Anything and everything to treat cramps

Disclaimer:

This is everything I've looked up for my condition and anything related to it that I could find. Though I have many potential treatments flagged under various diseases, they may not work in you and I can't and won't condone your trying them out based off the words of a medical student who most likely hasn't examined you yet alone finished his course, who was looking something entirely separate up altogether, over that of a doctor.

If you're dissatisfied with your doctor, I highly recommend you get a second opinion though. They're only human. They can make mistakes and can only do so much. Doing so has helped me immensely over the years. If I can't suggest a person personally for you, try looking up on trusted Foundation websites which can connect you to specialists and then patient groups/forums.

I also highly recommend seeing occupational therapists, speech pathologists, exercise physiologists, podiatrists, psychologists *talking version of psychiatrists* or psychiatrists (talking has done me as much if not more good than medicines in the past to be honest) - as well as immunologists, rheumatologist (arthritis - not necessarily bone arthritis too + joint doctors)... anyone who can make your life easier even in a small way I'm sure you can all attest can make a huge difference. I'll try and help where I can. If I'm too busy I'll get someone else to hopefully. If not I hope something in here can help you.

One of the only current studies out there on cramps and treatments;

Participants identified 49 different interventions used to prevent night-time calf cramp. Of all treatment ratings, 68% described the intervention used to prevent cramp as being 'useless' or of 'a little help'. Of 14 participants who provided additional information regarding their use of quinine, eight had a current prescription of quinine for muscle cramp at the time of the survey. None had been asked by their prescribing doctor to stop using quinine.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3361473/
Continued: same reference:
Thirty-three percent of participants reported experiencing night-time calf cramp most nights per week. Between people who experience calf cramp ≤ 3 nights per week and people who

experience calf cramp most nights per week, there was no statistically significant difference in mean usual pain intensity of night-time calf cramp

Seventy one (89%) participants reported that cramp could affect either leg. Cramps were mostly reported to occur at irregular times throughout the night (n = 32, 40%), during the middle of sleeping time (n = 24, 30%), within two hours of rising in the morning (n = 10, 12.5%), before falling asleep (n = 6, 7.5%) and within two hours of first falling asleep (n = 6, 7.5%). Two participants (2.5%) were unsure of cramp timing. Calf-muscle soreness or tenderness in the days following cramp was reported to occur sometimes by 32 (40%) participants, most of the time or always by 25 (32%) participants and never or rarely by 22 (28%) participants.

The treatments/ways of getting rid of it are mostly physical maniuplations (stretching etc) and things like fish oil and supplements. Only quinine was a major drug looked at.
Full table:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3361473/table/T3/

Intervention	Number of users	Perceived effectiveness					
		Useless	A little help	Quite helpful	Very helpful	100% effective	Unrated
During cramp to reduce pain							
Getting out of bed to stand or walk*	77	4	21	19	27	5	1
Stretching calf*	75	20	22	20	12	1	
Massage*	69	6	42	13	7		1
Heat application	4			3	1		
Running on the spot	1		1				
To prevent cramp							
Magnesium	46	12	16	11	5		2
Water, drinking more*	36	11	19	5			1
Stretching calf during day or before bed*	24	7	11	2	1		3
Massage during day*	21	5	11	5			
Quinine	18	1	1	7	7	2	
Crampeze tablet/capsule	13	5	6	2			

Tonic water	5	1	2	2	
Gatorade/poweraid	4	1		3	
Salt	3		1		2
Crampeze cream	2		1	1	
Vitamin B	2		1	1	
Akineton *(biperiden)*	2	1	1		
Hamstring stretching	2	1	1		
Lyrica *(pregabalin)*	1				1
Schuessler tissue salts (homeopathic preparation)	1				1
Camphor in bed	1			1	
Cramp away (homeopathic preparation)	1			1	
Exercise and stretching with personal trainer	1			1	
Filtered water	1			1	
Homeopathic drops containing ginkgo	1			1	

PubMed Central, Table 3: J Foot Ankle Res. 2012; 5: 7. Published online 2012 Mar 15. doi: 10.1186/1757-1146-5-7 - Google Chrome

Secure | https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3361473/table/T3/

J Foot Ankle Res

Iron tablets	1		1	
Japanese green tea	1		1	
Acupuncture	1	1		
Calcium	1	1		
Epsom salt bath	1	1		
Glucosamine	1	1		
Minerals	1	1		
Panadol osteo	1	1		
Tegretol (*carbamazepine*)	1	1		
Shaking of legs during shower	1	1		
Aspirin	1	1		
Fish oil	1	1		
Mandopar (*levodopa and benserazide*)	1	1		
Multi vitamins	1	1		

J Foot Ankle Res

otassium	1	1		
itamin E	1	1		
itamins	1	1		
inc	1	1		
ananas	1			1

Quinine - best drug ever for it apparently (works in me)

- Out of 14, 6 stopped taking it - 3 for GP safety concerns.
- 8 who did, 3 = daily. 1 = once every 2 days. 4 = sporadically. When they needed it.

Reasons for cramp: qualitative but still vital data

- 20/62 don't know.
- 11/62 from movements such as that in bed (like me)
- 9/62 think it's from poor circulation
- 5/62 from lots of physical activity.
- 1 from bad dreams.
- 4/62 lack of salt.
- 1 - 2 from lack of water.

My cramps; described/logged.

To read:
http://www.nature.com/bmt/journal/v43/n2/full/bmt2008297a.html
http://www.bloodjournal.org/content/114/3/719719 ted

Imatinib → calcium reducer.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1557796/

Carnitine
https://www.researchgate.net/publication/26776206_Carnitine_mitochondrial_function_and_therapy
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3730973/

Pain management/list of muscle relaxants
http://www.spine-health.com/treatment/pain-medication/muscle-relaxants
Metaxalone - unknown moa but a muscle relaxant in acute setting. Unlikely to cause drowsiness too

https://en.m.wikipedia.org/wiki/Chlorzoxazone

To write up:

https://en.wikipedia.org/wiki/Chlorzoxazone

Cyclobenzaprine
Side effects = seratonergic syndrome with duloxetine and also interacts with benzos

Muscle relaxant- acute

https://en.m.wikipedia.org/wiki/Cyclobenzaprine

TImeline/extent and how it's spread.

Cramps started in abdomen I believe, after first transplant and again after the second one.
I didn't notice it after the first one, but I was getting some cramping there when I'd never had it before → points to it being a side effect of radiation/chemo tx (I did have a burning neuropathy during one of my chemotherapies - high dose cytarabine I believe).

Started again in late 2013/early 2014 (9 months post second transplant i'd say), and kept waking me up when I cramped in calves.
2014 - seemed to impair my improvement in terms of performance in gym. Kept waking me up - remained in calves and abdomen, occasionally in legs too.
Early 2014, for 2 months, post quinine and, at times, baclofen therapy, there were almost 0 cramps.
Late 2014 - early 2015 - expanded to forearms/hands/glutes/quads. Rarely woke me up as I started sleeping with my legs against the bed head (other way) to stretch when they start
Kept progressing. Now are all over my body (back, abdominals, neck, even my digastric muscles/mentalis/buccinator - cheeks will cramp too, impairing speech. If neck muscles are cramping, can make trachea/oesophagus feel tight. Chest muscles/back can cramp and constrict breath, especially after I get up (as I'll describe below) = very short of breath (been admitted once for it - that's when they found the tumour in my right tib).

'Cramp' patterns/nature - are they really cramps?

I get

- Contractions of various muscle groups spontaneously, usually worse at night, though can be all day (especially after bad sleep or flare up of general inflammatory process in me - GVHD). They have gone on all day in the past.

Movement often induces cramp - tonic in nature;

- I will always cramp when I get up after sitting down/lying down in the afternoons (sometimes in the mornings too). My entire leg, mainly the quadriceps/hamstring/gluteal muscles (all of them), will contract at once, often my abdominal muscles and calves will seize up too, for about 60 seconds. My chest and arms can also follow in this pattern,

and this generally makes me reluctant to move at night time. Will also become extremely SOB at this point.

- Continuing on this trend of tonic cramps - if I move, say, my arm up to brush my teeth, often my biceps will 'cramp' and contract to cause a burning/cramp like pain
    - Similarly, my calves/hamstrings will cramp if I roll around in bed on a bad day (2 outta 3 nights) all the time.
    - My hands may cramp after a cramp occurs in my forearm (which may be sporadic or due to my gripping something) - the cramps here can also be sporadic; the hand cramps are extremely painful
        - Also induced by typing or just stretching out the arm.
    - Recently, my neck muscles and face would also contract if I move them.
    - I know these days, that at any time if I move my arm more than 150 degrees at the elbow, my tricep will cramp. I often "feel" like my cramp will start if I move my neck/legs too much too somehow. I don't wanna get up too fast, as my abs will contract and stay contracted for a bit.

Spontaneous cramps happen regularly too

- Movement not necessary to induce cramps though.
- Will also have contractions of random muscles that are painful at any time. Can range from twitching/fasciculations to full blown spasms. Especially painful in fingers, but can be v. painful in calves, gluteal muscles, arms, anywhere really.
    - Sometimes it can slowly come on - forearms will tense a bit and burn. Then the extensors of hand/fingers in particular will contract. The hand/triceps/biceps/flexors of forearm can also contract if I try and move my arms about to 'shake out' or relieve the cramp through stretching.
    - Sometimes there will be a sharp pain at a point in my back in particular, at major muscular/bony junctions which will then erupt into a contraction of a muscle.
    - Sometimes there will be dull/burning pain prior to (or separate from as well) the cramp, and it may not be the muscle contracting underneath that causes pain, but rather the membranes/fascia around them? In the fibromyalgia section, there's a description of a hypothesis for spontaneous cramps in these patients → pain → enhanced reaction to pull away and hence, contraction of muscles OR other factors, possibly as a result of general inflammation in me → activation of nerves (if this is the case though, why does it get worse with movement?)

