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Clinical Protocol: "Chronic Lyme Disease" or "Post-Lyme Syndrome"

INTRODUCTION

- Lyme Disease is an infectious disease caused by *Borrelia burgdorferi.* Three disease stages have been described; Lyme Disease is not treated at CCDP.
- Acute Lyme Disease benefits from early treatment with antibiotics. Cases may progress from Stage 1 (localized infection) to stages 2 (disseminated infection) and 3 (late or persistent infection). Stages 2 and 3 present with musculoskeletal manifestations such as arthritis, neurological, heart and skin signs. Treatment of Lyme Disease is provided in Primary Care (early Lyme) or by Infectious Diseases specialists, thought direct referral from Primary Care.
- For further information on Lyme disease, see http://www.bccdc.ca/health-info/diseases-conditions/lyme-disease-borrelia-burgdorferi-infection. For case definition, please refer to https://www.canada.ca/en/public-health/services/diseases/lyme-disease/surveillance-lyme-disease/case-definition.html.

- Chronic Lyme Disease" (CLD) or "Post-Lyme Syndrome" (PLS) presents with debilitating symptoms, such as fatigue, musculoskeletal symptoms, pain, cognitive and sleep dysfunction. The symptoms overlap with those of myalgic encephalomyelitis (ME/CFS) and fibromyalgia.
- CLD has been used to describe different groups of patients who carry different probabilities of having been infected with *Borrelia burgdorferi*. It does not presume continuing or persistent infection, thus the term "Post-Lyme Syndrome" is preferred by some
- CLD develops in people with previous Lyme Disease who have been appropriately treated with antibiotics (Post-Treatment Chronic Lyme Syndrome), but it has also been reported in people whose diagnosis has not been confirmed by serological tests conducted by CDC and other reference laboratories. When such cases are identified through "non-validated" laboratory tests, they may be referred to as cases of Alternatively Diagnosed Chronic Lyme Syndrome (ADCLS). Those diagnosed with Lyme disease by alternative laboratory methods most frequently do not have the infection https://academic.oup.com/cid/article/61/7/1084/289719
- While early Lyme disease is diagnosed on clinical grounds by an experienced physician and follow-up serology, "Chronic Lyme Disease" or "Post-Lyme Syndrome" is diagnosed clinically based on prolonged and debilitating symptoms, which overlap with typical ME/CFS and fibromyalgia. Diagnosis requires 6 months of symptoms that affect daily function and presumes the exclusion of diagnosis that explain the symptomatology.
- *We do not support recruitment for any form of private treatment nor any non-evidence-based treatments provided outside CCDP*, including CLD. However, we recognize that some patients chose to pursue other forms of treatment elsewhere. We are available to support these patients if they meet the CCDP criteria for referral.

- Much of the evidence used in developing this protocol comes from the treatment of ME/CFS and FM given the significant symptom overlap between these and CLD. These are broadly divided into 5 categories:
  - Fatigue (both physical and mental)
  - Pain
  - Neurocognitive symptoms
  - Sleep disturbances
  - Unexplained (or unusual) symptoms (e.g., palpitations, temperature instability, etc.)
- No one treatment (so far) targets all 5 categories effectively
- The order and combination of treatments undertaken will depend on prior treatment, patient preference, costs, etc.
- Given the different mechanisms of action, some patients are prescribed 2 or more drugs.

- Patients with CLD are often sensitive to medications and may need to be titrated slowly and may not tolerate higher doses of medications.
- It is expected that physicians would educate themselves about these drugs beyond the outline provided below, and that they will provide patient with information/dose adjustment handout

1. PATIENT EDUCATION

- Incorporated into multiple offerings, including in group activities based on self-management (e.g., handouts, web-based resources)
- "Family and Friends" evening session
  - To register for the next event contact infoccdp@cw.bc.ca

2. PHYSICAL ACTIVITY MANAGEMENT

- Pacing and keeping activities within the "energy envelope" limit are key to controlling symptoms and avoiding "crashes"
- Tai-chi and mild Yoga
  - Offerings in community rather than CCDP
- More information about pacing

3. SLEEP

- Sleep disturbance is a major component of CLD and pain disorders
- See Sleep Protocol for details

