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Treatment Approaches to Post-treatment Lyme disease & a new Clinical Trials Network

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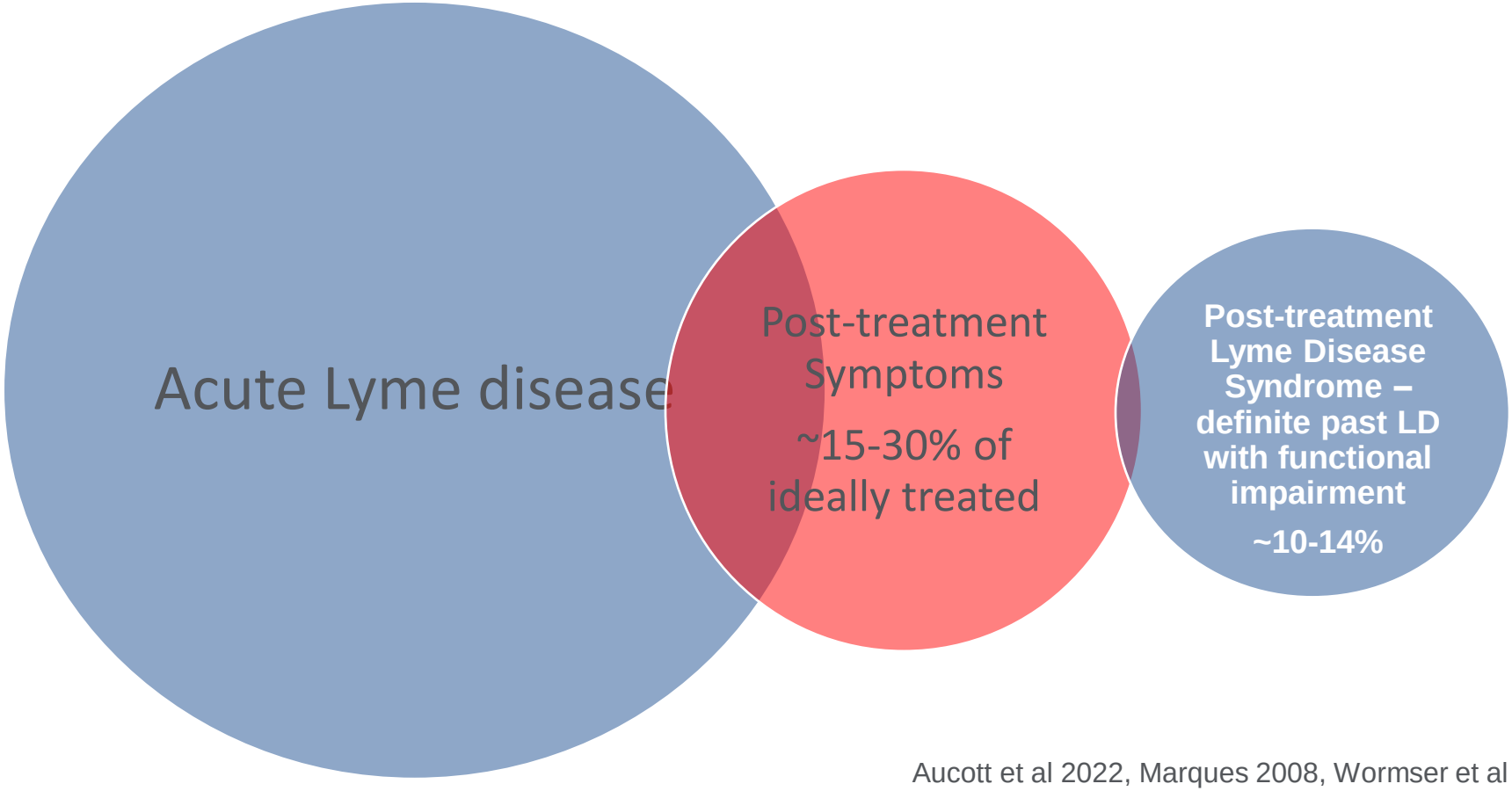
I will be discussing off-label use of medications.

Outline

- Prominent Symptoms of Post-treatment Lyme Disease
  - Including results from a nationwide study of mental disorders after Lyme disease
- Underlying Mechanisms for Persistent Symptoms
- Prior Clinical Trials
- The Lyme & other Tick-borne Diseases Clinical Trials Network
- Conclusions

Post-treatment Lyme Disease

Symptoms that persist for >6 months after treatment are not uncommon.
Risk of chronic symptoms increase with delayed treatment



Aucott et al 2022, Marques 2008, Wormser et al 2020

Ten Most Frequent Symptoms	Post-treatment Lyme disease Syndrome*	PASC/Long COVID**
1	Fatigue	Fatigue
2	Joint Pain	Dyspnea
3	Trouble Concentrating	Anosmia
4	Muscle pain	Concentration problems
5	Memory problems	Headache
6	Word finding problems	Memory impairment
8	Neck Pain	Chest Pain/discomfort
9	Paresthesias	Anxiety
10	Irritability	Myalgia

Source: *PTLDS: Rebman et al, Frontiers in Medicine, 2017
**PASC: Sneller et al, Ann Int Med, 2022

Cognitive Deficits in Post-treatment Lyme Disease

Up to 90 percent of people who meet criteria for PTLDS complain of cognitive difficulties (Aucott et al., 2013; Touradji et al., 2018).

A smaller percent (7-30%) of people with PTLDS have **objective measurable problems.** These impact short-term memory, verbal fluency, and processing speed (”brain fog”)(Kaplan et al 1992; Keilp et al 2006; Touradji et al 2018)

Unknown: Optimal treatment for persistent cognitive deficits

Lyme Encephalitis - though rare - can present with severe psychiatric disorders

A 55-year old woman presents with new onset manic psychosis (Pasareanu, Mygland, Kristensen, J Norwegian Medical Assoc 2012)

Note: **Mania was the initial symptom** followed several days later by radicular pain and weakness. **CSF Ab index wasn't positive until 8 wks after onset.** Mania, radicular pain, weakness resolved with Abx.