The cramps can 'move' and affect other muscles around it;

- Often, when I try and stretch out the cramp (moving it around/stretching generally, can help relieve it), the opposing muscle will cramp up, or else muscles down or upstream from it will cramp.
    - If I cramp in my forearm, and try to relieve it, my triceps/biceps/hand muscles will cramp. If I get one in the biceps/triceps/shoulder region, moving it around may induce cramps in the pectorals of the chest and vice versa. Stretching out a

cramp in the calf can result in the cramp moving up the leg to the hamstring/gluteal muscles. Cramps in one area can generally spread and affect other muscles around it too essentially.

They induce fatigue, or perhaps fatigue induces them

- I've noticed that after cramping for a while, or in the leadup to the cramping part of the day perhaps, my muscles don't have as much energy - it takes more to do the same effort as earlier in the day. Perhaps due to muscles being activated too much.
    - There's a period on most days for 30 mins - 2 hours where I can tell the cramps will be coming due to my arms/legs being tired and requiring more effort to move.
    - Often this 'prodrome' to a cramping session will also involve spontaneous cramps/twitching of muscles. Fasciculations can occur too though they happen every few days only.

Objective investigations;

- Objectively - peripheral neuropathy of axonal nature is present (see EMG below) Electrolytes always normal. No elevated CK (though a 24 hour urine test may help clarify/confirm this). Liver counts constitutively up due to GVHD, as are ESR/CRP mildly.

Emg report

PHYSICAL EXAMINATION: On examination today, there was marked wasting of the lower limbs distally and mild wasting of the left FDI and the left thenar eminence. Nikhil was unable to walk on his toes and heels. Romberg's test was negative. He was able to squat with ease. There was mild weakness of left FDI. The remainder of the upper limb muscle groups had normal strength. The upper limb reflexes were preserved. Joint position sense and vibration were normal. Pinprick was reduced to the mid forearms. In the lower limbs, tone was normal. Hip flexion was difficult to assess due to painful cramping, but his gait and ability to squat suggested that proximal strength was good. Knee flexion and extension were normal. Dorsiflexion was 1/5, plantar flexion 4/5. Lower limb reflexes were absent with downgoing planters. There was patchy pinprick loss as well as allodynia and hyperalgesia in the lower limbs. Joint position sense and vibration were normal in the lower limbs.

NEUROPHYSIOLOGY: Nerve conduction studies today revealed normal median and ulnar sensory responses. The left radial response was reduced and the lower limb SNAPs were absent. It is hard to know whether this was technical and partly related to oedema and thickening of the overlying skin. Lower limb motor amplitudes were markedly reduced. The upper limb motor studies revealed normal distal motor latencies and mild reduction in CMAP amplitudes, but marked increase in CMAP duration. There was mild slowing of conduction velocities. Upper limb F-waves were mildly prolonged. Insertional activity was reduced with spontaneous activity in TA and FDI (fibrillation potentials). There was also evidence of chronic neurogenic change. We were unsuccessful in recording EMG activity at a site of cramping and no features of peripheral nerve hyperexcitability were detected. Overall, the features were consistent with a predominantly axonal neuropathy with some demyelinating features.

Axonal excitability studies were also performed. The results deviated significantly from normal controls, but interpretation is difficult as Nikhil is clearly a very complicated case.

ULTRASOUND: Ultrasound revealed no evidence of muscle cramping and nerve size was normal.

IMPRESSION AND SUGGESTIONS: Nikhil's presentation is suggestive of neuromuscular complications related to graft-versus-host disease. We agree with your plans to increase the IVIg dose. Consideration could be given to increasing the nocte dose of Lyrica or adding amitriptyline. We have requested an MRI of the spine to assess the proximal nerve roots. I have also provided him with a form for blood tests to include voltage-gated potassium channel antibodies in addition to sending blood upstairs to the Neuroimmunology lab. We will review Nikhil again in about two months.

Thank you for the referral.

Complex repetative discharges

C omplex repetitive discharges (CRDs) are striking bursts of spontaneous electromyographic (EMG) activity, comprising trains of complex polyphasic potentials that repeat at a regular frequency (range, 5–100 Hz) and that characteristically begin and terminate abruptly.1, 8 Single‐fiber EMG recordings suggest that these discharges represent ephaptic activation of a small group of muscle fibers through a re‐entrant mechanism, with one fiber acting as a pacemaker.8 The clinical significance of CRDs is unclear. They have been described in both

myopathic and neuropathic conditions, as well as in subjects without overt neurological disease, and are often taken to suggest a chronic process.1, 3

Preliminary analysis of the data indicated that whereas all the cases had other evidence of neuromuscular disease on the basis of history, physical findings, and electrodiagnostic examination, almost half the comparison group (i.e., 382 of 775) did not have evidence of disease. Based on this finding, we conclude that CRDs will rarely be detected in patients with no other evidence of neuromuscular disease, at least as assessed by the techniques used in the routine clinical practice of EMG

Diagnosis	Cases (%)	Controls (%)	Total (%)	Unadjuste odds ratic for CRDs (95% CI)
Radiculopathy	41 (45)	166 (42)	207 (43)	1.07 (0.68 tc 1.70)
Plexopathy	9 (10)	22 (6)	31 (6)	1.81 (0.80 tc 4.07)
Mononeuropathy	11 (12)	126 (32)	137 (28)	0.28 (0.14 tc 0.55)
Polyneuropathy	14 (15)	59 (15)	73 (15)	1.00 (0.53 tc 1.89)
Motor neuron disease	5 (5)	7 (2)	12 (3)	3.13 (0.97 tc 10.1)
Myopathy	13	13 (3)	26	4.75 (2.12 tc

Two interpretations can be offered: that diseases of nerve root, plexus, or motor neurons are not strongly associated with CRDs; or that the study has inadequate ability to detect either an increased risk or a protective effect of any of these diagnoses for CRDs. Given the relatively wide confidence intervals, we favor the latter

Clinical significance of complex repetitive discharges: A case‐control study

Cutaneous leukoclastic vasculitis

Fibromuscular dysplasias?

https://en.wikipedia.org/wiki/Fibromuscular_dysplasia#Pathophysiology

Other effects whilst cramping

- Fatigue - in muscles.
- Anxious/more alert aware of movements. Reluctant to get up.
- Pain, of course, is the main one.
- Difficulty concentrating/"fuzzyness" in head.,

What has tried and worked?

- Quinine seemed to work for 2 months. Baclofen was being used simultaneously for 1 week of this. Stopped working though after a bit.
- Good sleep is correlated to less cramps. Bad sleep not so much.
- Mild exercise in the day with a massage with this special oil can help significantly (though more strenuous exercise, or overdoing the walk to make it a 3km walk instead of a 2km one, can just make the cramps worse).
- Massages are generally relieving.
- Perhaps high electrolyte tablets at v high doses help (shots branded electrolyte effervescents). High electrolyte doses have been tried and had a small positive effect perhaps

What has been tried to limited success?

- Lyrica
- Endep
- Sodium valproate
- Baclofen? (was done for a bit but I withdrew for some reason)
- Opiates helped at high doses (fentanyl after the surgery) but not sustainable I believe.

- High dose magnesium supplements.
- General vitamin supplements.
- Soap under legs at night (random suggestion by a friend)

What induces cramps

- As said above - movement, spontaneously happening
- Getting bad sleep the night before (less than 5 hours)
- Getting too much sleep perhaps (> 10 hours - which can happen as my sleep pattern has been disrupted lately - meaning I sleep and only get 2 - 4 hours in, and then wake up and sleep again in small bursts of 1 - 3 hours from there on).
- Infections/getting sick seems to cause GVHD to flare up and induces worse cramps → perhaps suggestive of inflammatory process.

What causes short term relief?

- Stretching is really the only one, though as described above, stretching out one muscle can also cause cramp to 'travel' to others - **Why is this? What does this say about the mechanism of this overactivation?**

Proposed mechanisms - why is this going on and HOW?

- Does the line above mean that there is a more central/brain mediated over-firing occurring as opposed to a reflex arc in muscle going on? If it travels from the calves to the gluteal muscles (gastrocs will feel relief, or less contraction, while the upper muscles of legs will contract painfully), does this point to a more primitive reflex of "move the leg away from danger after pain stimulus is activated" mechanism going on - one proposed as a mechanism for fibromyalgia?
    - Once there is some inflammatory process going on, and activation of pain fibres, brain will tell leg/arm/wherever to move and from there excessive contraction goes on.
    - Pain (due to inflammation/other stimuli) → brain response to withdraw from pain and hence contract → positive feedback loop where more pain occurs as more lactic acid is produced.
- Alteration of pain receptors/fibres to make them more hyperactive? (seen in fibromyalgia).
    -
        - Tx = Baclofen = inhibition of excitatory neurotransmitters at spinal/supraspinal sites can work here. Baclofen cream too.

