria for PTSD                 | 10                | 7                 | 6              | 4              | 13               |
| Body mass index (BMI)               | 29.7              | 29.4              | 29.1           | 27.22          | 26.5             |
| Weight in kg                        | 68.2              | 72.2              | 68.8           | 65.4           | 63.7             |
| Size in cm                          | 153               | 153.8             | 154            | 155            | 155              |
| Systolic arterial pressure in mmHg  | 90                | 128               | 137            | 118            | 125              |
| Diastolic arterial pressure in mmHg | 65                | 83                | 91             | 70             | 85               |
| Mean arterial pressure (MAP)        | 73.3              | 98                | 106            | 86             | 98               |
| Heart rate in beat/minute (BPM)     | 127               | 86                | 120            | 80             | 85               |
| Tumor Necrosis Factor Alpha         | 9.0 pg/ml         | <8.1 pg/ml        |                |                |                  |
| c-Reactive Protein (crp)            | 11.47 mg/l        | 19.6 mg/l         | 13.76 mg/l     | 11.79 mg/l     | 8.11 mg/l        |
| Interleukin-6                       | <1.5 pg/ml        | <1.5 pg/ml        |                |                |                  |

SDQ, Strengths and Difficulties Questionnaire; SSS-8, Somatic symptom scale-8 items; PHQ-9, Patient Health Questionnaire-9 items; GAD-7, Generalized Anxiety Disorder Scale-7 items; PCL-5, PTSD-Checklist for DSM-5; Lamotrigine treatment was started on 19th February 2020 with 25 mg/day and reaching the final dose (200 mg/day) at 20th April 2020. Recurrent self-injury behavior until August 2020. No self-injury behavior in September, October, and November 2020. Negative Sars-CoV-2 PCR (E-Gen) pharyngeal on 13th April, 13th May, and 28th July 2020.

We measured height and body weight, blood pressure, and heart rate, while we monitored the status of self-injury behavior by body checks. As there are known side effects from changes in the activity of the limbic-brain stress axis, we closely monitored inflammatory status, especially after initiation of LTG therapy on the 19th of February 2020. No other medications were taken by the patient. During treatment, we measured circulating C-reactive protein, interleukin-6 and tumor necrosis factor-α. All chronic stress parameters were progressively reduced during the LTG treatment, including body weight and inflammation markers (Table 2). All measurements were used 4 weeks before, in the course of and after the LTG treatment (Table 2).

For statistical analysis, the mean square were generated by using the data of 4 measurements (before and after beginning the treatment with lamotrigine) of the SSS-8, PHQ-9, GAD-7, PCL-5, body mass index (BMI), mean arterial pressure (MAP), heart rate in beat/minute (BPM), c-reactive protein (crp); a = computed using alpha = 05; $F_{(3,39)} = 3.73$, $p = 0.2$, power = 77%; respecting a possible injury of the sphericity (df-correction via Greenhouse-Geisser) the power is 61% ($p = 0.04$).

Ethics Statement
The patient was 17 years of age at the beginning of the study and gave a signed informed consent together with the legal guardian according to the description of the off-label used study with LTG. Moreover, on 25 January 2021, when the patient was already 18 years of age, she gave once again a signed informed consent for the publication of any potentially identifiable images or data included in this article.

DISCUSSION
Using the glutamate modulator LTG, we showed a reduction of stress-related symptoms, including self-injury behavior, as well a body weight reduction, effects expected and substantiated...
Moreover, after reducing the treatment dose of LTG, a recurrence of the focal symptoms took place, which is in line with previous findings (10–12).

The mechanism of the moderating role of glutamate within the limbic stress system circuits is largely unknown, however, lower glutamate levels in the amygdala of more active subjects seems to be associated with less anxiety and decreased plasma cortisol (CORT) levels (3). On the other hand, lower glutamate levels in the striatum were associated with lower adrenal 11-dehydrocortisterone and higher plasma CORT (5). These inverse reaction patterns of the limbic Glu-Cort circuits could be explained by the paradigms of caco- and hyper-stasis (2). We assume that cacostasis here is associated with chronic activation of regulatory systems away from their normal state of operation, to finally establish a new “lower” set point of responsiveness to stressors, while the inverse takes place in hyperstasis. Thus, we hypothesize that more active subjects reach faster higher hyperstatic set points, that the inactive ones, via chronic physical activation.

