

# Does Long-term Antibiotic Therapy Improve Persistent Symptoms Associated with Lyme Disease?

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# Case Presentation

- 43 yr woman Northern Maryland
  - July: myalgia, arthralgia, headache, low-grade fever x 7d
  - Notes enlarging rash
  - Tick bite not recollected
  - Doxycycline 100mg PO q12h given x 14d
  - Rash resolves, symptoms improve



# Case Presentation

- August: return of arthralgia, myalgia, fatigue
  - Lyme Serology
    - EIA positive
    - IgM WB negative (1/3 bands reactive)  
IgG WB positive (8/10 bands reactive)
  - Treated with doxycycline 100mg PO x 4 weeks
  - Some improvement
- November through next summer
  - Prominent fatigue, difficulty concentrating, poor sleep, myalgia/arthralgia – symptoms wax and wane
  - Prior to this illness, patient otherwise well

# Case Presentation

- PMH: occasional migraines, normal childbirth
- SH: Married, gardener. Lives on large lot with woods.
- FH: (-) autoimmune diseases
- Medications: ibuprofen
- PE: Afebrile, 102/68, P78 regular
  - Normal exam including musculoskeletal, neurological
  - No tender/trigger points

# Case Presentation

- Additional laboratories
  - Normal Heme 8, chemistries, urinalysis
  - Normal TSH
  - ESR 4mm/hr, CRP < 0.1



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# Lyme Disease: expectations

- Uncommon objective problems after treatment
  - Meningitis – rare, on initial or just after oral therapy
  - Facial Palsy – often within first week
  - Persistent inflammatory arthritis –  
~10% of treated chronic Lyme arthritis patients
- Subjective problems (prospective studies, EM)<sup>1</sup>
  - 24% with mild symptoms at 3 months
  - 5-17% with symptoms 6-12 months

<sup>1</sup>Ann Intern Med 2003; 138: 697. Am J Med 2003;115:91

# Lyme Disease: expectations

- Co-infection may increase early symptoms but not long-term outcome<sup>1</sup>
  - Babesia
  - Human granulocytic anaplasmosis

<sup>1</sup>JAMA 1996; 275:1657. CID 2000; 31: 1149. CID 2002; 34:1184

# Lyme Terminology

## ■ Favored

Late Lyme disease

*objective symptoms*

(neuroborreliosis, late  
arthritis)

Post-Lyme Disease  
Syndrome

*subjective symptoms*

## ■ Not Favored

Chronic Lyme disease

Chronic Lyme disease

# Proposed Post-Lyme Disease Syndrome Definition

- Lyme disease defined by CDC criteria
- Concluded appropriate antibiotic course
- 6 months after LD diagnosis or treatment
  - Fatigue
  - Widespread musculoskeletal pain
  - Cognitive problems
  - Substantial reduction in functional status
- Exclusions: coinfection, prior CFS/fibromyalgia or undiagnosed similar problems, other medical explanation, active – infectious Lyme disease (e.g., neuroborreliosis, persistent Lyme arthritis)

Wormser GP, et al. Clin Infect Dis 2006; 43: -

(accessed: <http://www.journals.uchicago.edu/CID/journal/issues/v43n9/40897/40897.html>)

# Longer-term Antibiotic Courses Do Not Influence Outcomes

- Prospective trials – longer therapy without benefit

- Early Lyme Disease<sup>1</sup>

- (n=108: PCN, TCN, erythromycin)

- Erythema migrans<sup>2</sup>

- (n=180: 10d doxy +/- CTX v 20d doxycycline)

- Late Lyme disease<sup>3</sup>

- (n=143: 14d vs. 28d CTX)

- Culture confirmed LD<sup>4</sup>

- n=96, 81 f/u > 1yr -10% sx (mean 5.6 yrs), only 4% at every visit. 15% had second case of EM

<sup>1</sup>Ann Intern Med 1983;99:22. <sup>2</sup>Ann Intern Med 2003. 138:697.