        - More anti-inflammatory substances in me - diet.
        - Naltrexeone (inhibits opiod receptors slightly).
- Peripheral neuropathy going on can accelerate this. Or can create cramps on its own.
    - Sensory is affected less than motor, but still affected → easier/wrong activation can induce centrally/reflexive arc mediated contraction
    - Motor neuropathy → less efficient conduction of fibres, that last for a longer duration (as described on EMG report) → more taken to induce same movement
        - Damage to golgi tendon organs/muscle spindles which regulate/detect the length of muscles → confused brain, which thinks muscles haven't been activated → more intense firing to create same action → hypercontraction → cramp.
        - This may explain why it continues to contract and cramp when I make movements.
    - Tx = nerve regeneration help → neurotrophic substances like GCSF as discussed by Dr Pollard may cause this. Vitamin E too.
- Lack of blood supply/nutrients to muscles (or altered nutrient production)/mitrochondrial damage in muscles due ot chemo/radiation may be occurring. This may be due to impaired glucose and lipid oxidation - as seen in description of effects of chemo/radiation on skeletal muscle by a researcher I contacted below.
    - This leads to higher buildup of lactic acid → pain induced → contraction which causes cramp.
    - Deeper capillaries and vessels seem to be affected more in many pts with fibromyalgia/cramps.
-
    - Tx = anti-inflammatory stuff again to mitigate this, is there a space for simple nsaids to work in me? Ask haematologists.
    - Carnitine described below and other supplements which may increase availabiliy of nutrients for muscle contraction.
- Potassium/sodium/chlorine channel disorders/attack by immune system.
    - Could a few of these mechanisms be working in me at once?
    - myotonia/channelopathies → due to impaired relaxation after contraction?
    - Many of their symptoms similar to mine in various forms - overactivtion/stiffness in muscles for instance. See below for tx.

The anatomic site of muscle cramp generation still is a matter of debate, ranging from abnormal discharges of anterior horn cells, ephaptic transmission in the injured peripheral nerve, to aberrant excitation of motor nerve terminals

Possible mechanisms for these

- Simply hyperactive/reactive nerves
- Pain (due to inflammation/other stimuli) → brain response to withdraw from pain and hence contract → positive feedback loop where more pain occurs as more lactic acid is produced.
- Researcher (Enda Hardeman) sent this regarding altered skeletal muscle use of drugs; Our research has been focussed on how irradiation imparts a memory in the largest target tissue, skeletal muscle, that is realised later in life and manifests as a metabolic disorder. We have carried out our studies on mice and so far, we have identified that following irradiation there is altered fat utilisation and compromised mitochondrial function in skeletal muscle. Also, both the muscle from irradiated mice and the stem cells derived from the muscle display impaired energy production. We think this is due to impaired lipid and glucose oxidation. You can see that our research has focussed entirely on metabolic aspects of cancer treatment and doesn't address the types of late effects that you are experiencing.

Additional --. Muscle wasting review in general:

- the loss of muscle mass is due to an imbalance between protein catabolism and protein anabolism [7]
- ubiquitin-proteasome system (UPS), which is the most important proteolytic pathway, are systemically activated in muscle wasting due to multiple factors including proinflammatory cytokines [e.g., interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α], positive acute phase proteins [e.g., C-reactive protein (CRP)] and, in the case of cancer cachexia, tumor-derived factors [e.g., proteolysis-inducing factor (PIF)] [8, 9].
- Decreased antioxidant abilities = muscle wasting too - (ROS) are also potent inducers of the UPS [11, 12]
- skeletal muscle apoptosis (myonuclear apoptosis) induced by ROS or proinflammatory mediators is a further mechanism which may contribute to skeletal muscle atrophy under pathologic conditions.
- protein anabolism is impaired during muscle wasting due to a relative deficiency of anabolic hormones (e.g., IGF-1, testosterone) and/or a reduced tissue sensitivity to anabolic hormones (e.g., insulin resistance) [13].

Agents seen in literature that may help

Quinine + theophylline → All trials summarised + a drug that works with it

Effective and had worked well in me as we know. This drug works with it though and is described in one paper (77 people) and it worked better
But there are significant adverse effects of that drug (it's used in COPD patients btdubs)
https://www.ncbi.nlm.nih.gov/pubmed/25842375

Lots of side effects tho; Seizures, increased BP, heart rate, nausea, diarrhoea, abnormal heart rhythms, toxicity = v high as it has narrow therapeutic index and eating with high fat meal can even trigger it to be toxic. #triggered
https://en.wikipedia.org/wiki/Theophylline

https://www.ncbi.nlm.nih.gov/pubmed/25842375

Quinidine

- Class 1 antiarrhythmic.
    - Blocks fast inward na+ pump
    - Quinidine also blocks the slowly inactivating, tetrodotoxin-sensitive Na current, the slow inward calcium current (I_{Ca}), the rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed potassium rectifier current, the inward potassium rectifier current (I_{KI}), the ATP-sensitive potassium channel (I_{KATP}) and I_{to}.
    - At micromolar levels, also inhibits na/k atpase.
    - Use dependent block. At higher heart rate, block increases. At lower, less block evident.
- Side effects
    - potentiates/increases plasma levels of ADs, beta blockers, lidocaine, etc.
    - Thrombocytopenia, myasthenia gravis,
    - **Cinchonism** → Symptoms of mild cinchonism (which may occur from standard therapeutic doses of quinine) include flushed and sweaty skin, ringing of the ears (tinnitus), blurred vision, impaired hearing, confusion, reversible high-frequency hearing loss, headache, abdominal pain, rashes, drug-induced lichenoid reaction (lichenoid photosensitivity),[1] vertigo, dizziness, dysphoria, nausea, vomiting and diarrhea.
    - Symptoms may persist but usually come from withdrawal of quinine.

    - Torsades de Pointes - a rapid and dangerous ventricular rhythm
- https://en.wikipedia.org/wiki/Quinidine

dextromethorphan

- Found in cough syrup.
- Dissociative anaesthetic.
- Treats pseudobulbar effect (random crying/laughing/other emotional bursts).
- Acts as an NMDA receptor antagonist and selective seratonine reuptake inhibitor.
- eurotoxic changes, including vacuolation, have been observed in posterior cingulate and retrosplenial cortices of rats administered other NMDA antagonists such as PCP, but not with dextromethorphan.

Tart cherry juice?

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4566454/
Apparently reduced pain significantly in people with peripheral neuropathy but not diabetic ones (including chemotherapy induced neuropathy). Did not work in me.

Patches;

Lidnocaine

Side effects little other than skin irritation. Systemic effects unlikely.

Capsaicin

= extract of chilli. Patch can be applied = Qutenza
Severe pain where applied.

Menthol

Activates TRPM8 receptor = endogenous cooling analgesia. Small studies show benefit only thus far.

Amitriptyline, ketamine and baclofen

Small studies = small benefits.

Anticholinergics;

Benzatropine

- Parkinson's drug
- Benzatropine partially blocks cholinergic activity in the basal ganglia and has also been shown to increase the availability of dopamine by blocking its reuptake and storage in central sites, and as a result, increasing dopaminergic activity.
- Good for parkinson's but also dystonias
    - **Dystonia** is a neurological movement disorder syndrome in which sustained or repetitive muscle contractions result in twisting and repetitive movements or abnormal fixed postures.[1] The movements may resemble a tremor. Dystonia is often intensified or exacerbated by physical activity, and symptoms may progress into adjacent muscles
    - May have some impact in me but there are hundreds of dystonias.
- Side effects = bad tho.
    - While some studies suggest that use of anticholinergics increases the risk of tardive dyskinesia (a long-term side effect of antipsychotics),[2][3] other studies have found no association between anticholinergic exposure and risk of developing tardive dyskinesia,[4] although symptoms may be worsened (tardive dyskinesia = incurable lip smacking/other uncontrollable movements that can come with antipsychotics).
    - Constipation, anxiety, other neurological effects.

Muscarinic antagonist/Antimuscarinics

- Acts on ACh receptors of the muscarinic type.

Trihexyphenidyl

- Not precisely understood, but it is known that trihexyphenidyl blocks efferent impulses in parasympathetically innervated structures like smooth muscles (spasmolytic activity), salivary glands, and eyes (mydriasis). In higher doses direct central inhibition of cerebral

motor centers may contribute. In very high doses central toxicity as seen in atropine overdose is noted.
- Binds to m1 muscuranic receptor and maybe dopamine one too.
- Does raise seizure threshhold though.

Imatinib

- One case study of a pt who used to get imatinib and developed cramps when off it, which were ameliorated by reinduction of imatinib.
- Also good against reducing gvhd of the fascia. It is thought to impede fibrosis through its actions on the PDGFR. In fasciitis

Cartinine/levocarnitine

Carnitine - lipid metabolism in mitochondria = main fn.
Used successfully to relieve cramps in 2 pts with them undergoing TK therapy - imatinib for CML. Also in dialysis patients it helped relieve symptoms.

https://www.ncbi.nlm.nih.gov/pubmed/27169456 → Paper = japanese though...
Side effects may be higher risk of atherosclerosis, some epileptic attack symptoms (though this is apparently disproven)
Dosage wise - 100g of lamb = highest dose in meat. 190mg of cartinine exists in this.
2000mg/day is where absorption = saturated. .
It's thought cartinine enhances some bacteria which creates TMAO = atherosclerosis?

Appetite suppressant and reduces fatigue too = more energy in muscles? = possibly reversing mitochondrial deficiency induced by chemo/radiation which may be causing higher levels of lactic acid buildup in me?
https://en.wikipedia.org/wiki/Carnitine#Atherosclerosis

In line with this, a recent experimental study showed that LC administration reduces proteolysis in skeletal muscle, increases muscle weights, and improves parameters of physical performance in tumor-bearing rats
http://www.sciencedirect.com.ezproxy.uws.edu.au/science/article/pii/S0261561412000660

Gr8 review article whicho had all the above.
http://link.springer.com.ezproxy.uws.edu.au/article/10.1007/s00394-013-0511-0.