A 42-year old woman presents with new onset schizophrenia-like disorder (Hess et al, Biol. Psychiatry 1999)

Note: Cognitive problems and irritability followed by paranoia and hallucinations for 8 months – finally after a LP, NB was diagnosed.

No systemic physical signs or symptoms suggestive of LB were present. Full recovery after Antibiotic therapy.

Suicidal Ideation is common in patients with persistent symptoms related to Lyme disease

- 81 adults with well-documented treated LD & persistent cognitive symptoms evaluated at our Lyme Center at Columbia
- 1 in 5 reported suicidal thoughts (20%).
- Of the post-treatment Lyme patients with > mild depression, 63% had suicidal ideation
- This sample is biased against suicidal ideation, as they were not hopeless – coming to a Research Center to obtain treatment. This frequency is comparable to research patients with HIV at our site.

Doshi et al., Psychosomatics, 2018

Limitations in Some of the Neuropsychiatric Studies

- Small sample size
- Unclear diagnostic criteria
- Ascertainment bias
  - Patients from psychiatric practices or research clinics
- Lack of an appropriate control group
- How do we resolve these issues?

To address these limitations:

A Nationwide Cohort Study in Denmark of the entire population over a 22-year period

Is Lyme Borreliosis (all manifestations) associated with a higher rate of mental disorders, affective disorders, suicide attempts, & suicide?

# of Persons in Study: **6,945,837**

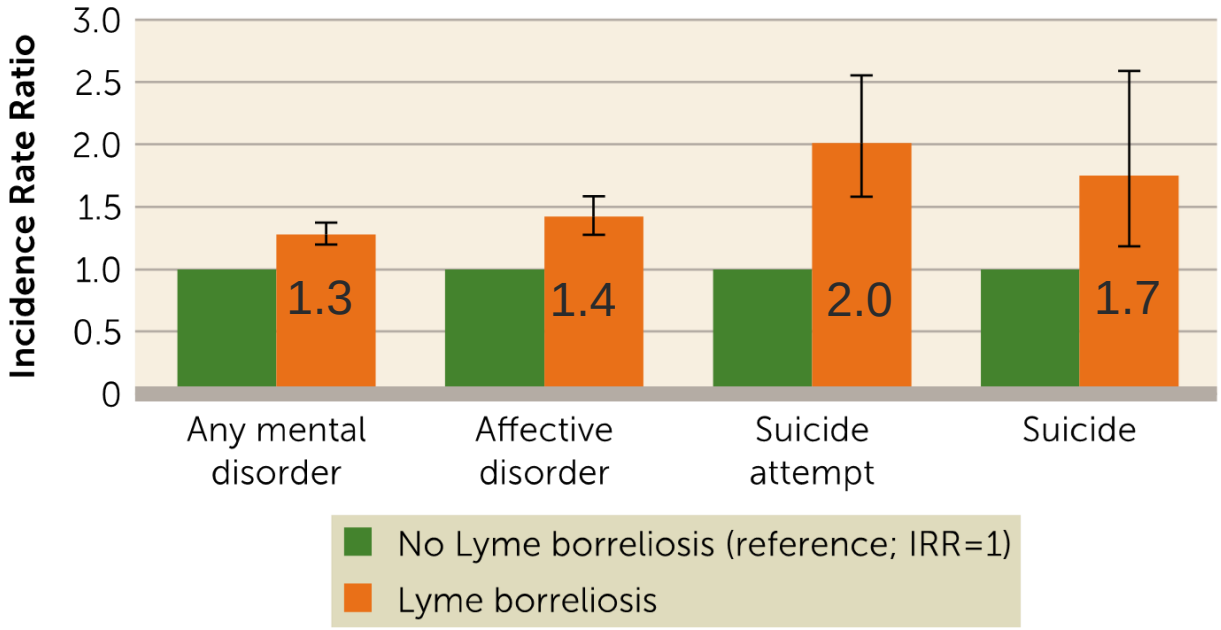
with Lyme Disease (no prior mental disorder diagnosis): **n=12,616**

Funded by Global Lyme Alliance, Inc.

Fallon et al, Amer J Psychiatry 2021

Is a hospital-based diagnosis of Lyme disease associated with a subsequently increased risk of mental disorders? YES

FIGURE 1. Incidence rate ratios for any mental disorder, affective disorder, suicide attempt, and suicide among individuals with Lyme borreliosis compared with individuals with no Lyme borreliosis in Denmark (1994–2016)[a]



(Fallon et al, 2021)

Potential mechanisms for ongoing Symptoms

Persistence of infection or remnants

- Reactivation of dormant Borrelia or other microbes

Immune dysregulation

- Ongoing activation/inflammation
- Autoimmune mechanisms

Neurologic

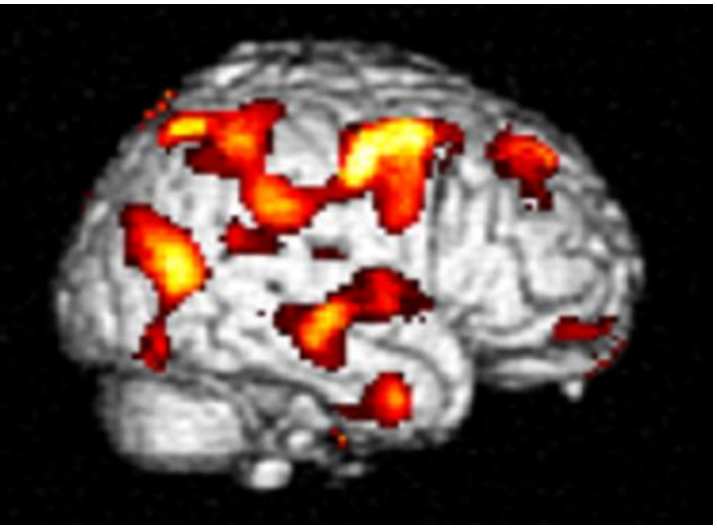
- Altered Brain metabolism/blood flow/Neural circuits
- Dysautonomia

Other possibilities: Microclots, altered GI microbiome, mitochondrial dysfunction