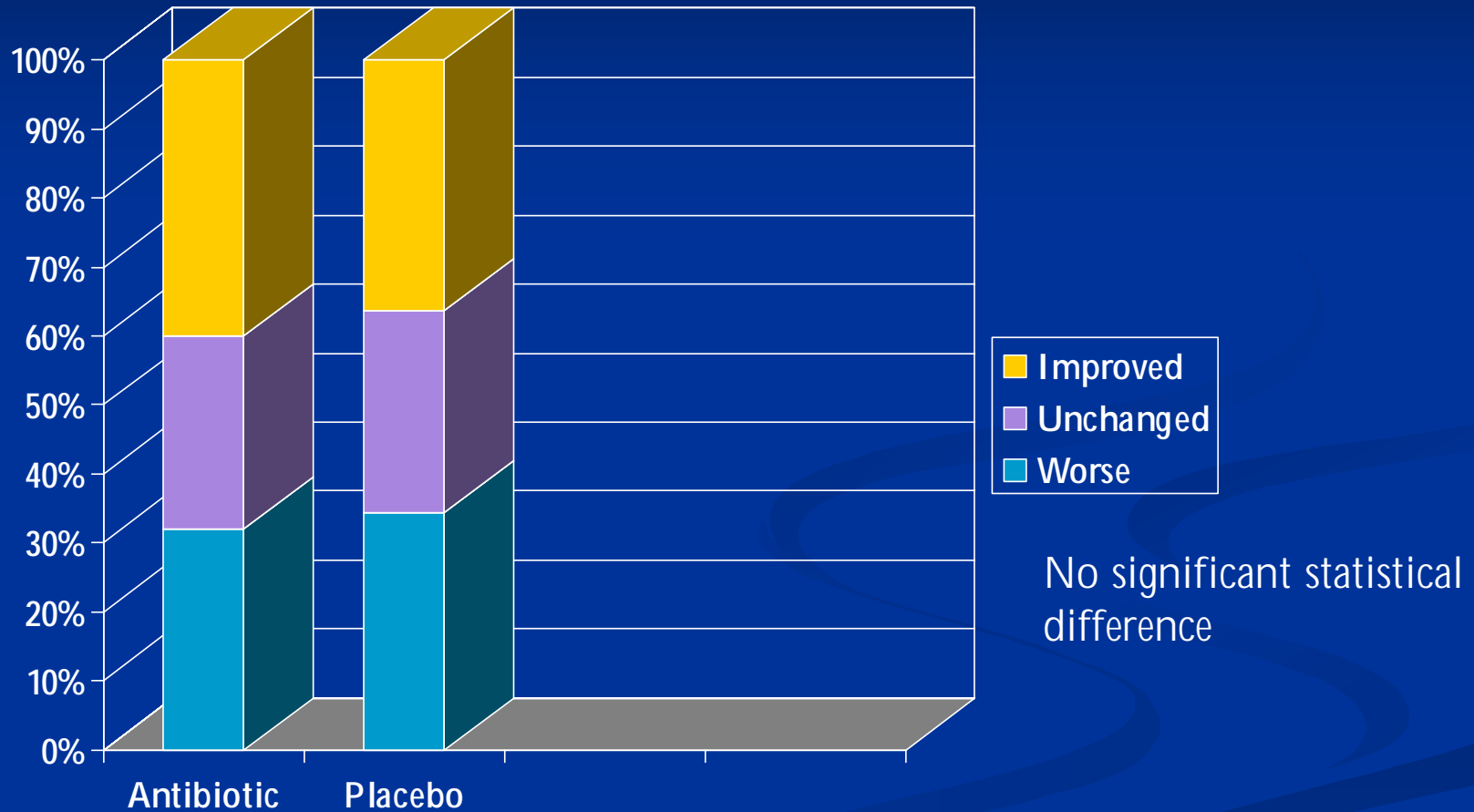
<sup>3</sup>Wein Klin Wochenschr 2005; 117:393. <sup>4</sup>Am J Med 2003. 115:91

# Persistent Symptoms – Controlled Trials

## Antibiotic Treatment v. Placebo

- 78 pts seropositive IgG antibodies and 51 pts seronegative but all had clinical Lyme disease
- Entry criteria
  - Well documented Lyme disease, prior abx treatment
  - Persistent musculoskeletal pain, neurocognitive symptoms (>70%), dysesthesia, fatigue (90%)
  - Average duration of symptoms: 4 years
- Ceftriaxone 2 gm IV q24h x 30d then doxycycline 200 mg x 60d vs. matched placebos
- Primary outcome: SF-36 scale measuring the health-related quality of life – at d180