Muslce wasting review in general - stuff l-carnitine may have a role in:

- the loss of muscle mass is due to an imbalance between protein catabolism and protein anabolism [7]
- ubiquitin-proteasome system (UPS), which is the most important proteolytic pathway, are systemically activated in muscle wasting due to multiple factors including proinflammatory cytokines [e.g., interleukin (IL)-6, IL-8, tumor necrosis factor (TNF)-α], positive acute phase proteins [e.g., C-reactive protein (CRP)] and, in the case of cancer cachexia, tumor-derived factors [e.g., proteolysis-inducing factor (PIF)] [8, 9].
- Decreased antioxidant abilities = muscle wasting too - (ROS) are also potent inducers of the UPS [11, 12]
- keletal muscle apoptosis (myonuclear apoptosis) induced by ROS or proinflammatory mediators is a further mechanism which may contribute to skeletal muscle atrophy under pathologic conditions.
- protein anabolism is impaired during muscle wasting due to a relative deficiency of anabolic hormones (e.g., IGF-1, testosterone) and/or a reduced tissue sensitivity to anabolic hormones (e.g., insulin resistance) [13].

MSM

supplement - suggestion made from some random article on fibromyalgia in reference to cramp. Apparently helpful to cartilage. I'm on it now.

ZMA

In some self funded trials (and hence biased) - increased testosterone + muscle build up in some subjects. Thought to help in muscle recovery. Also to help sleep. Much of the former stuff wasn't replicated though - to take on empty stomach.

Botox.

Helps in post radiation and post surgery pain (in cramps/neuropathy pts) as an injection..
https://www.ncbi.nlm.nih.gov/pubmed/26771640

Random case study of adolescent with acanthosis nigricans and cramps and insulin resistance:

https://www.ncbi.nlm.nih.gov/pubmed/24912440

Related/possible diseases/syndromes and their tx

GVHD myositis/fasciitis descriptions in literature

Cramp description in GVHD

Limited studies on it. Indeed - this is the main one:
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0044922

- 27 patients studied.
- Nine patients had polyneuropathy, 4 had muscle cramps, and 14 had both.
- Neurophysiology revealed a predominantly axonal polyneuropathy in 20 of 26 patient
- In 4 of 19 patients electromyography showed signs of myopathy or myositis.
- More frequent in cGVHD than aGVHD. Affected more than calf muscle in 15/18.
- Daily in most patients, affecting them for medium - severe bouts. 4 were refractory to tx.
- Serological studies revealed antinuclear or antimitochondrial antibodies in a subset of patients. 2/16 had serum antibody vs tissue.
- incipient demyelinating polyneuropathy

Another study; looking at muscle biopsies of pts.

- The common clinical symptoms of myositis are moderate-to-severe proximal muscle weakness, myalgia, fever, contractures and skin indurations over the areas of muscle involvement.[1,2] The majority of patients present with elevated creatinine phosphokinase and aldolase enzymes. The histopathology of muscle biopsies demonstrates the

degeneration, necrosis and regeneration of muscle fibers and infiltrates of inflammatory cells.

- Patients with fasciitis develop skin swelling, and thereafter the skin becomes taut, bound down to the underlying tissue, and irregularly thickened, and thereafter demonstrating multiple small depressed areas, which has been called a 'peau d'orange' (or an orange peel) appearance.[7] Contractures and joint stiffness are also observed. The pathological findings of fasciitis include lymphocytic infiltration in edematous fascia and a subsequent increase of collagen fibers. The infiltration is diffuse and it often extends from the fascia into the interstitium of the muscle.
    - MRI images suggested the presence of inflammation on the fascia (e.g., thickening of fascia).
    - The MRI images of patients with fasciitis showed high intensity along the fascia in short T1 inversion recovery method
    - The typical pathological finding of fasciitis was inflammatory cells infiltrating on the fascia.
    - The laboratory data at onset showed a slight elevation of C-reactive protein ($\geqslant$ 0.3 mg/mg/dl) in three patients. An eosinophilia $\geqslant$ 5% was observed in two patients. The serum creatinine phosphokinase level was normal in all cases. In four cases, antinuclear antibodies were positive. Anti-Jo-1 and anti-Scl-70 antibodies were negative in the tested samples.
    - Predominantly cd8+ t cells. Biopsy reqd
    - Aggregations of inflammatory cells around capillaries seen.
- Imatinib in fasciitis helps many ts
- https://www.nature.com/bmt/journal/v43/n2/full/bmt2008297a.html

EMS → eosinophilic myalgia syndrome

- Characterised by eosinophils in biopsy.
- L-tryptophan (seratonin and dopamine precursor) intake high → this. Supplements can cause essentially, but 100g of lamb has it for instance. Vit k can make it worse.
- https://www.ncbi.nlm.nih.gov/pubmed/8185148?dopt=Abstract&holding=npg

EF - eosinophilic fasciitis/shulman's - sometimes seen post xplant and is distinct from cgvhd caused

- One pt responded to pred
- Eosinophils in fascia (duH)
- https://www.ncbi.nlm.nih.gov/pubmed/2359082?dopt=Abstract&holding=npg
- Tx with hydrochloroquinine also possible. http://www.semarthritisrheumatism.com/article/0049-0172(88)90008-X/abstract
-

Mononeuroapthy with axonal loss;

Mononeuropathy with axonal loss as opposed to peripheral polyneuropathy → emgs where SNAP (sensory) vs CMAP (compound muscle action potential) decrease needn't be correlated. We conclude that in the electrodiagnosis of mononeuropathy with axonal loss: 1) a significant quantitative correlation between CMAP and SNAP amplitude percentage decrease does not exist (r = 0.274, p = 0.06), 2) SNAP amplitude percentage decrease [75.3 +/- 31.8%] is greater than CMAP amplitude percentage decrease [43.9 +/- 31.3%] (paired t-test, p = 0.0001), and 3) CMAP amplitude decrease is positively correlated with the presence of denervation potentials (Xtrend2 = 6.22, p = 0.013).

Chronic fatigue/myalgic encephalomyelitis

Surpringly large correlation between chronic fatigue and mycotoxins in this study.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3705282/

A few case studies of associations with water damaged buildings/mould exposure and various chronic illnesses. Tenuous links with an anti-fungal nasal spray is also made via a few case studies.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3920250/

Currently, i've tried anti-fungal prophylaxis for this. No benefit.

EMS is

- Characterised by eosinophils in biopsy.
- L-tryptophan (seratonin and dopamine precursor) intake high → this. Supplements can cause essentially, but 100g of lamb has it for instance. Vit k can make it worse.
- https://www.ncbi.nlm.nih.gov/pubmed/8185148?dopt=Abstract&holding=npg

Gaucher's disease

- glucocerebroside function reduced - can lead to neurologic signs and myotonia.
- Type 1 **Gaucher disease** by using a blood **test** (called an assay) that measures activity levels of the enzyme glucocerebrosidase.

Fibromyalgia and treatments for it that may apply:

When someone with fibromyalgia is in pain the brain misinterprets the pain signals for reasons not yet understood and takes the pain message as a signal to contract these same postural muscles in preparation to move an arm or leg. In this way the postural muscles of the trunk are being sent brain signals to stay in a state of constant contraction – or muscle spasm – night and day – for as long s there are pain signals being sent. Producing this constant state of involuntary muscle contraction in one or more postural muscles wastes a lot of energy and explains the intense fatigue people with fibromyalgia feel.

Basically - it could be this. But it's not necessarily 100% likely. But if it is this in particular, treating the pain can treat the cramps. And there may be pain receptors that are being activated for some weird reason.

3 MOAs for FM

1. mitochondria disfunction in muscle cells
2. pain fibre metabolism issues leading to higher sensitivity.
3. microvascular changes in muscular areas --> fewer capillaries or contstant activation.

Often in me - the pain leads on to the cramps (ie - pain in hands/in arms, particularly forearms can lead to it), but also movement.

http://drlumbago.com/muscle-spasms-spasm-muscles-fibromyalgia-cramp-cramps-knots-contraction/

Another thing to consider is that it comes on when I move often, when movement is detected --> feedback loop? Inefficient clearing of lactic acid --> pain triggered --> contraction --> further contraction as more pain develops.

Could be another triggerer of pain and then this is a mechanism by which it spreads.

Other MOAs:

→ The characteristic widespread pain and decreased pressure pain thresholds (e.g., increased sensitivity to the light touch of a child or a hug) experienced with FM is thought to be multifactorial and may include altered hypothalamic–pituitary axis chemistry [47],

→ abnormal levels of corticotropin-releasing factor in cerebrospinal fluid [48],

→ abnormal *N*-methyl d-aspartate and neurokinin-1 receptors in the dorsal horn [49] and, finally,

→ emotional affective response to pain [50]

-->. Importantly, the analgesic effect associated with SNRIs has been demonstrated to be independent of effect on mood [51-53].

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3056054/

Enthesis = connective tissue between tendon/bone. There are fibro and fibrocartilagenous ones.