The behavioral outcomes of the above inverse LHPA chronic stress reactions are unknown. Regarding the eating behavior of chronically stressed obese subjects indicates that hyperstatic scenarios lead to a less food intake (4). This could be similar to behavioral changes related to PTSD that should be examined in future studies.

The strengths of our approach in our adolescent patient with PTSD are the continuous evaluation and monitoring of the case by a consultant in child and adolescent psychiatry and psychotherapy, underpinned, in parallel, by our standardized psychometric inventory. Moreover, we focused not only on psychometric data, but also on anthropometric data, inflammation markers, and self-injury behavior, as indicators of CPTSD, while we minimized side effects from a potential SARS-CoV-2 infection. Our sample of one precludes any measure of a useful effect size and does not allow any general conclusions, however, earlier data indicated similar results in adults. Thus, LTG-treated patients showed improvement in PTSD symptoms compared to placebo, as well a significant body weight reduction (10–12). For patients with non-suicidal self-injury behavior diagnosed, for instance, with a Borderline Personality Disorder (BPD), limited data are available, indicating no clinical effectiveness of LTG in this condition (19). We interpreted these differences of treatment benefits between PTSD and BPD as an apparent marker for the clinical distinction of these two disorders, which should be considered, especially as the new diagnosis of “CPTSD” has been introduced within the new ICD-11 nomenclature (7, 8).

From this case we can conclude that LTG is a potentially efficacious therapeutic approach in patients with PTSD with/without self-injury and disruptions in eating behavior leading to overweight/obesity.

**Patient Perspective**

Chronic stress scenarios with phenotypic psychological and emotional challenges are to be expected in the course of the current COVID-19 pandemic. PTSD/CPTSD, as well as self-harm and disruptions in eating behavior, are just a few diagnostic examples. Mid- and long-term psychotherapeutic approaches can be supported by a temporary LTG treatment leading to a damping and/or balancing of the stress system dyshomeostatic set-points spanning the range from caco- to hyper-stasis. More evidence is needed to translate our basic research results to humans, and large cohorts of patients should be studied in placebo-controlled pharmaceutical trials.

**DATA AVAILABILITY STATEMENT**

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

**ETHICS STATEMENT**

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants’ legal guardian/next of kin. The patient was 17 years of age at the beginning of the study and gave a signed informed consent together with the legal guardian according to the description of the off-label used study with LTG. Moreover, at 25 January 2021, when the patient was already 18 years of age, she gave once again a signed informed consent for the publication of any potentially identifiable images or data included in this article.

**AUTHOR CONTRIBUTIONS**

EU and AM organized the study, analyzed the data, drafted the manuscript, and prepared the figures and tables. TP and EU collected the samples and analyzed the data. KP and GC provided intellectual and scientific input and data analyzes and interpretation. All authors reviewed the manuscript.

**REFERENCES**

1. Tang W, Hu T, Hu B, Jin C, Wang G, Xie C, et al. Prevalence and correlates of PTSD and depressive symptoms one month after the outbreak of the COVID-19 epidemic in a sample of home-quarantined Chinese university students. J Affect Disord. (2020) 274:1–7. doi: 10.1016/j.jad.2020.05.009

2. Chrousos GP. Stress and disorders of the stress system. Nat Rev Endocrinol. (2009) 5:374–81. doi: 10.1038/nrendo.2009.106

3. Ullmann E, Perry SW, Licinio J, Wong M-L, Dremencov E, Zavjalov EL, et al. From allostatic load to allostatic state—an endogenous sympathetic strategy to deal with chronic anxiety and stress? Front Behav Neurosci. (2019) 13:47. doi: 10.2139/ssrn.3242356