- Misdiagnosis

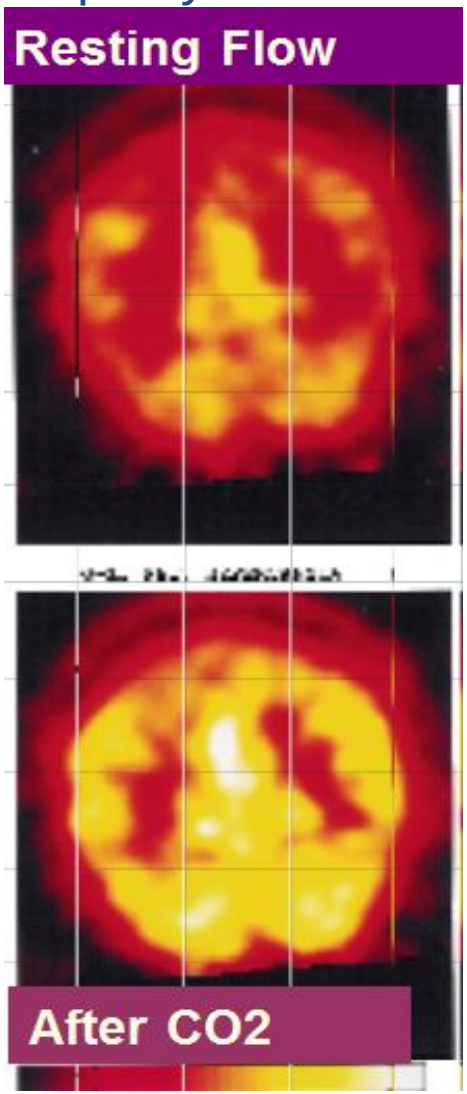
PTLDS has neurologic dysfunction: Brain metabolism and blood flow are decreased in Post-treatment Lyme Encephalopathy

(Fallon et al, 2009)



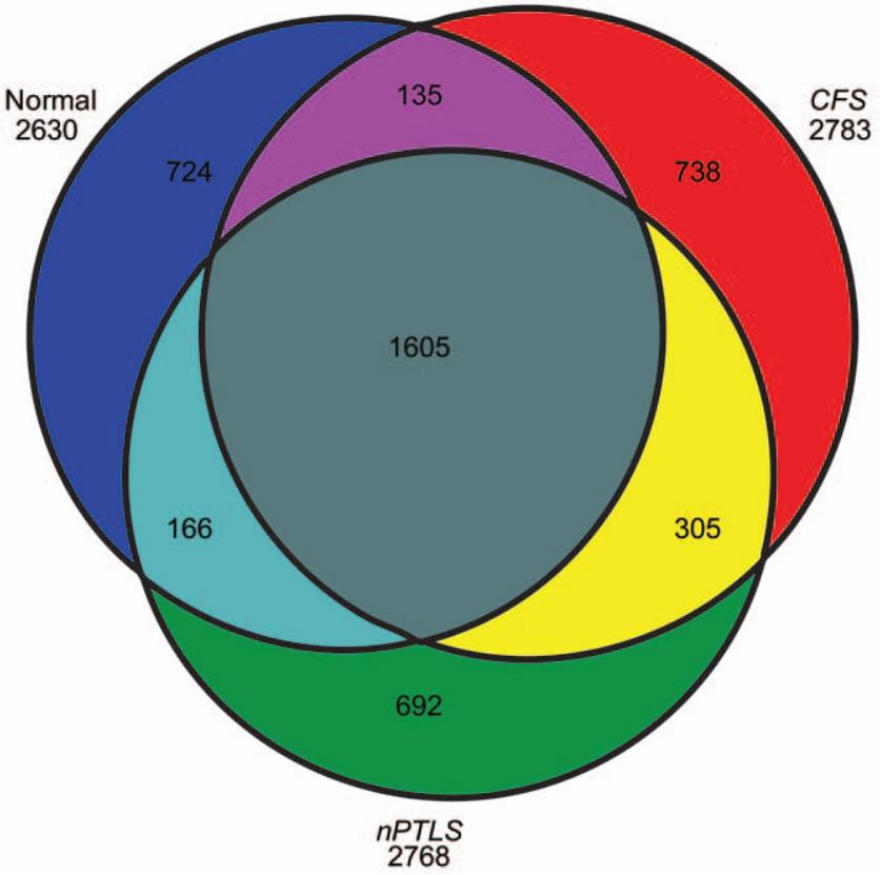
Metabolism: FDG PET (37 pts vs 18 matched controls)

O-15 PET before and after a CO2 challenge



The LYME group showed decreased regional metabolism & a diminished ability to enhance blood flow compared to controls. (**8.2% for patients vs 28.1% for controls**, p<.02)

Post-treatment Lyme disease (encephalopathy) is associated with a distinct Cerebrospinal Fluid protein profile (692 unique proteins)



- This proteomic CSF profile differentiated post-treatment Lyme disease from ME/CFS
- Greater overlap in proteins between Lyme and ME/CFS than between either and controls
- Both disorders were associated with an increase in complement cascade proteins

(Schutzer et al 2010)

PRIOR CLINICAL TRIALS OF POST-TREATMENT LYME DISEASE

Four NIH-funded Randomized Placebo-controlled Antibiotic Studies and One European controlled trial– i.e., focusing on the persistent infection hypothesis

Two Symptom-Specific Studies

- Columbia – Persistent Cognitive Impairment after Lyme (Fallon 2008)
- Stonybrook – Persistent Fatigue after Lyme (Krupp 2003)

Two Heterogeneous Symptom Studies

- New England Med Center - Persistent post-Lyme Symptoms (Klempner 2001) – seropositive & seronegative studies

One Heterogeneous Symptom Study of patients with possible/confirmed Past Lyme

- Netherlands Study (Berende NEJM 2016) Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease (Berende 2016)

Columbia Lyme Encephalopathy Study: randomized, placebo controlled

Aim: to assess improvement in cognition after 10 weeks of IV ceftriaxone vs IV placebo

- Primary Outcome – cognition/memory
- Secondary Outcomes – fatigue, pain, physical functioning
- Primary endpoint: 12 wks Sustainability – 24 wks