# Overall Outcomes d180 SF-36



Klempner M, et al. NEJM 2001; 345:85

\*No evidence of persistent infection  
*B. burgdorferi* by Cx or PCR in blood, CSF  
(700 samples in 129 patients)

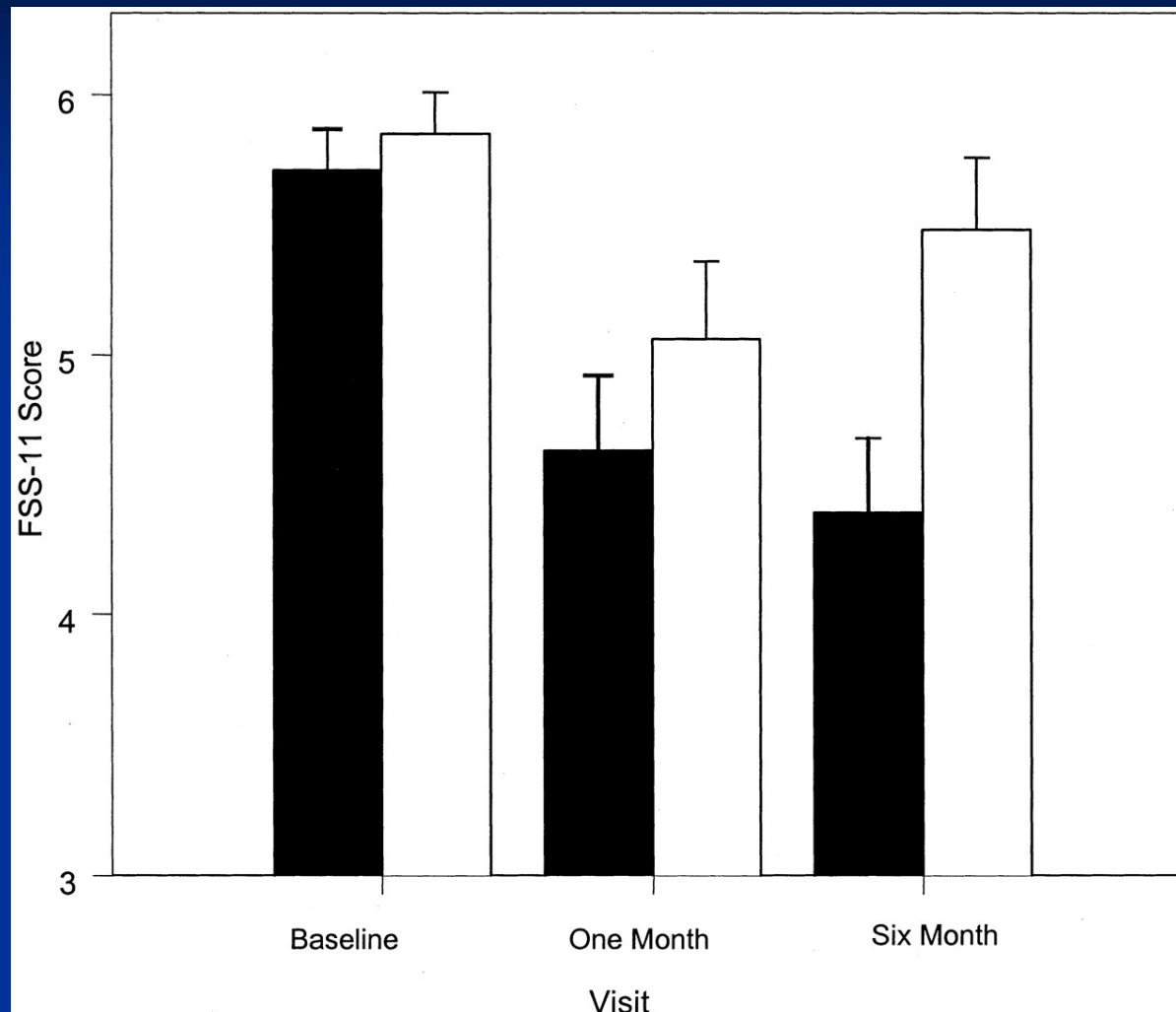
# Cognitive Function: Lyme disease

- Companion study, n=129
- Used cognitive objective testing, mood scores
- >70% gave cognitive dysfunction as complaint at study entry
  - Patients had normal baseline neuropsych testing
  - Suggests symptom report    objective evidence
- No significant differences between groups