4. DIET

- Many patients benefit from a low-inflammatory diet
- Some patients have non-celiac gluten sensitivity and benefit from a gluten-free diet
- The major emphasis, however, is a healthy diet

5. ALTERNATIVE AND COMPLEMENTARY THERAPIES

- Some agents are crossing into mainstream medicine and may be worth trying:

5.1 Co-enzyme Q

- 200 mg TID

5.2 D-Ribose

- 5 g TID

5.3 Magnesium Malate

- 250 mg QID

5.4 Vitamin D

- 2000 IU daily

6. PSYCHOLOGICAL WELLBEING

- Combines education on psychological health, Pacing, CBT &, Mindfulness

7. INTERVENTIONS

7.1 Trigger Point Injection, etc.

- For patients with pain, especially in the neck, shoulders, back, and jaw
- Maneuvers that target muscular trigger points, lengthen muscle contractures, and release painful scars and other connective tissue restrictions
- For example:
  - Myofascial release
  - Trigger Point Injections
  - Nerve blocks
- Currently available:
  - Externally (outside referral):
    - Change Pain Clinic: http://www.changepain.ca
    - Muscle MD Clinic: http://musclemd.ca
    - Myo Clinic (Victoria): http://www.myoclinic.ca
    - Other practitioners across the province

7.2 Acupressure

Available through group sessions

8. MEDICATIONS

8.1 Iron

- Iron helps with fatigue in patients with ferritin below 50
- Need to watch for constipation (especially IBS-C)
- May need to add PEG +/- Milk of Magnesia (see IBS protocol)
- Patients unable to tolerate oral iron, may need IV replacement
- The rule of thumb is "the easier the iron is on the stomach the less bioavailable iron there is"
- New guidelines suggest that iron should not be taken every day (or multiple times a day) as it decreases absorption. The current recommendation is to only take iron every 2nd day on an empty stomach with acid (e.g., Vitamin C or orange juice)

8.1 A Ferrous fumarate

- Available OTC
- High amount of iron
- Very effective, but less well tolerated
- 300 mg (one capsule) every 2nd day; each capsule contains 100 mg elemental iron

8.1 B Ferrous gluconate

- Available OTC
- Less iron than fumarate but somewhat easier on the stomach
- Effective, better tolerated than fumarate
- 300 mg (one tablet) every 2nd day**;** each tablet contains 35 mg elemental iron

8.1 C Iron polysaccharide

- Available OTC
- Although it contains the highest amount of elemental iron and is well tolerated, it is not usually effective at repleting iron stores.
- 150 mg daily (as elemental iron)

8.1 D Iron sucrose

- IV iron, usually administered in a medical short stay unit
- 300 mg over 3 hrs x 3 doses (1 – 2 weeks between doses)
- Ferritin falsely elevated (often above 100) for a few months

8.2 Modafinil

- Helps with mental alertness/brain fog and may give the sense of increased energy
- We do not use this medication very often given that many of our patients have anxiety and autonomic dysfunction; modafinil can make these worse
- Also, the false sense of increased energy is at risk of pushing patients beyond their energy envelope and causing crashes of symptoms (post-exertional malaise)
- Start with 100 mg daily
- May increase to 200 mg daily
- Watch for anxiety, insomnia, and adrenergic side effects

8.3 Tricyclics

- Used for pain
- Also improves sleep architecture
- Not used during the day
- Watch for:
  - Dry mouth
  - Hangover effect
  - Blurred vision
  - Urinary retention
- May need to taper at higher doses when discontinuing
- May need to decrease sleep medication to prevent a hang-over effect

8.3 A Amitriptyline

- Start 5 mg 2 hrs before bed (or 12 hrs before getting up in the morning)
- Increase to 10 mg after 1 week
- Increase by 5 mg increments at 2 week intervals if required
- Increase to 70 mg as tolerated, depending on benefit & side effects
- Many patients cannot tolerate more than 20-30 mg

8.3 B Cyclobenzaprine

- Alternative to amitriptyline
- Also helps muscle spasms
- Start 5 mg 2 hrs before bed (or 12 hrs before getting up in the morning)
- Increase by 5 mg increments at 2 week intervals
- Increase to 20 mg as tolerated, depending on benefit & side effects
- Not generally used during the day, but occasional patients may benefit from 3 divided doses
  - by 5 mg increments at 2-week intervals
  - Maximum dose 20 mg TID with last dose taken 2 hours before bed