Screening: Of 3700 evaluated, only 1% were enrolled

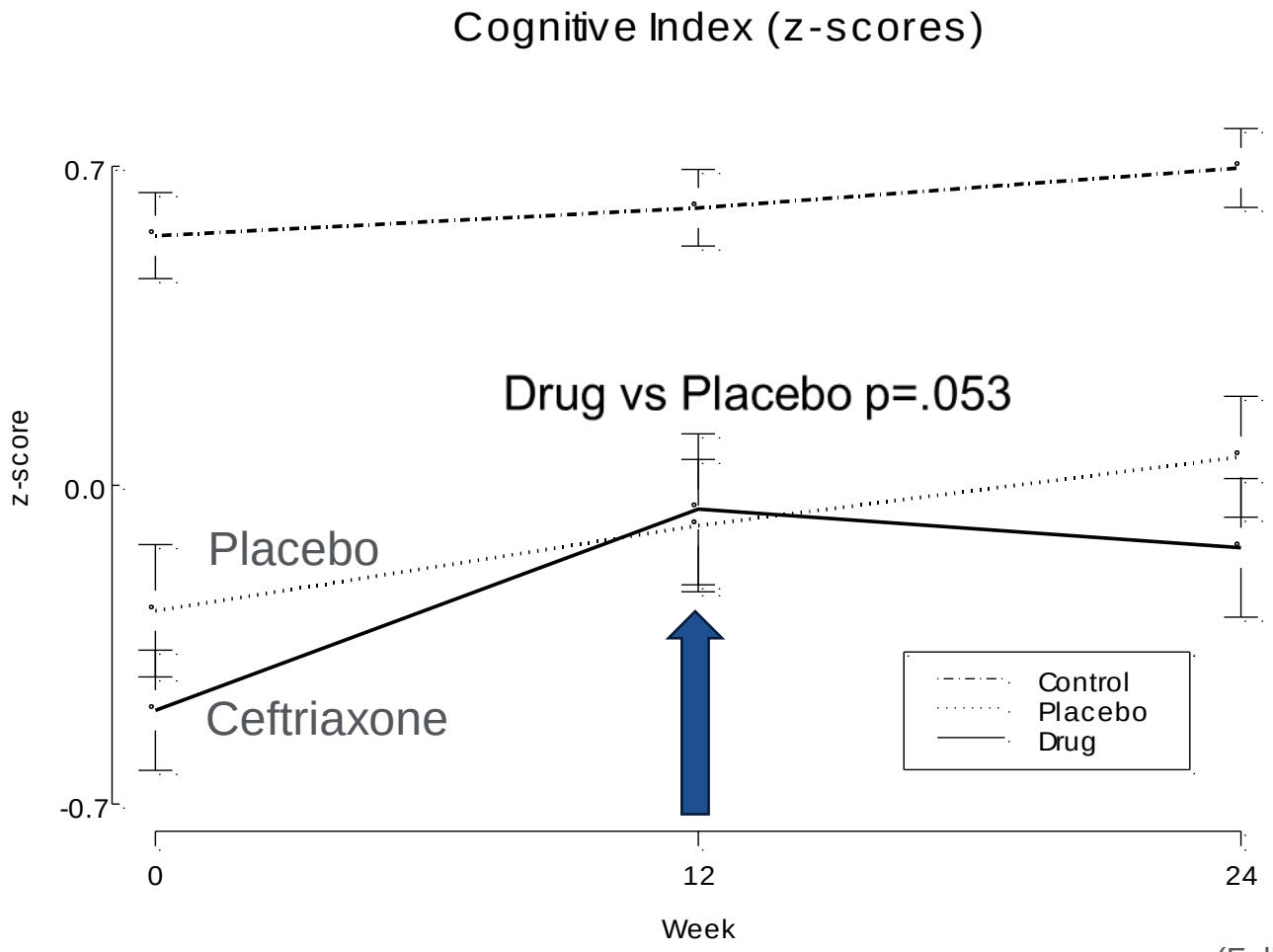
- Why? Conservative entry criteria
  - Well-documented Lyme disease meeting CDC surveillance criteria
  - Prior treatment with at least 3 weeks of IV ceftriaxone
  - Memory deficit (-1SD) confirmed by cognitive testing
  - Current positive IgG Western blot at our reference lab

Fallon et al, Neurology 2008

Significant Change in Cognition over time for 3 groups (p=.04):

10 wks of IV Drug vs Placebo followed by no treatment

Response then Relapse when off antibiotics – no sustained cognitive benefit



(Fallon et al, Neurology, 2008)

Stonybrook STOP-LD Study (Krupp et al, Neurology 2003)

55 patients with persistent fatigue despite at least 3 weeks of prior antibiotic therapy

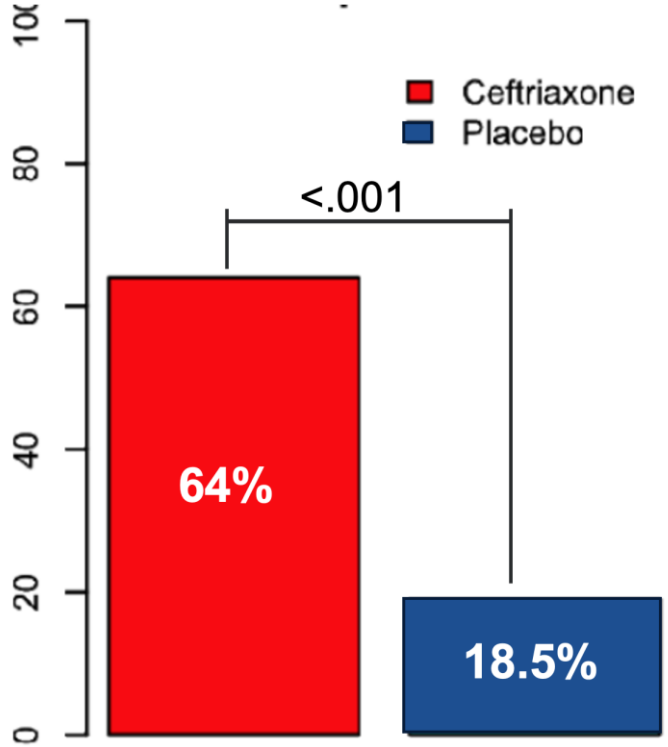
The focus for enrollment was patients with moderate severity on the Fatigue Severity Scale (also primary outcome).