Other MOA (in more recent study) for FM

- pentosidine serum levels (is an AGE) - elevated in patients with FM due to lowered oxygenation.
- There is lowered/altered capillary microcirculation,
- lower capillary density per muscle fiber,
- reduced capillary permeability, and changes in the capillary endothelium thickness have been described as well (18, 19).
- endogenic and exogenic factors (e.g. psychogenic factors [2], muscle overload, disturbed posture of spine [3], disturbed sleep [4], etc.) lead to chronic local hypoxia [5, 6]
- Besides decreased levels of adenosine diphosphate and phosphoryl creatine, they described slight, but frequent histopathological and also histochemical changes as compared with normal muscle tissue.
- In 1973- degenerative change was noticed in some patients
    - Changes evident on histopathology.
    - Step-wise destruction of myofilaments and swollen endothelial ends.
    - AGEs may cause some - via interaction with RAGE receptors.
    - Seen in dialysis pts, and elevation of it is seen in chronic rheumatoid arthritis too.
    - Pentoside was significantly age related in healthy people, not in FM
- 10 of 48 on drugs were on valium® (diazepam), musaril®(tetrazepam)]. A washout of 3 days was done on all patients - the rest on paracetamol (I editted this basically 38 of the latter and 10 on the former)
- A number of studies of muscle histology and energy metabolism suggest a possible pathological and pathobiochemical basis in the muscle tissue [21–23].
- AGE-induced and RAGE-mediated NFκB activation has been demonstrable in neurons, endothelial cells, mesangial cells, smooth muscle cells and monocytes/macrophages and is much more prolonged than the activation of NFκB by cytokines [28].+

    - A combined extract of clove, oregano, thyme, walnuts, and coffee synergistically inhibited lipopolysaccaride (LPS)-induced NF-κB activation in a monocytic cell line, compared with the sum of effects from the single extracts.
        - Coffee (Arabica, Medium roast), walnuts, oregano (dried), clove (dried), and thyme (dried) were purchased from a grocery store in Oslo, Norway. All samples were pulverized and extracted and concentrated by use of water/methanol (50:50,v/v) as previously described (**20**). The final extract was diluted in corn oil (extract used for mice) or a 50:50 mix of PBS/DMSO (v/v; for cells).
    - NF-κB activity the first 6 hours by 35% compared with control mice. Organ-specific NF-κB activation was inhibited in intestine, liver, testis, and epididymis of the mice receiving the combination extract.
    - http://cancerpreventionresearch.aacrjournals.org/content/3/5/653
- They showed that there are visible collagen cuff sheaths around pre-terminal nerve fibres in the subepidermal connective tissue of FM skin taken from tender points of the trapezius region. . No such changes were observed in any control samples [29]
- significant alterations in the excretion of collagen cross-links (pyridinoline, deoxypyridinoline) and hydroxyproline; a tendency toward normalizing, especially of the pyridinoline/deoxypyridinoline ratio, after effective therapy with acupuncture [30].
- AGE modification, particularly of long-lived proteins like collagens, leads to an alteration of the tissue protein structure and function. May contribute to deposition around nerve fibres.
- **This collagen deposition [29, 30]) may be involved in the development of inflammatory pain, hypothesized by Weihe *et al.* [31] as 'neurogenic inflammation'. It is known that afferent sensitive neurons act as pain receptors [32] - link between this and GVHD.**
- Age modified proteins, or just AGE driven (from the oxidation - important to note this study indicates microcirculation disruptions is a fact) attachment to macrophages, fibroblasts or nerve cells may stimulate proinflammation in RAGE bearing cells.
- https://academic.oup.com/rheumatology/article/41/10/1163/1784317/Are-advanced-glycation-end-product-modified

- Pyridinoline (Pyd) and deoxypyridinoline (Dpyd)

  The Pyd/Dpyd ratios in the urine and serum and the Hyp in the urine were significantly lower in patients with fibromyalgia than in healthy controls.

- Dpyd is a specific marker of collagen I resorption in bone, whereas Pyd is released from types I and II collagen in bone and cartilage
    - In another study → A positive correlation was found between the inflammatory activity (measured by CrP) and the level of collagen crosslinks in urine. A correlation between serum and urine concentrations was demonstrable for Pyd, but not for Dpyd. Different elimination kinetics for fragments containing either Pyd or Dpyd are a possible explanation for this observation.
    - The ratio of Pyd/Dpyd is known to be a useful marker to distinguish between destruction of cartilage and bone collagen.
    - Because the Pyd/Dpyd ratio in urine does not necessarily correspond to that in serum, probably as a result of metabolic or elimination processes, the usefulness of the relationship between the crosslinks in urine as a method of differentiating between cartilage and bone degradation must be questioned.

Tx for fibromyalgia.

Antidepressants; SSRIs = preferable
5ht3 antagonists = decent apparently.
Gabapentin = beneficial in 30% of pts, but has side effects. Pregabalin = 10% of peopel (not me thus far) = also good in diabetics. But higher risk of suicide.
Growth hormone somehwat effective (IGF-1) but also has risk of abuse.
Opiods otherwise.

Duloxetine (SSRI) milnacipram (SNRI) = others approved fo ruse.

Myositis - polymyositis and dermatomyositis

- If heliotrope (purple) rash or Gottron's papules are also present, then the diagnosis is DM
- The usual criteria for a diagnosis of PM are weakness in muscles of the head, neck, trunk, upper arms or upper legs; raised blood serum concentrations of some muscle enzymes such as creatine kinase; unhealthy muscle changes on electromyography; and biopsy findings of

(i) muscle cell degeneration and regeneration and (ii) chronic inflammatory infiltrates in muscle cells.

- Tx for all these are antiinflammatory drugs - things I've done already I guess.

Sleep and its relation to cramps and other conditions;

Links to fibromyalgia and a sleep disorder seen in this study;

- Chronic diffuse myalgia, localized areas of tenderness, fatigue, and unrefreshing sleep are related to the alpha EEG NREM sleep anomaly.
    - Hauri and Hawkins [17], who used the term alpha–delta sleep to characterize a mixture of alpha (8–12 Hz) and delta (0.5–3.5 Hz) wave in psych patients with feeling of chronic malaise and fatigue. Similar study found [10] in patients with FM
    - These waves seen in not just Slow wave sleep but all stages.
    - Most papers have found that the alpha-EEG sleep anomaly is a consistent feature in patients with FM (see [3] for a review).
    - In one study, the amount of alpha-EEG was correlated to an overnight increase in pain and a decrease in energy [18].
    - alpha-EEG sleep anomaly might lead to more vigilance and arousabilityand the heightened state of perceptual sensitivity may partly explain the subjective complaints of unrefreshed sleep [19, 20].
    - more alpha-EEG activity in stages NREM2–4 combined in all sleep cycles, and the variability of the alpha power was higher in the patient group [21].
    - Also seen in RA, sjorgen's syndroime, OA too. Also seen in non RA pts. - eg chroic fatigue pts, post-infectious/trauma pts.
    -
- Pathogenic mechanisms that link nonrestorative sleep physiology to pain and fatigue may involve metabolic dysfunction of the brain with sleep-related alteration in immunologic and neurotransmitter functions (serotonin, substance P, endorphins).

https://www.ncbi.nlm.nih.gov/pubmed/2644681

- Sleep difficulties, as well as related daytime symptoms such as fatigue and morning stiffness, reported in >75% of patients with FM, prevalence of awakenings and non-restorative sleep is greater than reported in RA [3].
- the musculoskeletal symptoms and number of tender points were strongly associated with the non-restorative sleep pattern [13].
- An altered chronobiological distribution in symptoms was reported in patients with FM [4] and, correspondingly, a change in the normal diurnal rhythm of cortisol has also been reported [14].
- Serotonin metabolism in the central nervous system seems to play a role in the regulation of NREM sleep, pain and affective states [15]
- tryptophan, which is a serotonin precursor, may be important for the symptoms, and lower concentrations of tryptophan and metabolites have been found in the cerebrospinal fluid of patients with FM [16].
- sleep disturbances in FM have also been related to Growth Hormone (GH) secretion and lower levels of growth hormone-related peptide have been found in these patients
- Sleep difficulties in stage 3 of NREM sleep = less GH secretion. Neuroendocrine axis aberrations also at play.

https://academic.oup.com/rheumatology/article/38/11/1035/1783277/Pain-and-sleep-disturbances-with-special-reference

- We have shown that patients with FM had less power in the two lowest frequency bands [22, 23] of EEG. Lowest = best marker for sleep homeostasis = less restoration in FM patients.
- These results were reproduced by Moldofsky *et al*. [10], who deprived six healthy subjects of NREM4 sleep.
- It was concluded that the alpha-EEG induction, together with a decrease in NREM4 sleep, was able to induce FM-like symptoms in healthy subjects.
- In subsequent studies, however, the musculoskeletal symptoms following SWS deprivation could not be reproduced ([27, 28],
- Experimental studies, where different pain stimuli were given during sleep in healthy subjects, resulted in EEG alterations comparable to those seen in the patient groups [29],

Drugs =

- in rheumatic diseases 15–70% regularly took hypnotics/analgesics (most likely just hypnotics). [30–32]
- NSAIDS can reduce PG synthesis in central nervous system and interact with body temp/sleep/wake functions.
- In healthy pts, NSAIDS havd negative effects [3]
- In RA patients, NSAIDS do not cause sleep changes and subbjective feeling of sleep may improve [34].
- Opiates and tricyclic antidepressant amitriptyline = negative sleep profile induction - limited use in pts with pain. Tryciclics seem to work as SNRIs (blocks SERT - seratonin transporter and NET norepinphrine xporter → have negligible afinity for dopamine transporter. Also agonist on many seratonin receptors, alpha adrenergic ones and NMDA (glutamate) receptors.
- In FM → Third-generation hypnotics may be of some value in patients with FM [35, 36],
    - Looked into some third generation hypnotics (zolpidem and zopiclone) and though not benzos, they work on similar receptors (GABA A) and ARE addictive/tolerance developing but do have small improvements.
    - Looked up on wiki sites.
    - CBT for sleep is good however.
- In RA, daytime sleepiness, morning stiffness and sleep score were improved in one study following treatment with a hypnotic [37], whereas we were only able to confirm the effect on the subjective assessment of sleep [38]

- Pain in FM = multifactoral with a primarily central pain moduatory disorder, in RA, it's peripheral nocioceptive joints that are impacted and more responsive to inflammation. In me- a combination likely exists.

Sleep physiology

NREM sleep

3 stages.