8.3 C Nortriptyline

- Alternative to amitriptyline
- Useful in patients who have tried amitriptyline in the past and didn't tolerate it (usually because it was started at too high a dose)
- Generally less benefit for pain, but also fewer side effects
- Start 10 mg 2 hrs before bed (or 12 hrs before getting up in the morning)
- Increase by 10 mg increments at 2 week intervals

- Increase to 50-70 mg as tolerated, depending on benefit & side effects
- Most patients cannot tolerate more than 20-30 mg and some even less

8.4 Anticonvulsants

- Used for pain
- Also helps with sleep, anxiety, dysesthesia, and restless leg
- Start with evening dosing and add during the day later
- Watch for:
  - Sedation (common)
  - Cognitive dysfunction
  - Weight gain (or weight loss with topiramate)
  - Edema
- Not a good choice in obesity, metabolic syndrome, or fear of gaining weight
- Topiramate may be an alternative in these patients as it causes weight loss (used off-label as a diet drug in the US).
- Avoid abrupt withdrawal; need to taper
- Balance pain relief (benefit) with day time somnolence (side effect)
  - Start with evening dose rather than BID dosing
  - Titrate the evening dose to maximum before adding any during the day
  - Many patients don't tolerate daytime dosing
- Monitor weight

8.4 A Pregabalin (Lyrica)

- Expensive $$$ (not a Pharmacare benefit)
- Patient dosing schedule
  - Inform patients not to expect benefit until 100 mg (to prevent early discontinuation)
  - Titrate the evening dose to maximum before adding any during the day
  - Rather than splitting the dose BID, use more in the evening

AM	Evening	
	25 mg	
	50 mg	
	75 mg	
	100 mg	Patient review at 100 mg
	125 mg	
	150	
	175	
	200	
	225	
	250	
	275	
	300	
25	300 mg	
50	300 mg	
75	300 mg	
100	300 mg	
125	300 mg	
150	300 mg	
Physician review for higher doses / multidrug regimens Maximum dose 450 mg / day		

- Increase dose at 1 (or more) week intervals depending on side effects (dizziness and drowsiness are common)

- If unsure current dose is helping, trial of tapering warranted

8.4 B Gabapentin

- Alternative to pregabalin if cost is a factor (is a Pharmacare Benefit)
- Patient dosing schedule
  - Inform patients not to expect benefit until 600 mg (to prevent early discontinuation)
  - Titrate the evening dose to maximum before adding any during the day

AM	Afternoon	HS	
		100 mg	
		200 mg	
		300 mg	
		400 mg	
		500 mg	
		600 mg	Patient review at 600 mg
		700 mg	
		800 mg	
		900 mg	
100 mg		900 mg	
100 mg	100 mg	900 mg	
200 mg	100 mg	900 mg	
200 mg	200 mg	900 mg	
300 mg	200 mg	900 mg	
300 mg	300 mg	900 mg	
Physician review for higher doses Maximum dose 3600 mg / day			

- Increase dose at 1 (or more) week intervals depending on side effects (dizziness and drowsiness are common)
- If unsure current dose is helping, trial of tapering warranted

8.4 C Topiramate

- No specific evidence for fibromyalgia but clinical experience has found it to be helpful
- Strong evidence for other pain syndromes
- May be useful when gabapentinoids can't be used due to obesity, metabolic syndrome or fear of gaining weight
  - Used off-label as a weight loss drug in the US
- Also, useful if patient has migraines
- Watch for:
  - Drowsiness
  - Cognitive dysfunction
  - GI upset
  - Good water intake (prevent renal stones)
  - Weight loss
- Check blood work at baseline; 2 mo; 4 mo; 10 mo; 16 mo:
- Lytes (metabolic acidosis)
- Neutropenia
- Elevated liver enzymes
- Patients who benefit but have daytime somnolence may do better with just night time dosing
- Patient dosing schedule
  - Inform patients not to expect benefit until 50 mg BID (to prevent early discontinuation)