Random assignment to 1 month of IV ceftriaxone or placebo followed by 5 months of no treatment.

Primary end-point: 6 months

Stonybrook STOP-LD Primary Outcomes

Significantly more responders for the ceftriaxone group on the primary clinical outcome of Fatigue



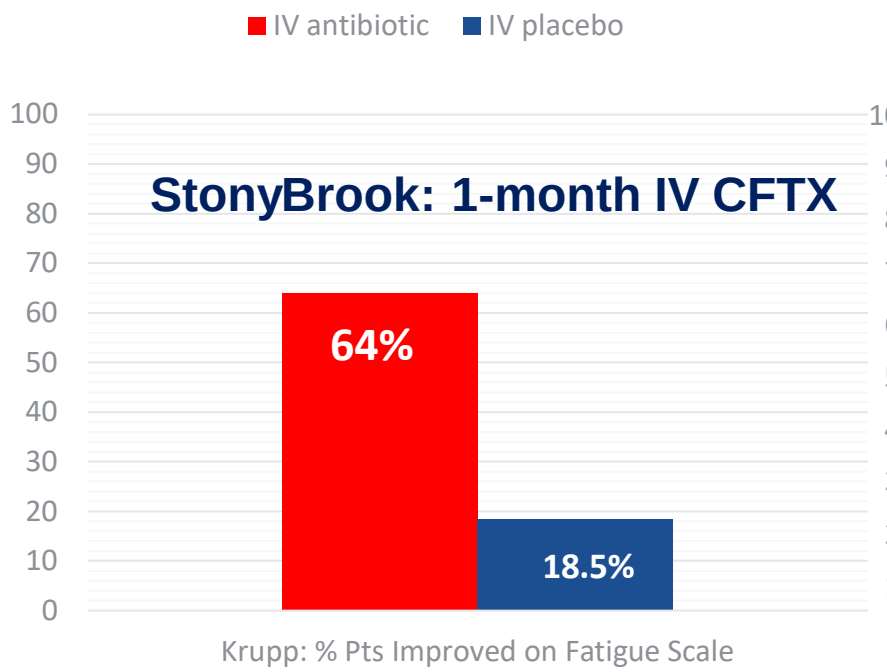
% of Responders on Fatigue

No improvement in reaction times, but "deficits were relatively mild which may have contributed to a lack of a treatment effect"

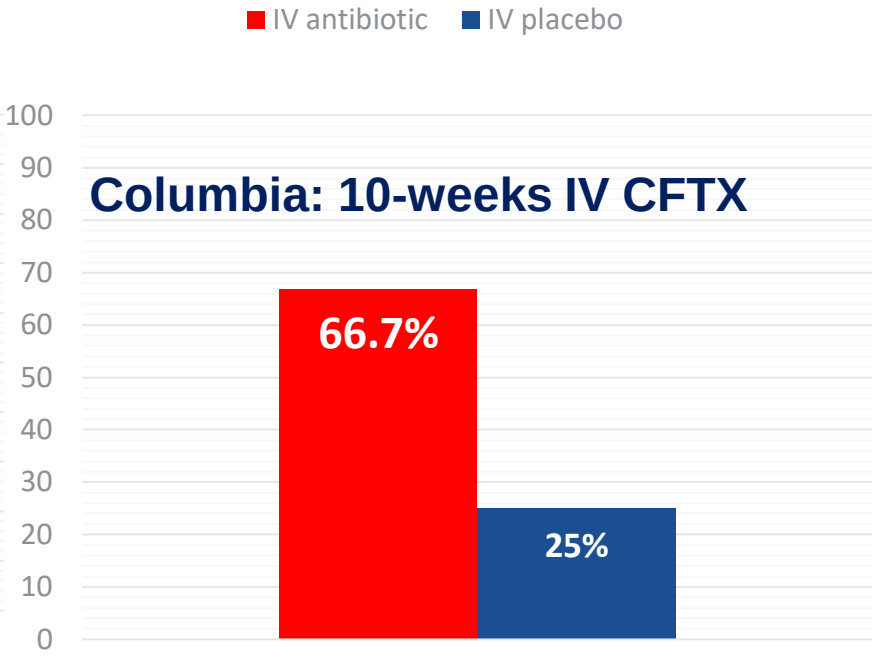
No reduction in OspA antigen but "only 16% had this marker at baseline… it was not a useful measure of outcome"

STOP-LD Study (Krupp, Neurology 2003)

Comparing Two PTLDS Studies – Similar % of responders on fatigue severity scale at 6 months (Krupp 2003; Fallon 2008, 2012)



Krupp: % Pts Improved on Fatigue Scale



Fallon: % Improved on Fatigue Scale

Effect Size: Moderate to Large

But both studies reported safety concerns related to IV administration, leading to not recommending this treatment given risk/benefit issues

New England Medical Center Study of PTLDS

129 seronegative & seropositive patients

- Enrolled based on report of functional impairment – but moderate or greater degree of impairment on a measure was not used for enrollment.

Randomly assigned to:

- 30 days of IV Ceftriaxone + 60 days of oral doxy
- 30 days of IV placebo + 60 days of oral placebo

Primary outcome results:

- No difference in functional outcome at 6 months as assessed by the SF-36 measure between drug and placebo

Secondary outcome results:

- No difference in change for cognition or depression.

Klempner et al, NEJM, 2001

Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease (Berende et al, NEJM 2016)

280 patients with symptoms from Netherlands

- The sample was heterogeneous, including patients with previously treated confirmed LD and those with probable past LD based on typical symptoms and a positive IgM or IgG Western blot. 11% had never before been treated for Lyme
- Physical functioning was primary outcome (but not used for enrollment).