# STOP-LD Trial

- Single prospective center trial, n=55
- Patients with severe fatigue
- CTX 2g IV q24h x 28d vs. placebo
- End point 6 months: three primary outcomes
  - fatigue score (11-item questionnaire)
  - Change in mental speed
  - Clearance of borrelial antigen in CSF

**Fatigue Severity Scale (FSS-11) scores**  
**ceftriaxone (black columns; n = 26) and placebo (white columns; n = 22)**



Krupp LB, et al. Neurology 2003;60:1923

# STOP-LD

- Fatigue benefit but...
- No change in any other primary endpoint
  - Neurocognitive functioning, biomarkers
- Serious adverse events – requiring hospitalization
  - 7% (4/55)
- Authors conclude CTX unjustified due to single (non-specific) factor improvement and adverse events
- Criticisms:
  - Lack of blinding, patients guessed who received active therapy
  - Loss of patients especially in placebo group

# "Lyme" Patients Presenting to a Lyme Center

- N = 788
- Active Lyme disease 23%
- Prior Lyme disease 20%
- Not Lyme disease  
(CFS, fibromyalgia) 57%

Majority without active LD or never had LD

Implication: use of serology with poor-predictive value  
in patients without objective symptoms

# Findings in “normal populations”

- Non-deployed military personnel  
(Gulf War Syndrome Study, n=4886)
  - Depression 10.9%
  - Anxiety 1.8%
  - Alcohol abuse 12.6%
  - Fibromyalgia 9.6%
  - Chronic fatigue synd 0.3%

# Symptoms in General Populations

- Chronic Fatigue 20-30%<sup>1</sup>
- Arthritis 21.5%<sup>2</sup>
- Serious pain 3.72-12.1%<sup>3</sup>
- Fibromyalgia 2%<sup>4</sup>
- Background problems in average population make difficult interpretation of LD non-specific symptoms

<sup>1</sup>Ann Int Med 1995; 123:81. Ann Intern Med 2001; 124:838

<sup>2</sup>MMWR 2005;54:484

<sup>3</sup>J Rheumatol 1993; 20:710

<sup>4</sup>Arthritis Rheum 1995;38:19

# Lyme Is Not Unique for Causing Post-infectious Fatigue

- Bacterial
  - *Coxiella burnetti* (Q fever)<sup>1</sup>
  - Brucella<sup>2</sup>
- Viral
  - EBV<sup>3</sup>
  - Viral hepatitis<sup>4</sup>
  - Viral Meningitis<sup>5</sup>
- Parasitic
  - Toxoplasmosis<sup>6</sup>
- Toxin
  - Toxic Shock Syndromes<sup>7</sup>
- Sepsis<sup>8</sup>

<sup>1</sup>QJM 1998; 91:105, <sup>2</sup>JAMA 1934;103:665, <sup>3</sup>Brit J Gen Prac 2002; 52:844,

<sup>4</sup>J Viral Hepat 1995; 3:133, <sup>5</sup>J Neurol Neurosurg Psych 1996; 60:495, <sup>6</sup>Prin Prac ID; Chap 257 1995

<sup>7</sup>Ann Intern Med 1982;96:865 <sup>8</sup>Crit Care Med 2000; 28:3599

# Post-infectious Fatigue

- No link to pedestrian viral illness –
  - Routine viral (upper respiratory tract) illnesses<sup>1</sup>
- Prospective cohort study<sup>2</sup>
  - 253 patients, Dubbo Australia with acute EBV, Q fever, Ross River Virus
  - 6 months: 12% w/ fatigue, musculoskeletal problems, mood disturbance, neurocognitive problems
  - 11% fit definition for chronic fatigue syndrome
  - Conclusions:
    1. Uniform post-infective syndrome may arise from different viral and non-viral infections.
    2. Infection may cause CFS.