AM	Evening	
	12.5 mg	
	25 mg	
	50 mg	
	50 mg	
	70 mg	
	100 mg	Patient review at 100 mg
	125 mg	
	150 mg	
	175 mg	
	200 mg	
25 mg	200 mg	
50 mg	200 mg	
75 mg	200 mg	
100 mg	200 mg	
125 mg	200 mg	
150 mg	200 mg	
175 mg	200 mg	
200 mg	200 mg	
		Maximum dose 200 mg BID

- Increase dose at weekly (or more) intervals
- If unsure current dose is helping, trial of tapering warranted

8.5 SNRIs

- Used for pain
- Norepinephrine effect (i.e., pain modulation) occurs at higher doses
- Also helps with comorbid depression or anxiety, and some physical symptoms (but not fatigue)
- If patient is currently on SSRI, consider a trial of switching from SSRI to SNRI
  - Can switch from one day to the next
  - Use same relative dose of SNRI
  - E.g., If patient is on 50% of a maximum dose of an SSRI, switch to 50% of a maximum dose of SNRI
  - Coming off SNRI requires slow taper
- Tell patient to expect "transition" effects in the first 7-10 days
  - Otherwise patient will think these are side effects and discontinue drug
  - Patient may feel "off," anxious, not like themselves, etc.
- Watch for:
  - Agitation, insomnia
  - Dyspepsia, and other GI side effects
  - Sexual dysfunction
  - Suicidal ideation
- Monitor blood pressure

8.5 A Duloxetine (Cymbalta)

- Expensive $$$ (not a Pharmacare Benefit, except if failure gabapentin and pregabalin)
- Inform patient not to expect benefit for 4-6 weeks (prevent premature discontinuation)
- Start 30 mg daily (or q 2 days in drug sensitive patients; compounding of smaller doses is also an option)
- Increase to 60 mg daily after 3 weeks if tolerated
- Stay on 60 mg for at least 2 months before considering further dose increase

- Physician review for doses above 60 mg daily
- Above 60 mg go to BID dosing
- Can increase to 90-120 mg daily in select patients who benefit
  - Pain benefit (i.e., norepinephrine reuptake inhibition) occurs at higher doses

8.5 B Venlafaxine XR

- Alternative to duloxetine if cost is a factor (is a Pharmacare Benefit)
- Can also be tried in patients who did not tolerate duloxetine
  - Venlafaxine XR comes in much smaller incremental doses
- Inform patient not to expect benefit for 4-6 weeks after reaching dose of 112.5 mg
  - Prevent premature discontinuation
- Start 37.5 mg daily
- Increase by 37.5 mg increments at q 2-week intervals
- Reassess after 112.5 mg daily
- Target dose 225 mg daily
  - Can increase to 300 mg daily in select patient who benefit
  - Pain benefit (i.e., norepinephrine reuptake inhibition) occurs at higher doses

8.6 Cannabinoids

- Used for pain
- Also helpful for anxiety, nausea, appetite, and sleep
- Can assist with opioid tapering
- Can be used both as regular dosing and prn

8.4 A Nabilone (Cesamet)

- Expensive $$$ (is a Pharmacare Benefit)
  - Both 0.25 and 0.5 mg covered by Pharmacare
- Watch for:
  - Drowsiness
  - Cognitive dysfunction
  - Psychoactive side effects
  - Dizziness
  - Dry mouth
  - Weight gain
- Use with caution in patients with orthostatic intolerance:
  - POTS (Postural Orthostatic Tachycardia Syndrome)
  - NMH (Neurally Mediated Hypotension)

- Patient dosing schedule
  - Start with 0.25 mg in the evening or at bedtime
    - If patient feels too drowsy if taken earlier, can be taken at bedtime
  - Increase dose according to table
  - Titrate the evening dose to maximum before adding any during the day
  - Try adding prn doses during the day to see if patient tolerates it before adding regular daily dosing
  - Maximum 6 mg per day

AM	**Afternoon**	**Evening/Bedtime**	
		0.25 mg	
		0.5 mg	
		0.75 mg	
		1.0 mg	

		1.25 mg	
		1.5 mg	
		1.75 mg	
		2 mg	Patient review at 2 mg total/day
0.25 mg			
0.25 mg	0.25 mg		
0.5 mg	0.25 mg		
0.5 mg	0.5 mg		
0.75 mg	0.5 mg		
0.75 mg	0.75 mg		
1 mg	0.75 mg		
1 mg	1 mg		Patient review at 4 mg total/day
Increase dose at weekly (or more) intervals Physician review for doses above 4 mg per day Consider regular + prn dosing Maximum 6 mg daily (2 mg TID)			