All received 2 weeks of IV ceftriaxone plus

- Group 1: 12 weeks of oral placebo pills, or
- Group 2: 12 weeks of oral doxycycline, or
- Group 3: 12 weeks of oral clarithyromycin and hydroxychloroquine ("Biaxin & Plaquenil")

Results of Netherlands Trial

Was there sustained benefit with longer-term antibiotic therapy compared to placebo? No, all groups improved in physical functioning SF-36 score

Did the initial 2 weeks of IV ceftriaxone lead to benefit? Perhaps, all groups (including the CFTX followed by Placebo) demonstrated improvement

Strengths of this study: large sample size, testing whether response was sustained among people with probable and confirmed Lyme disease.

Comments/Limitations:

a. This was not a study to assess impact of repeated antibiotic therapy – but a study of whether longer term antibiotics led to sustained improvement.

b Sample heterogeneity may have diminished likelihood of response

c. Patients were not enrolled based on severity score of primary outcome

Other published controlled trials & clinical series for patients with post-treatment Lyme Symptoms

Amoxicillin Randomized, Placebo controlled. Persistent LD. (Cameron et al 2008)

Dapsone Clinical series. Chronic Lyme/PTLDS. (Horowitz et al, 2019, 2020, 2022)

Disulfiram Clinical series. Persistent Lyme Disease. (Gao et al 2020; Liegner 2019)

Gabapentin: Open label. Chronic Neuropathic Lyme Pain (Weissenbacher et al 2005)

Kundalini Yoga: Randomized, Wait-list Controlled. Persistent Lyme Fatigue and Pain (Murray et al 2022)

Global Symptom Questionnaire – 30 items

(Fallon et al, Frontiers in Medicine 2019) (in collaboration with Drs. Aucott and Zubcevik)

Validated infection-associated multisystem burden questionnaire – sensitive to detecting change over time – symptom burden is associated with functional impairment.

SYMPTOMS. During the past 2 weeks, how much have you been **bothered** by any of the following?

Rate "bother" for the past 2 weeks	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. Shortness of breath	0	1	2	3	4
2. Feeling feverish	0	1	2	3	4
3. Sweats and/or chills	0	1	2	3	4
4. Nausea and/or vomiting	0	1	2	3	4
5. Back pain	0	1	2	3	4
6. Headaches	0	1	2	3	4
7. Stiff or painful neck	0	1	2	3	4
8. Muscle aches or pains	0	1	2	3	4
9. Joint pain or swelling	0	1	2	3	4
10. Muscle weakness	0	1	2	3	4
11. Feeling fatigued or having low energy	0	1	2	3	4
12. Feeling worse after normal physical exertion	0	1	2	3	4
13. Trouble falling or staying asleep	0	1	2	3	4
14. Needing more sleep than usual	0	1	2	3	4
15. Not feeling rested on awakening	0	1	2	3	4
16. Numbness or tingling	0	1	2	3	4
17. Shooting, stabbing or burning pains	0	1	2	3	4

THE LYME & OTHER TICK-BORNE DISEASES CLINICAL TRIALS NETWORK

Launching a Clinical trials Network for Lyme and other Tick-borne Diseases

Need: well-designed treatment studies to improve treatment guidelines internationally

Advantages of a clinical trials network

- Harness strengths across academic centers (e.g., biosignatures, diagnostics, clinical trials)
- Multi-site trials allow for larger sample sizes and faster recruitment & study completion & and larger biorepository of samples for biomarker studies
- Conduct studies that use common measures to assist comparison

Approaches to treatment selection:

- Draw from in vitro, animal, and human TBD studies and clinical reports
- Draw from successful treatments in related disorders
- Draw from large data mining studies using registries or EHRs
- Draw from recommendations from the patient and medical community

General aim: Maintain a portfolio of treatment studies that address a variety of disease mechanisms that may underly ongoing symptoms.

Lyme Tick-borne Diseases Clinical Trials Network

Columbia University: central network coordinating center

Initial node principal investigators:

- Columbia: Brian Fallon, MD, Mara Kuvaldina, PhD
- Hopkins: John Aucott, MD
- Children's National Hospital: Roberta DeBiasi, MD

Network is being expanded

Pilot study grants have been awarded

Website: www.lymectn.org

Funding support: Steven & Alexandra Cohen Foundation, Inc

Current and Upcoming Network Studies

Columbia: Long Lyme Fatigue: taVagus Nerve Simulation (Fallon/Kuvaldina)

Long Lyme Brain Fog: Transcranial Direct Current Stimulation with Cognitive Retraining (Gorlyn)

Long Lyme Depression: Intravenous Ketamine with Cognitive Retraining (Keilp)

Hopkins: Tetracycline for Post-Treatment Lyme Dis (Aucott)

Psilocybin for PTLDS (Garcia-Romeu) (not CTN)

Children's National Hospital: Early neurodevelopmental outcomes of exposure to Lyme disease when treated during pregnancy (Mulkey/DeBiasi)

University of North Carolina: Mast Cell Treatments for post-tick bite illness (Commins)

Underlying Premise for CTN Studies

Effective treatments modify the underlying mechanism of disease. Multiple mechanisms may be contributing either individually or in combination to cause persistent symptoms. These mechanisms are varied and interact. Examples:

- Persistent infection or remnants of infection may trigger ongoing inflammation.
- Autoimmune reactions to Bb may lead to arthritis or neurologic symptoms.
- Neural network dysregulation secondary to blood flow, metabolic, neuroreceptor, or neurotransmitter changes can lead to a wide range of problems, including changes in mood, cognition, sleep, energy, and pain.
- Gut microbiome changes may impact immune function or brain activation.