1. Slow eye movement. “Relaxed wakefullness”. Being woken up here = you feel fully awake.
    a. Hypnic jerks (involunatary twitches which may cause you come awake) occur here most. Can wake me up possibly. Occurs more in irregular sleepers. Primal response by primal ancestors to waking up in case we’re falling out of a branch perhaps? This comes with a sense of falling. I don’t think I’ve experienced that.
2. Stage 2 - easily awakened. No eye movements. Jerking rare. Sleep spindles and K-complexes (bursts of brain activity occur here)
3. Slow wave - deep stage. *used to be split into stage 3 and 4*
    a. Parasomnias - sleep disorders which involve abnormal movements, behaviours, emotions, perceptions/dreams occur here most. I do’t have many of these. Dissociated sleep states. I don’t believe I’m dissociated when I wake either.
    b. Highest arousal threshold at this point. Will feel groggy and performance mentally is impaired for 30 mins after.
    c. After sleep deprivation , there is a big rebound of this = big need for this stage.
    d. There seems to be a reinforcing of memory of tasks done prior to sleep or in the day past in this stage. Puts in a need for this stage.

All this from wiki page on it; https://en.wikipedia.org/wiki/Non-rapid_eye_movement_sleep

Purpose of sleep

- During deepest stages of rest → homeostatic process of the mind and body occur. Anabolic steroids and boosting of immune system occurs @ night [9].
- Sleep disturbances may be influenced by pain, and sleep disturbances may lower pain thresholds.

Where my sleep is stuffed up.

- Wake up often -4 - 5 times/night. First sleep stage is between 2 and 4 hours long. After that I get 1 at a time.
- Been going on for 6 months. Correlated to worst cramping periods, but I can cramp despite getting good sleep.
- Sometimes, but not always associated with muscles cramping up all over - my calves often are the ones I notice, and it’s almost always the calves to hamstrings that I do feel

cramp up in this stage. Dunno if this is a response to muscles already tired to hypnic jerks? See physiology for that reference.
- Possible improvement when I sleep for just 7 hours, no more no less (ie - get my solid block of sleep and not renap or whatever I do).

Patients receiving Dialysis w/ cramps and things that may work in me.

Biotin

= vit b7, coenzyme used in general metabolism of fatty acids, glucose, valine (a substance we need to ingest) and isoleucine;
Needed to cause it, biotinase is important in cleaving it.
https://en.wikipedia.org/wiki/Biotin
In this study - it was shown this can ameliorate cramps, but also that patients who were getting cramps had high levels of biotin metabolites in them (TABS = total avidine binding solutes) which can inhibit the fn of biotin.
https://www.ncbi.nlm.nih.gov/pubmed/27466017

Charcot-Marie-tooth disease; an inherited disease which i have similar symptoms to

Baclofen,

I've been on it in the past, butnot for long.
Works on GABAb receptor (similar to phenibut) - blocks mono/polysnyaptic reflexes by acting as an inhibitory neurotransmitter - blocks release of excitatory transmitters. Doesn't have abuse potential.
Needs to be taken regularly for antispasmatic effects.
Intrathecal pump is also available (has to be replaced every 5 yeras, and ins inserted from spine through abdomen, and pump is implanted under ribcage's skin) .

Withdrawal effects on cessation can occur. Tapering needs to occur - symptoms can be hallucinations, mania, heaps of other bad things. Some abuse potential but not much.

naltrexone hydrochloride

Naltrexone hydrochloride = used in MS and in fibromyalgia too. Also stops gambling (though I don't have a problem b/c I always win, clearly).
In fibromyalgia → ESR high = better responses to low dose naltrexone (4.5mg) Study was on 10 women, and it helped everyone by 30%
Opioid antagonist.
Naltrexone (longer lasting version of nalexone) reduces proinflammatory cytokines and neurotoxic superoxides via suppression of microglia. Potentially works on TLR4 to do this (toll like receptor) - works to increase cytokine production and has various other effects. Perhaps also modulates mitochondrial apoptotic pathways (reduces pro-apoptotic Fas, FasL, Bad and Bax).
2 patients reported more vivid dreams and one = insomnia and nausea (out of 10). All mild symptoms and no dosage change occurred.
High dose impacted liver in some (50mg/day) , but in low dose, none reported thus far (4.5mg). Also not too costly.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2891387/

d-sorbitol = drugs used in similar case.

Sorbitol if in retinal/Schwann cells too much, can damage the cells. Aldose reductase inhibitors (which inhibit conversion of glucose to sorbitol) → possibly helpful? More likely in diabetics. In treating hyperkalaemia, there's a risk of GI bleeding and intestinal lesions so watch out.
Signs = motor and sensory neuropathy occurs - foot drop, muscle wasting, hammer toe and wasting of legs/forearms/hands, painful muscle contractions. Overuse can activate numbness, spasm and painful cramping.
Genetic = this disease. But many of the things I share. Vincristine = no good for people with it.

Combination therapy may be effective in helping this;
The ncbi link = a trial in rats of 3 drugs that may help improve axonal regenration and remyelination, and also improved nerve conduction and improved myelination.
Drugs = baclofen, naltrexone hydrochloride (used in alcohol/opioid dependence/ mitigating the impact of it) and d-sorbitol

https://www.ncbi.nlm.nih.gov/pubmed/25491744

https://en.wikipedia.org/wiki/Charcot%E2%80%93Marie%E2%80%93Tooth_disease

Dantrolene

Ryanodine receptor antagonist. Stops calcium release in muscle cells.
https://en.wikipedia.org/wiki/Dantrolene
RYR1, 2 and 3 are the 3 receptors. Dantrolene affects 1 and 3 -
RYR 1 = skeletal muscle
RYR 2= cariac
RYR 3 = neuronal.
On surface of sarcoplasmic reticulum, responsible for release of Ca2+
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2702250/

Potentially neuroprotective in strokes/ischaemia.
In localised scleroderma - proposed MOA is that scleroderma causes constriction of muscle → cramps. Focal nerve entrapment → cramp.
https://www.researchgate.net/publication/283729786_The_efficacy_of_dantrolene_sodium_for_muscle_cramps_in_patients_with_localized_scleroderma
2.4mg/kg = maximal depression of twitches + grip strength in 1 patient.

Safety;

Hepatic injury -

300 + mg dosages →
19/1044 patients (1.8%). 15 of these stopped therapy. 3 only showed increased fluctuations.
Twice as likely in females, though this wasn't significant
6/1044 = icteric hepatitis (0.6%) - 0.3% died.
Most patients = between1 - 6 months(71%), 29% in over 6 months, none under 1 month.
https://www.gastrojournal.org/article/S0016-5085(77)80141-8/pdf

Other noteworthy adverse effects are rare cases of dantrolene-induced eosinophilic pleural and pericardial effusion [29, 30], which rapidly resolve after short steroid therapy [31]. Prolonged oral exposure to dantrolene has been associated with an acneiform rash [19].

Most commonly reported side effects are dizziness, lightheadedness and drowsiness, but no other CNS effects with IV or oral administration have been reported [19, 20]. Oral administration can result in diarrhea. The most serious reported adverse effect, hepatotoxicity, has accompanied its chronic administration by mouth [24, 25]. However, there have been several reports indicating the contrary, so that it remains unclear whether dantrolene is truly hepatotoxic. Flewellen et al. [22] were unable to show any changes in liver function tests after prolonged oral exposure. No hepatotoxicity was achieved in mice exposed to dantrolene, even after enhancement of any

hepatotoxic potential by the inhibition of acetylation, depletion of glutathione, induction of biotransformation and the promotion of reductive metabolism [26]. In fact, dantrolene is hepato-protective in an *in vivo* rat model of liver injury [27]. In a hepatocyte culture model, dantrolene did not produce any hepatotoxicity [28].

In rats it was shown to increase hippocampal cell survival prior to bleeds.

Protects cell death, upregulates BCL-2 = less apoptosis. In alzheimer's models, it also improves outcomes.
Neuronal membrane stabilizer
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2702250/
Also used to reduce vasospasm in patients who had spasm
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5539667/

Oxybutin + dantrolene + carbamazepine = interaction. Unsure which causes which tho.
https://www.nature.com/articles/3101689

Dopaminergic stuff.

Physiology:

Centrally - parkinsonian stuff.
Peripherally →

- Copt inhibitors block the enzyme copt which breaks L-Dopa down into dopamine which we suspect activates muscle receptors.
- Also, decarboxylase does the same.
- Could also increase central available dopamine = stimulated mind, gambling, or otherwise alleviation of performance drop/fatigued feeling, difficulty concentrating etc.

Dopamine at NMJ

- In rats - positive impact on tone seen in muscles.
- We know it's there at the neuromuscular junction - on both sides of the NMJ.
- D1 like receptors were responsible for tone in rats.

https://www.ncbi.nlm.nih.gov/pubmed/21653722

- Confirmed in humans to have twitch like impact + dantrolene seen to have a positive effect. 2015 study.

- http://search.proquest.com.ezproxy.uws.edu.au/docview/1735950529?accountid=36155&rfr_id=info%3Axri%2Fsid%3Aprimo

The news correspondents obtained a quote from the research from the University of Alexandria, "Dopamine potentiated indirect muscle twitches in normal and gallamine-presensitized preparations amounting to a maximum of 31.14 +/- 0.71% and 69.23 +/- 1.96%, respectively. The dopamine-induced facilitation was well maintained in presence of 10 mu M propranolol but greatly reduced in presence of 6 mu M SCH 23390 or 3 mu M dantrolene. In addition, SKF 81297 attained a plateau at 16 mu M as opposed to 64 mu M dopamine, with a percentage potentiation of 69.47 +/- 1.76. The facilitatory effect of dopamine was potentiated in nicotine treated rats. This study revealed for the first time that the facilitatory effect exerted by dopamine on neuromuscular transmission is mediated via the dopamine D-1-like receptors.