<sup>1</sup>Lancet 1995; 345:1333, <sup>2</sup>BMJ 2006; 333:575

# Arguments Against Prolonged Antibiotics for Lyme Disease

1. Lack of objective disease progression
2. Long-term outcome studies
3. Interventional antibiotic trials
4. Other spirochetal illnesses don't require long-term rx
  - Syphilis
  - Endemic syphilis (Yaws, Pinta)
  - Other *Borrelia* (Relapsing Fever, tick/lice borne)
  - Leptospirosis
  - Rat-bite fever (*Spirillum minus* without endocarditis)

# Arguments Against Prolonged Antibiotics for Lyme Disease

5. Lack of antibiotic resistance *Borrelia burgdorferi*<sup>1</sup>
6. Primum non nocere
  - Risk of antibiotics: ADRs, *C. difficile* colitis, line infections, antibiotic resistance
  - May argue theory and some studies, but no convincing evidence to suggest long-term antibiotics beneficial
7. Concern: if functional impaired patients told they're ill, need treatment—tendency to reinforce symptoms, self-perpetuate illness<sup>2</sup>

<sup>1</sup>Hunfeld KP, et al. Antimicrob Agents Chemother 2005;49:1294.

<sup>2</sup>Barsky AJ, Borus JF. Functional somatic syndromes. Ann Int Med 1999;130:910

# Why the controversy?

- Subjective complaints as basis for post Lyme disease syndrome
- Prior studies without standardized case definition
- Symptom complex common in populations
- Patients may not have/had Lyme disease
- No objective laboratory tests

# IDSA Guidelines

- Based on clinical evidence and biological plausibility – what is best for patients
- Refrains from applying LD diagnosis to patients without specific symptoms, objective findings
- Prospective data does not suggest significant benefit from longer term courses of antibiotics
- Need for uniform definitions (with objective evidence of infection), validated testing for additional study



# Can *B. burgdorferi* Persist?

- Biopsy post-abx of prior EM negative for organisms<sup>1</sup>
- Blood and CSF cultures and PCR negative after initial abx in pts presenting w/ long-term sx<sup>2</sup>
- Serologic titers tend to decline over time<sup>3</sup>

<sup>1</sup>Nadelman RB, et al. Am J Med 1993;94:583. Berger BW, et al. J Am Acad Derm 1992;27:34

<sup>2</sup>Klempner MS, et al. NEJM 2001; 345:85.

<sup>3</sup>Fallon BA, et al. J Spirochetal Tick-borne Dis 1999;5:94. Nowakowski J, et al. AMJ 2003; 115:91

# Can *B. burgdorferi* Persist?

- Animal studies showing rare culture positivity and more often PCR (+)<sup>1</sup>
  - Uncertain significance of PCR, ?DNA debris
  - Culture as gold standard for infectivity
  - No evidence clinically, pathologically of infection
  - Failure to demonstrate T>MIC in different animals may contribute to persistence
  - Monkey model uses dexamethasone, no antibiotic treatment
- Urine PCR study, amplicons not sequenced<sup>2</sup>
- Cases could reflect laboratory contamination or human reinfection<sup>3</sup>

<sup>1</sup>NBockenstedt LK, et al. JID 2002;186:1430. Straubinger RK, et al. J Clin Micro 1997;35:111.

Straubinger RK, et al. JID 2000; 181:1069. <sup>2</sup>Bayer ME, et al. Infection 1996;24:347.

<sup>3</sup>Preac-Mursic V, et al 1989;17:355.

# Long-term Antibiotics?

- Examples of long-term treatment not analogous to *B. burgdorferi*
  - TB, Q fever, leprosy-- etc: objective signs, biological correlates to suggest success or failure
- Evidence includes single case reports and small series
- Data includes many European reports, different organisms than N. American LD

<sup>1</sup>NBockenstedt LK, et al. JID 2002;186;1430. Straubinger RK, et al. J Clin Micro 1997;35:111. Straubinger RK, et al. JID 2000; 181:1069. <sup>2</sup>Bayer ME, et al. Infection 1996;24:347.3  
<sup>3</sup>Preac-Mursic V, et al 1989;17:355.