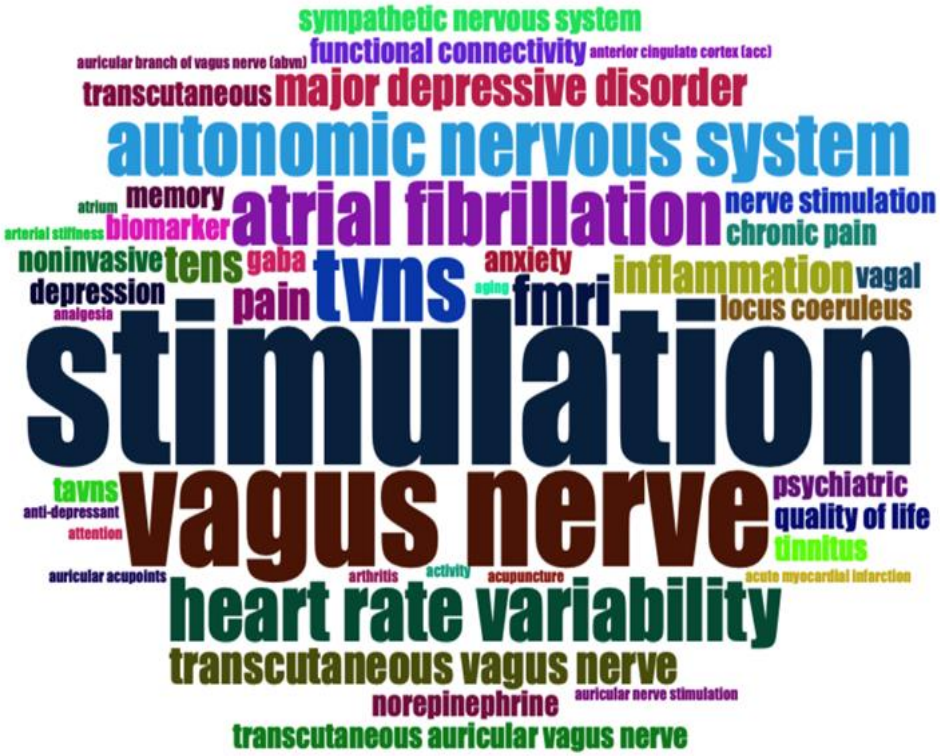
Other factors may impact an individual's recovery trajectory, such as:

- Genetic vulnerabilities to autoimmune disease may impact an individual's response to infection.
- Unrecognized coinfections or a history of other medical conditions may also alter an individual's recovery trajectory.

Potential Therapies

- Targeting persistent Infection
  - Repeated antimicrobial therapy
- Targeting immune activation
  - Consideration of IV Ig? (e.g, autoimmune neuropathies)
  - Consideration of specific immune biologics (e.g., rheumatoid arthritis)
- Targeting altered neurotransmitter systems
  - Glutamate, GABA, Serotonin, Norepinephrine
  - Autonomic nervous system focused therapies
- Targeting an altered microbiome
- Neuromodulation: tDCS, taVNS
- Stress reduction and Psychotherapy
  - Meditation/Yoga, Coping Skills Training, CBT
- Rehab: cognitive and physical

Why the Vagus Nerve?



- Innervates multiple organ systems
- Modulates Inflammation & neural activation
- Over 300 VNS studies underway: neurologic, psychiatric, rheumatologic GI, cardiac, peri-infectious, pain
- FDA approved for epilepsy, depression, migraines, stroke rehabilitation

Transcutaneous auricular Vagus Nerve study: Lupus erythematosus

A randomized, double-blind, sham-controlled trial of 18 patients with SLE and pain

12 with taVNS and 6 with sham stimulation

Results:

In this small study, taVNS led to a significant reduction of fatigue and of pain and of joint swelling compared to sham taVNS after only 4 sessions.

Substance P was decreased to a greater extent in taVNS compared to sham taVNS.

(Aranow et al, Annals of Rheumatic Disease 2021)

tVNS and COVID

Case studies show subjective improvement in symptoms:

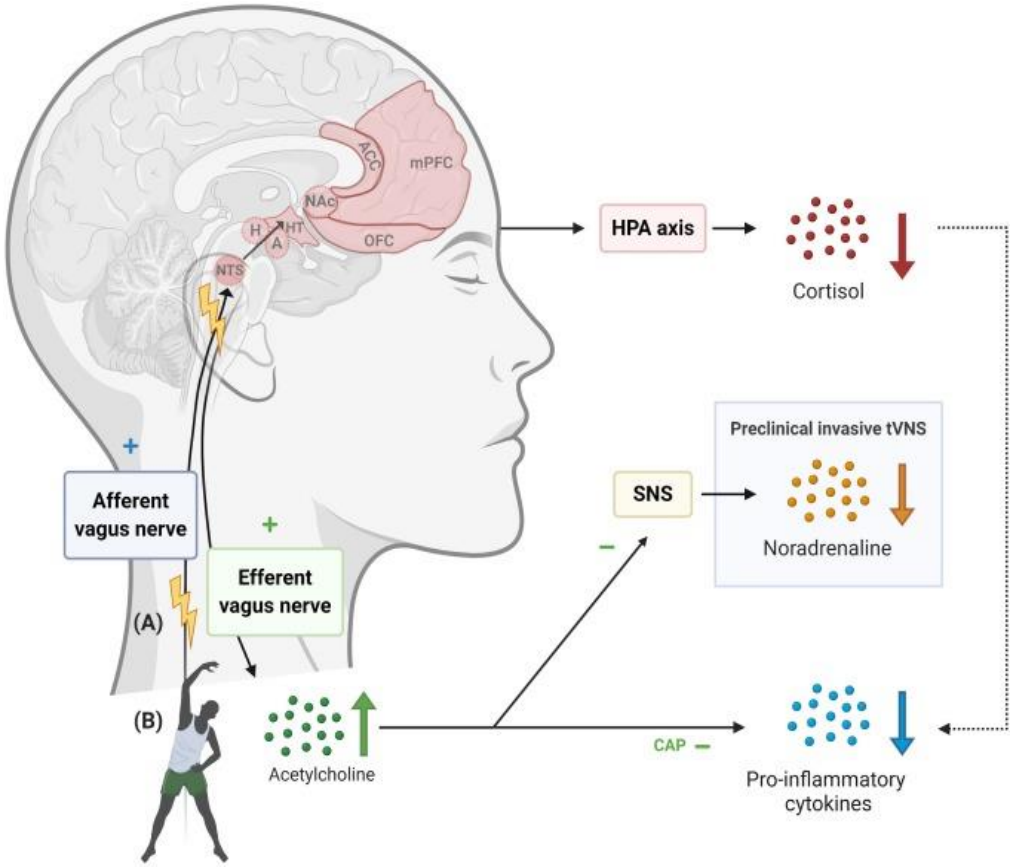
- *Staats P et, Neuromodulation. 2020*

Clinical Trials:

- ***Pilot open label at home taVNS for Long COVID with ME/CFS*** *(Natelson 2022).*
- ***8/14 (57%) were ME/CFS responders*** *with no adverse events*

- ***Pilot-randomized at home taVNS for Long COVID*** *(Badran et al 2022) –* ***n=13*** *taVNS was* ***feasible, safe, trend in reducing mental fatigue***

- ***Randomized Controlled Trial of non-invasive Vagus Nerve Stimulation for acute hospitalized CoViD-19 Respiratory Symptoms*** *(Tornero SAVIOR I, 2022)- USA* ***(n=97)*** *VNS led to* ***sig reduction in inflammatory markers (CRP and procalcitonin) but not in respiratory outcomes***



Pathways by which vagal function-enhancing interventions can normalize biological functioning and improve mental health (from Dedonker et al., 2021)

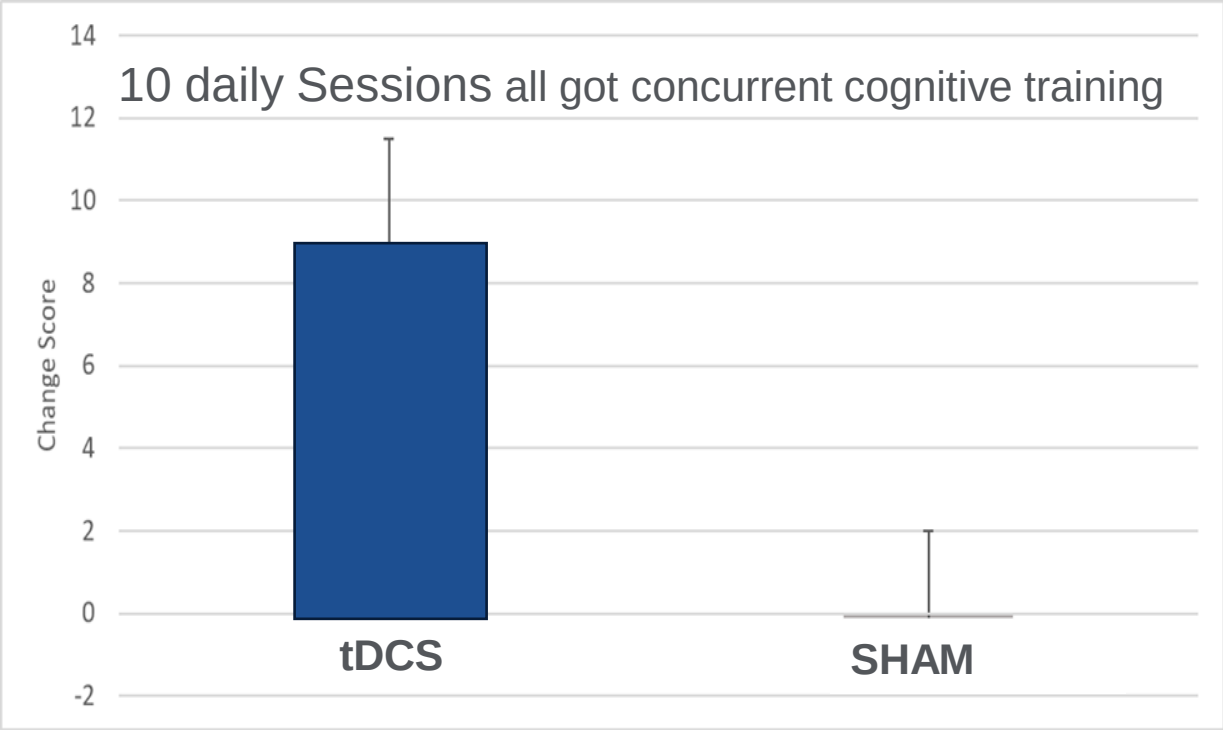
Dedoncker et al Mental health during the COVID-19 pandemic and beyond: The importance of the vagus nerve for biopsychosocial resilience. *Neuroscience & Biobehavioral Reviews*, 2021

Transcranial Direct Current Stimulation to improve Processing Speed in Multiple Sclerosis

- tDCS effects are cumulative - daily applications needed
- Cognitive Improvement with tDCS is enhanced if given concurrently with a cognitive task & may be sustained to 6 months (Mattioli 2016)

Processing Speed Significantly improved after tDCS among patients with *Multiple Sclerosis*

from Mattioli et al., 2016; *Multiple Sclerosis Journal*



Learning from Lyme

Learning from Lyme – to help other Long Hauler Syndromes

- Patients are suffering
- Lives may be profoundly altered
- Patients do not know when -or if- they will return to their pre-illness state
- Symptoms will vary – good days & bad days
- Social isolation occurs due to light sensitivity, sound sensitivity, profound fatigue, brain fog, pain
- Family, work, & economic stressors increase

Learning from Lyme – to help all Long Haulers

How might some medical providers respond?

a) Invalidation because symptoms are “subjective”. This is often quite traumatic to the patient

b) validation & acknowledgement of uncertainty is helpful

Some clinicians may turn patients away because:

a) ”evidence-based treatments” are not yet available – they have no guidelines

b) The presentation is too complex for a 30’ evaluation

c) The neuropsychiatric symptoms cloud the evaluation

A message of hope to convey to patients:

Our long-term follow-up study of Lyme encephalopathy indicated that most patients - even the very ill- can get substantially better (or recover) over time.

Agenda for the future

- Conduct research studies targeting different mechanisms of disease to identify most effective treatment approaches for Lyme & other TBD
  - Collect biological samples for biomarker studies
  - Enroll patients who meet severity criteria for primary clinical outcomes
- Expand the research study populations to include those with probable and possible Lyme/other tick-borne disease, as these patients comprise a large portion of those with chronic symptoms & have been neglected by research
- Educate health care providers about the multiple presentations, including the neuropsychiatric ones and the need to screen for suicidal thoughts/behaviors
- Encourage creation of “infection-associated multisystem illness clinics” in major medical centers that include clinicians from multiple disciplines so as to best help these patients with chronic illness.

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Our patients, our collaborators, our donors, & LTD CTN investigators