Dopamine 2 also plays a role in skeletal muscles;

Modulation of things which had an effect of it had an effect on muscle
https://www.ncbi.nlm.nih.gov/pubmed/27060487

Dopamine 2/3 in the brain:

Affects neuroplasticity in the brain.
https://www.ncbi.nlm.nih.gov/pubmed/25100602
D2/d3 have various functions in the brain. In parkinsons - they play a major role in causing activity. When there is dopamine loss - parkinsons occur.
https://www.hindawi.com/journals/ijmc/2011/403039/

To read:

Effect of multiple neuroxmitters in NMJ of worms.
http://www.sciencedirect.com.ezproxy.uws.edu.au/science/article/pii/0306449281900411
Side effects of various inhibitors etc on pancreatic secretions
https://www.ncbi.nlm.nih.gov/pubmed/4717022

Peripheral hyperexcitabilities; the next 3 (bening/cramp FS and neuromyotonia)

Benign/Cramp fasciculation syndrome (both benign and cramp versions of this syndrome)

Tx →

- beta-blockers and anti-seizure meds (tried the latter, not the former yet).
- Reducing stress.
- Exercise more/sleep more/work less/meditation/eliminating caffeine
- Over the counter pain meds like ibuprofen.

Difference →
Not really peripheral hyperexcitability
curare stopped them (poison arrow toxin) but mainly carbamazepine/benzos = good tx
https://www.ncbi.nlm.nih.gov/pubmed/1648679

Neuromyotonia + myotonias

Myotonias = non relaxation after contraction

Lamotrigine

In a RCT - similar to mexiletine in efficacy. Works on sodium channels and results in lowered glutamate release in the brain. Also there in skeletal muscle. Skin rash = major side effect.
https://www.ncbi.nlm.nih.gov/pubmed/29050397

Myoclonus - epilepsy is what this is usually associated with

- **Cortical reflex** myoclonus is thought to be a type of epilepsy that originates in the cerebral cortex – the outer layer, or "gray matter," of the brain, responsible for much of the information processing that takes place in the brain. In this type of myoclonus, jerks usually involve only a few muscles in one part of the body, but jerks involving many

muscles may occur. Cortical reflex myoclonus can be intensified when patients attempt to move in a certain way or perceive a particular sensation.

- **Progressive myoclonus epilepsy** (PME

Action myoclonus is characterized by muscular jerking triggered or intensified by voluntary movement or even the intention to move. It may be made worse by attempts at precise, coordinated movements. Action myoclonus is the most disabling form of myoclonus and can affect the arms, legs, face, and even the voice. It is often associated with tonic-clonic seizures and diffuse neuronal disease such as post-hypoxic encephalopathy, uremia, and the various forms of PME, although, in the case of focal cerebral damage, the disease may be restricted to one limb. This type of myoclonus often is caused by brain damage that results from a lack of oxygen and blood flow to the brain when breathing or heartbeat is temporarily stopped. Over-excitement of the sensorimotor cortex (cortical reflex myoclonus) or reticular formation (reticular reflex myoclonus) is also a cause of action myoclonus. Serotonin and GABA neurotransmitters are thought to cause this lack of inhibition, which is a possible explanation as to why improvements are made with the administration of serotonin precursors. Systems involved include the cerebellodentatorubral, pyramidal, extrapyramidal, optic, auditory, posterior columns and gracile and cuneate nuclei, spinocerebellar tracts, motor neurons of cranial nerves and anterior horns, and muscle fibers.[6]

Short term help for cramps;

Insights into mechanisms that may help;

More likely to get a cramp after a cramp →

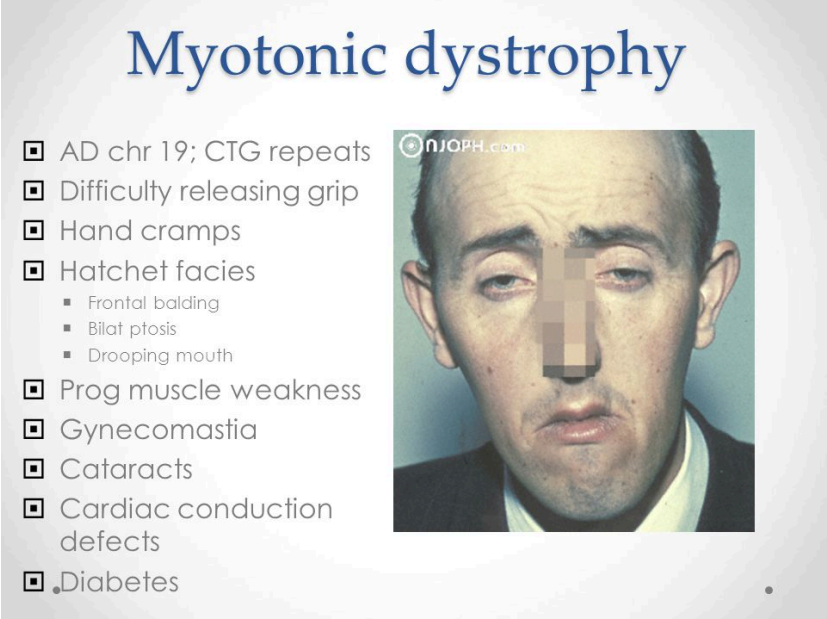
Acute volitionally-induced cramps increase cramp susceptibility. Clinicians should apply treatments for at least 60 minutes post-cramp to decrease the probability of cramp recurrence

https://www.ncbi.nlm.nih.gov/pubmed/28063158

MYOTONIAS - CHANNELOPATHIES - IMPAIRED RELAXATION AFTER CONTRACTION (THEREFORE LONGER CONTRACTION)

Essentially - Individuals with the disorder may have trouble releasing their grip on objects or may have difficulty rising from a sitting position and a stiff, awkward gait.
There are three diagnosed kinds → Myotonia congenita, Paramyotonia Congenita and myotonic dystrophy.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2858942/

Myotonia dystrophy type 1 → CTG repeat accumulates in nucleus = impairs RNA binding/impairs production of some proteins. Myotonia in hands and legs, but also affects other parts of body - eg cataracts, often comes with diabetes. I don't have it but tx may be simlar.



A case of a girl who had molecular workup done to find channelopathy in her

- Molecular analysis did not show a defect in the chloride channel, but instead a defect in the sodium channel of the muscle fibre.
- https://www.ncbi.nlm.nih.gov/pubmed/17137100

Other descriptors of myotonias and channelopathies (very rare otherwise)

- Sodium channel genetic alteration
- Calcium channelopathies otherwise.
- https://www.ncbi.nlm.nih.gov/pubmed/19917643
- Advanced clinical neurophysiology can help combat this issue though.
- More clinical trials needed.

mexiletine helps here →

= class 1b antiarrhythmic → voltage gated sodium-ion channel blocker. Used in pain.
According to this book on central pain syndrome - pathophysioloy, diagnosis and management - many of the drugs I've tried - valproate, phenytoin, carbepazemine and topiramate (i haven't tried this) have no effect here.
IV lidnocaine or it's oral similar version, metaxalone, act in activity driven manner - high depolarisation rate = more effect. Has a central effect that works in movement allodynia (excessive pain to movement).
https://books.google.com.au/books?id=GMzES57AGnoC&pg=PA286&redir_esc=y#v=onepage&q&f=false

Mexiletine: In other diseases;

- Machado-Joseph disease - Of 20 consecutive patients, 16 (80%) had frequent, severe muscle cramps in the legs, trunk or arms that disturbed their daily activities
    - Higher than ALS, peripheral neuropathies.
    - Electrotonus (spread of charge in neuron), refractivity (the insensitivity to further immediate stimulation that develops in irritable and especially nervous tissue as a result of intense or prolonged stimulation.) and supernormality =/= significantly different.
    - 8/20 benefited from mexiletine - expected to.
    - Threshold tracking showed that tau(sd) was elevated - as expected with Na+ channelopathies.
    - https://www.ncbi.nlm.nih.gov/pubmed/12615652

Large ALS trial: Dosage of mexiletine:

- Mexiletine was safe at both doses and well-tolerated at 300 mg/d but adverse effects at 900 mg/d led to a high rate of discontinuation. Mexiletine treatment resulted in large dose-dependent reductions in muscle cramp frequency and severity. No effect on rate of progression was detected, but clinically important differences could not be excluded in this small and short-duration study.
- https://www.ncbi.nlm.nih.gov/pubmed/26911633
- Phase 2 study.

MOA of peripheral neuropathy and mexiletine working:

- In peripheral neuropathy, persistent sodium currents usually increase possibly due to over-expression of sodium channels associated with axonal regeneration, and could be responsible for ectopic firings.

- Administration of sodium channel blockers such as mexiletine, results in marked alleviation of muscle cramping in parallel with a decrease in nodal persistent sodium currents
- https://www.ncbi.nlm.nih.gov/pubmed/20021424

Study showing efficacy of mexiletine in channelopathies.