# Antibiotic Responsiveness in LD patients with persisting Symptoms?

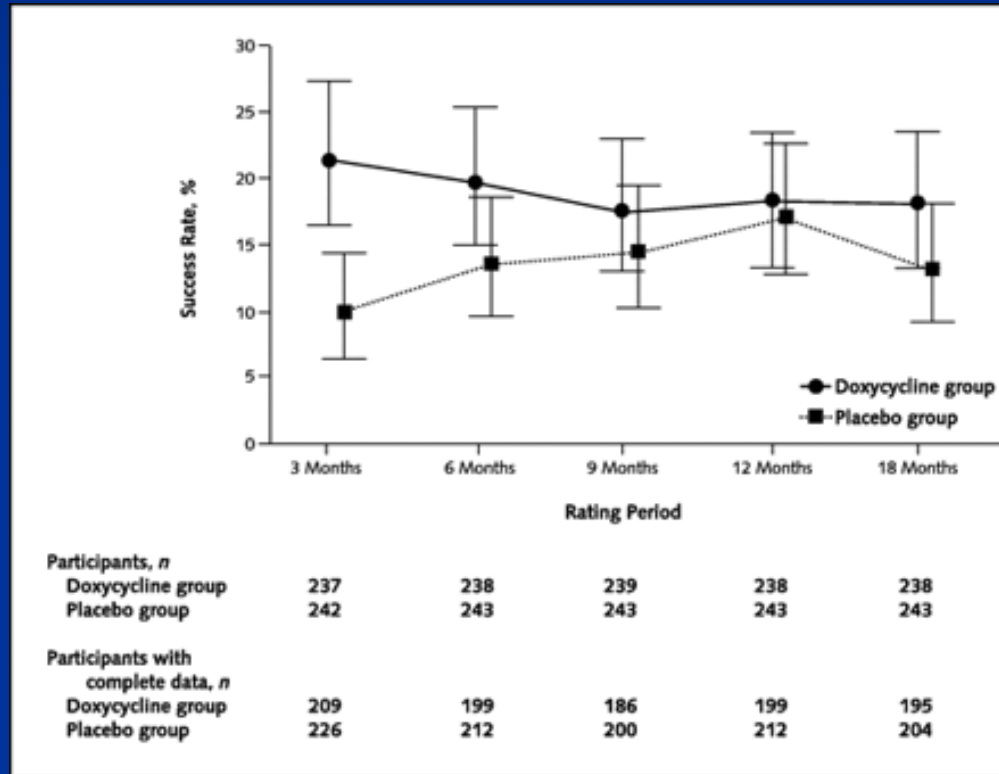
- Some studies suggestive, but open-label<sup>1</sup>
- Placebo effect?
- Other studies without objective criteria documenting Lyme disease
- Doxycycline w/ immunomodulatory properties, anti-collagenase properties<sup>2</sup>
- Unpublished study-required objective cognitive abnormalities (i.e., ?treating true neuroborreliosis), no change in cognitive but physical function<sup>3</sup>

<sup>1</sup>Fallon BA, et al. J Spirochetal Tick-Borne Dis 1999;5:94. Donta ST. CID 1997;25:S52. Donta ST. Med Sci Monit 2003;9:PI136.

<sup>2</sup>Rheumatol Int. 1998;17(5):175, Curr Med Chem 2001;8:317.

<sup>3</sup>Fallon BA. Abstract 196 Austrian Society Hygiene, Microb & Prev Med, 2006.

# Gulf War Study (prospective): Doxycycline v. placebo, SF-36 scores



# This Patient: How to Handle Post Lyme Disease Syndrome?

- Rule out alternative medical illness, sleep disorders
- Consider psychiatric problems, functional somatic syndromes
- Develop collaborative efforts
- Goal: improve function capabilities
  - Analgesics (NSAIDs)
  - Low impact, conditioning exercises: graduated
  - Consider trials tricyclic agents, dual SSRI/norepi drugs
  - Cognitive behavioral therapy if not otherwise improved

# Conclusions

- Unknowns always exist in medicine
  - Base treatment on best available evidence for health of patients
  - Persistent symptoms
    - Lyme v. not Lyme disease
    - Frustrating for both patients and physicians –
- Long-term antibiotics are not in the best interest of our patients with chronic subjective complaints and Lyme disease histories