8.7 Low Dose Naltrexone

- Used for pain
- Some patients report benefit with cognitive symptoms and fatigue
- Anti-opioid: Not to be used for patients on opioids
- May have beneficial effects on inflammation and gliopathy
- Inexpensive drug but needs to compounded
  - Cost of compounding $$
  - Not a Pharmacare benefit
  - Compounding not usually covered by drug benefit programs
- Few side effects at lower doses but watch for:
  - Insomnia
  - Vivid dreams
  - "Activation:" nervous energy
  - Headaches
  - Dizziness
  - GI sided effects
- Inform patients not to expect benefit until on 4 mg daily for 2 months (prevent early discontinuation)
- There are theoretical reasons to take it at bedtime but side effects (especially insomnia and vivid dreams are more common)
  - Can start with nighttime dose and switch to AM if side effects occur
- Use one of the 2 regimens below
  - FM patient can usually start at 1 mg: Regimen 1
  - ME/CFS patients are more sensitive and should start at 0.5 mg: Regimen 2
- Target (max) dose: 4.5 mg daily as tolerated
  - Give new script for 4.5 mg dose
- The optimal dose of naltrexone is unknown – studies were done using 4.5 mg
  - Responders may benefit from a trial of incrementally increasing the dose up to 9 mg per day and in some cases 12 mg per day

Regimen 1:

- Give patient 2 prescriptions: 1 mg and 4.5 mg
- Start with 1 mg qhs or qAM
- Increase dose according to table below
- Many patients will need to increase the dose more slowly

- Use 1 mg capsules until you get to 4 mg

HS or AM	
1 mg daily	For 1 week
2 mg daily	For 1 week
3 mg daily	For 1 week
4 mg daily	For 1 week
4.5 mg daily	Stay on this dose for at least 1 month
Follow up with clinic to assess continued use	

Regimen 2 – patients very sensitive to medications:

- Start with 0.5 mg qhs or qAM
- Increase dose by 0.5 mg every 2 weeks
- Many patients will need to increase the dose more slowly
- Patients may or may not get to the target dose of 4.5 mg
- Patients should stay at the same dose (stop increasing) if they get side effects
- Prescribe 0.5 mg capsules to start
  - Give a script for 2 mg capsules so that patient doesn't need to take too many capsules at once when they got to this dose (also reduces cost of compounding)
  - When final dose is established, can be prescribed as single capsule

HS or AM	
0.5 mg daily	For 2 week
1 mg daily	For 2 week
1.5 mg daily	For 2 week
2 mg daily	For 2 week (switch to large capsule)
2.5 mg daily	For 2 week
3 mg daily	For 2 week
3.5 mg daily	For 2 week
4 mg daily	For 2 week
4.5 mg daily	For 2 week (prescribe as single capsule)

8.8 NSAIDs

- No evidence of efficacy in fibromyalgia
- May benefit patients with "peripheral pain generators" (e.g., OA, back pain, etc.)
  - i.e., Secondary pain drivers
- Best used for short periods or prn
- Long term use associated with GI, renal, and cardiac side effects
- E.g., diclofenac 25-75 mg TID
- May need to provide gastro-protection
  - Addition of PPI
    - e.g., pantoprazole 40 mg daily
  - Combination drugs
    - e.g., Arthrotec (diclofenac + misoprostol)
      - Expensive $$$; not covered
    - e.g., Vimovo (naproxen + esomeprazole)
      - Expensive $$$; not covered
- Toradol may be helpful in acute severe flares

8.9 Opioids

- Avoid opioids in these patient populations
  - Opioid induced hyperalgesia more common
  - No evidence of efficacy for stronger opioids
- Tramadol (with or without acetaminophen) may be helpful in refractory cases
- Try to get patients off opioids if other meds have not been tried
  - See Opioid Taper and Discontinuation protocol
- Opioids are not prescribed by CCDP (except for tramadol)

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