4. Herhaus B, Ullmann E, Chrousos G, Petrovski K. High/low cortisol reactivity and food intake in people with obesity and healthy weight. Transl Psychiatry. (2020) 10:40. doi: 10.1038/s41398-020-0729-6
5. Ullmann E, Chrousos G, Perry SW, Wong M-L, Licinio J, Bornstein SR, et al. Offensive behavior, striatal glutamate metabolites, and limbic-hypothalamic-pituitary-adrenal responses to stress in chronic anxiety. *Int J Mol Sci.* (2020) 21:7440. doi: 10.3390/ijms2107440
6. McEwen BS, Nasca C, Gray JD. Stress effects on neuronal structure: hippocampus, amygdala, prefrontal cortex. *Neuropsychopharmacology.* (2016) 41:3–23. doi: 10.1038/npp.2015.171
7. Brewin CR, Cloitre M, Hyland P, Shevlin M, Maercker A, Bryant RA, et al. A review of current evidence regarding the ICD-11 proposals for diagnosing PTSD and complex PTSD. *Clin Psychol Rev.* (2017) 58:1–15. doi: 10.1016/j.cpr.2017.09.001
8. Sar V. Developmental trauma, complex PTSD, and the current proposal of DSM-5. *Eur J Psychotraumatol.* (2011) 2. doi: 10.3402/ejpt.v2i0.5622
9. Cloitre M, Courtois CA, Charuvastra A, Carapezza R, Stolbach BC, Green BL. Treatment of complex PTSD: results of the ISTSS expert clinician survey on best practices. *J Trauma Stress.* (2011) 24:615–27. doi: 10.1002/jts.20697
10. Averill LA, Purohit P, Averill CL, Boesl MA, Krystal JH, Abdallah CG. Glutamate dysregulation and glutamatergic therapeutics for PTSD: evidence from human studies. *Neurosci Lett.* (2017) 649:147–55. doi: 10.1016/j.neulet.2016.11.064
11. Hertzberg MA, Butterfield MI, Feldman ME, Beckham JC, Sutherland SM, Connor KM, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. *Biol Psychiatry.* (1999) 45:1226–9. doi: 10.1016/S0006-3223(99)00011-6
12. Bowden CL, Calabrese JR, Ketter TA, Sachs GS, White RL, Thompson TR. Impact of lamotrigine and lithium on weight in obese and nonobese patients with bipolar i disorder. *Am J Psychiatry.* (2006) 163:1199–201. doi: 10.1176/ajp.2006.163.7.1199
13. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol Psychiatry.* (2016) 21:642–9. doi: 10.1038/mp.2015.67
14. Weathers FW, Litz BT, Keane TM, Palmieri PA, Marx BP, Schnurr PP. The *PTSD Checklist for DSM-5 (PCL-5)* (2013). Available online at: www.ptsd.va.gov
15. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J General Internal Med.* (2001) 16:606–13. doi: 10.1046/j.1525-1497.2001.016009606.x
16. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* (2006) 166:1092–1097. doi: 10.1001/archinte.166.10.1092
17. Gierk B, Kohlmann S, Kroenke K, Spangenberg L, Zenger M, Brähler E, et al. The somatic symptom scale-8 (SSS-8): a brief measure of somatic symptom burden. *JAMA Intern Med.* (2014) 174:399–407. doi: 10.1001/jamainternmed.2013.12179
18. Goodman R. The strengths and difficulties questionnaire: a research note. *J Child Psychol Psychiatry.* (1997) 38:581–6. doi: 10.1111/j.1469-7610.1997.tb01545.x
19. Crawford MJ, Sanatinia R, Barrett B, Cunningham G, Dale O, Ganguli P, et al. The clinical effectiveness and cost-effectiveness of lamotrigine in borderline personality disorder: a randomized placebo-controlled trial. *Am J Psychiatry.* (2018) 175:756–64. doi: 10.1176/appi.ajp.2018.17091006

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

*Copyright © 2021 Pham, Chrousos, Merkenschlager, Petrofski and Ullmann. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.*