PATIENT-LED RESEARCH COLLABORATIVE

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TO: RECOVER-TLC Low-Dose Naltrexone (LDN) Treatment Trial

We at the Patient-Led Research Collaborative are writing in response to RECOVER-TLC Low-Dose Naltrexone (LDN) Treatment Trial decision to retain dosage and titration schedule, despite public feedback strongly recommending adjustments. As patients, our collective lived experience starting on and titrating up medications shows that people with Long COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are more likely to be sensitive to medication. Our experience is also supported by ME/CFS clinician and expert consensus which recommends that medications should be initiated at lower dosages and slowly titrated up to avoid triggering drug sensitivities. [1–4] In pediatric patients, the recommended starting dose is ¼ to ½ the lowest therapeutic dose.[5] Research on medication sensitivity and tolerance in Long COVID and ME/CFS remains scarce, but the limited studies available suggest that drug intolerance is prevalent in these patient populations.[6] In a survey of 1309 people with ME/CFS, 16% of men and 24.8% of women reported drug allergies.[7]

It's been hypothesized that chronic inflammation in Long COVID slows down medication clearance, affecting tolerability and safety.[8] Emerging research has also identified altered cellular energy metabolism in Long COVID and ME/CFS patients,[9,10] which can be associated with changes in drug metabolism. These observations are consistent with patients' lived experience suggesting that people with Long COVID and ME/CFS metabolize compounds at different rates than other patient populations. This has been the case for LDN; over the past five years people in our communities have started taking LDN and have frequently reported needing to be on very low-dose naltrexone (0.1-0.5 mg) due to side effects, and with significant patient-to-patient variation in the time between titration doses and maximum therapeutic dose. Common side effects include insomnia, headaches, gastrointestinal problems, and vivid dreams. These side effects are most frequently reported when patients start on a dose that is too high for them, or titrate up too quickly. Anecdotally, patient reports of LDN cessation due to severe insomnia are common; sleep disturbances in Long COVID and ME/CFS can worsen post-exertional malaise (PEM) and lead to a 'crash' (a severe symptom exacerbation). These side effects can be abrogated by 1) starting at a lower medication dose than the currently proposed 1.5 mg, and 2) titrating the dose up more slowly. Some adult patients cannot tolerate the "full" 4.5 mg LDN dosage, yet experience significant positive effects from doses no higher than 1 mg/day. A retrospective review of 59 adult Long COVID patients on LDN doses 0.5-6mg (median of 2mg) reported no correlation between dosage and symptom scores, even though taking LDN was associated with symptom improvement.[11] This suggests patient-to-patient variation in what constitutes clinically meaningful doses.

Notably, even adult patients with other conditions are generally recommended starting doses lower than the 1.5 mg/day proposed in RECOVER-TLC pediatric LDN trial. It has been reported that severely ill adults with ME/CFS are more likely to experience LDN side effects, and thus lower starting doses are preferred.[12] Clinicians experienced in prescribing LDN for

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people with ME/CFS and rheumatological conditions have noted that when side-effects do occur, lower doses are better tolerated, and a 'low and slow' titration regiment starting at 0.1 mg/day is advised.[13,14] The LDN research trust recommends the following dose titration for post-viral illnesses: "*Start slow and build up slowly: 0.5-1mg daily for 14 days increasing by 0.5 to 1mg every 2 weeks until at 4.5mg or highest tolerated dose. [...] Children under 40kg - 0.1mg / kg start at 0.1mg and increase over a period of 4 weeks to calculated dose. Children > 40kg—treat as adult.*" Starting at 0.5 mg, patients >40kg can begin taking a single capsule daily containing a 0.5 mg dose and increase this to 3x daily. Once the dose is stable at 1.5 mg, capsule size can increase to 1.5 mg. From here, the dose can again be increased to 3x daily until the 4.5mg dose is achieved, or can stop at the maximal dose tolerated by each patient. This allows the study to compound capsules at 0.5 and 1.5 mg for adults and pediatric participants over 40kg. This formulation strategy should be feasible to scale throughout the clinical trial.

We applaud RECOVER for targeting LDN as a treatment for Long COVID and for including children in this clinical trial. Many Long COVID patients have described LDN as 'life-changing'-- but there are still too many barriers to getting a prescription, especially for children and teenagers. However, without careful attention to the medication dosage, the results of this trial may be murky and drop-out rates may be high, and its benefit to the patient community will be minimized. We strongly recommend the RECOVER-TLC pediatric LDN trial to use the dose titration regimen recommended by the LDN research trust. We believe this recommendation is feasible and is the safest and most effective for the pediatric population and will help retain participants through trial completion. A recent preprint study of LDN in children and adolescents with Long COVID that started a treatment regimen at 1.5 mg had a 25% rate of medication discontinuation attributed to side effects.[15] Starting at a lower dose and slowly titrating up will help understand whether and how patient subgroups differ in maximum dose tolerated, advancing our understanding of LDN mode of action and disease-causing mechanisms, and providing extremely valuable information to clinicians about how to dose LDN in pediatric populations for maximum benefit.

If you have any questions or would like to further discuss the recommendations made here, please reach out to us at team@patientledresearch.com.

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