Well tolerated, effects were significant.
Most likely it will work in patients with the disease in particular.
Mexiletine, a sodium channel blocker, targets the primary defect in sodium channelopathies (excessive activation of the sodium channel SCN4A channel protein)[10] but targets more downstream cell pathophysiology in the chloride channel, adding cellular heterogeneity to the genetic and allelic heterogeneity

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4352340/

Molecular evidence of mexiletine working:

Mexiletine is a class 1b antiarrhythmic drug used for ventricular arrhythmias but is also found to be effective for paramyotonia congenita, potassium-aggravated myotonia, long QT-3 syndrome, and neuropathic pain
Our results together support the hypothesis that the in vivo efficacy of mexiletine is primarily due to the open-channel block of persistent late Na(+) currents, which may arise during various pathological conditions.

https://www.ncbi.nlm.nih.gov/pubmed/14608007

Safe and effective at 150-300mg 3times a day in DM1

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2871004/
Safe and effective in nondystrophic myotonia:
At 200mg/day 3times/day for 4 weeks. Only GI symptoms.
https://www.ncbi.nlm.nih.gov/pubmed/23032552

Way of assessing safety in mexiletine.

SIGNIFICANCE:
Measurements of the excitability indices can be used for non-invasive assessment and monitoring of the effects of mexiletine in patients with neuropathic pain or muscle cramps.

https://www.ncbi.nlm.nih.gov/pubmed/15661106
Another study:
https://www.ncbi.nlm.nih.gov/pubmed/28552278

Metaxalone + tocainide - think this should be mexiletine

- Lidnocaine derivative.
- Used in myotonias commonly.
- Tocainide also has antiarrhythmic effects.
- https://www.ncbi.nlm.nih.gov/pubmed/93043
- Improved therapy of myotonia with the lidocaine derivative tocainide.
- Tocainide is orally effective and has been administered in doses of up to
- 3 x 700 mg/d in prolonged tests (Anderson et al., 1978). Its efficiency in abolishing
- experimental myotonia has been demonstrated by Dengler and Rfidel (1979).

https://link-springer-com.ezproxy.uws.edu.au/content/pdf/10.1007%2FBF00313157.pdf
The complaints of the other four patients were
mild dizziness and nausea on the first day, dizziness after taking two tablets at a
time, palpitations after exercise, and impaired sleep, respectively. ECG examination
of four patients with myotonic dystrophy disclosed no change of the usual
parameters except a lowering of frequency from 77 to 58/min in one patient.
EMG showed that post activity EMG activity was significatly lowered.fmet

Orphenadrine =

- Anticholinergic of ethanolamine antihistamine class.
- Good for muscle pain.
- Side effects = somewhat there.
- Can be good for 20% of parkinson's patients.
- Superceded by other anticholinergics.

Aldose reductase inhibitors: A drug that works on diabetic neuropathy:

- In diabetic neuropathy, the activation of the polyol pathway mediated by an enzyme, aldose reductase, leads to reduced Na(+)/K(+) pump activity, and intra-axonal sodium accumulation; sodium currents are reduced presumably due to decreased trans-axonal sodium gradien

- . Aldose reductase inhibitiors improve nodal sodium currents, as well as nerve conduction, and this can be objectively assessed by threshold tracking
- https://www.ncbi.nlm.nih.gov/pubmed/20021424
- Epalrestat is one.
- 76 % improvement. Only 2.5% adverse reactions, with none being bad.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2771994/
- Epalrestat in a dose of 150 mg/day improved the effects of diabetic neuropathy like upper limb spontaneous pain, motor nerve conduction velocity, thresholds of vibratory sensation and autonomic nerve function as compared to a placebo. These effects were significantly better in those with poorer control of diabetes.[9]

Creatinine monophosphate →

limited evidence showing it works. Not necessarily recommended..

Chloride channel myotonias:

A characteristic sign for all chloride channel myotonias is the athletic habitus, the warm-up phenomenon, i.e. an improvement of muscle stiffness by repeated muscle contractions, and that males are usually more severely affected than females
In this, genetic mutation = chloridne channels not working. Muscle rexation = impaired = longer period of stiffness of muscles after activation. This may not be happening in me - as a warm up phenomenon (delay in relaxaton of fingers due to lack of chloride channel functioning is a test for it) isn't present, but things may be considered here as treatment (many of the signs - i have. Athletic build without training, altered leg tone).

Tx = the drug above (mexiletine) + carbamazepine, phenytoin.

Sodium channel myopathies.

Less likely. Sodium channel is activated and depolarisation phase increased.
Some more dangerous drugs here - propafenone and flecainide may work on this but not indicated in me (liver + lung + heart side effects. Class 1c antiarrhythmics).

Potassium channel ones -

Unlike others - extracellular potassium can induce cramps here.
Avoid dried fruits, nuts, meat.

Peripheral axonal neuropathies;

non-systemic vasculitic neuropathy.

- Monoclonal antibodies may work against antigens that lymphocytes display. These are listed in the link below.
- Signs of this should come up in bloodwork thouh
- Usually when it affects peripheral nerves, it affects one side at a time.
- https://www.ncbi.nlm.nih.gov/pubmed/28550073

Chemotherapy induced neuropathy, mechanism of action

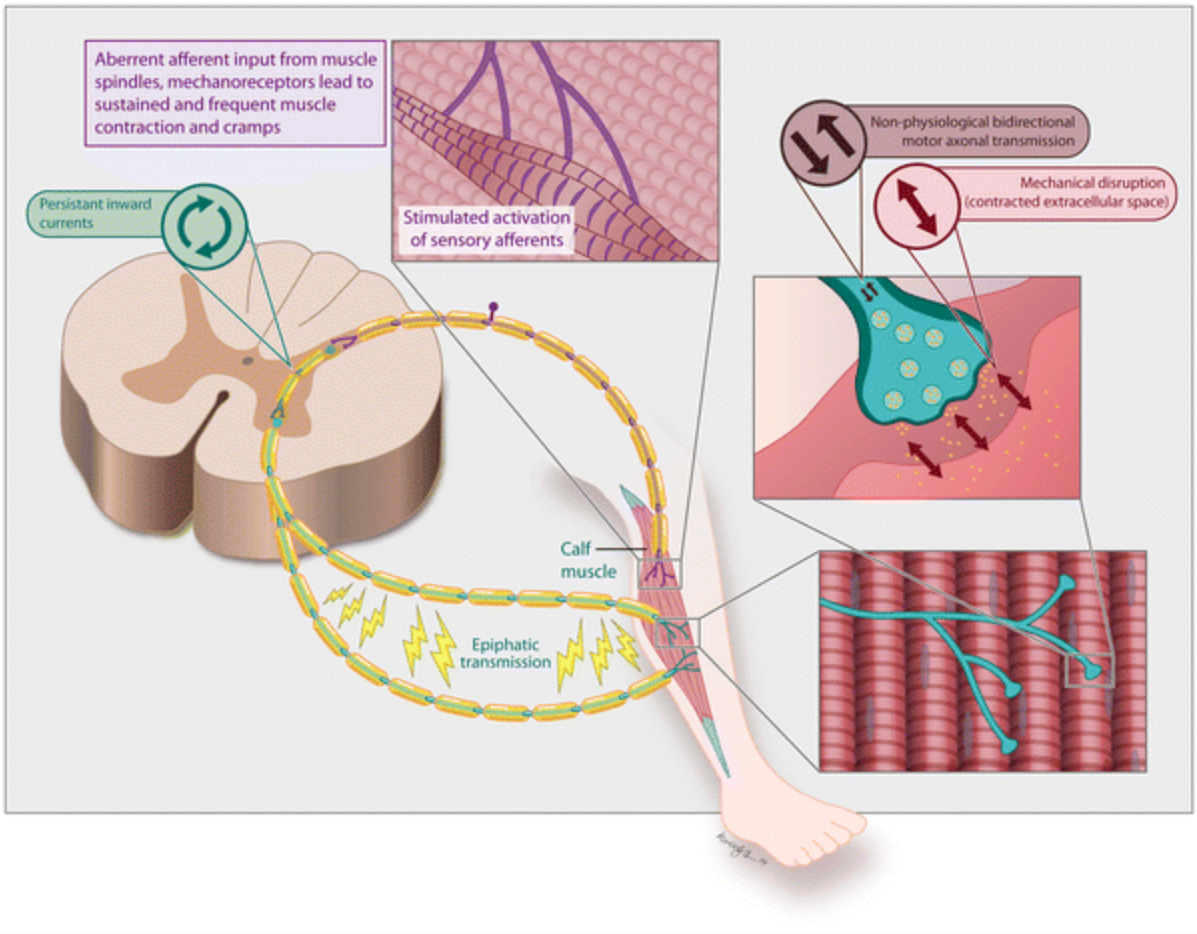
Paclitaxel induced activating transcription factor 3 expression, a marker of neuronal stress/injury. Paclitaxel also increased expression levels of acetylated tubulin and end binding protein 1

Mechanism of peripheral neuropathy damage:

- Peroxisomal dysfunctions cause lysosomal storage and axonal Kv1 channel redistribution in peripheral neuropathy.
- Perixosomal enzymes break down fatty acids and make precursors for myelin.
- In humans, *loss-of-function* mutations of ABCD1 are responsible for the disease X-linked Adrenoleukodystrophy (X-ALD). → a disease with demyelination a major characteristic. Generally being disruptive and having seizures/episodes like that are an issue. Progresses to affect cerebral fn but this isn't present in me.
- the β-oxidation of virtually all peroxisome-specific substrates, including VLCFA, is inhibited (Verheijden et al., 2013).
- Kv1 channels have been proposed to play a role in regulating fiber excitability (Baker et al., 2011; Glasscock et al., 2012), but the exact in vivo function of these fast-opening/slowly inactivating channels remains unknown (Arancibia-Carcamo and Attwell, 2014). Implicated thoughi n this.
- Kv1.1 clusters were in the majority of cases still maintained at juxtaparanodes, suggesting that internodal mislocalization is secondary (Figure 2—figure supplement 1d,e; Figure 2a).
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5417850/
-

Neurogenic cramps review.

- Mechanical disruption, ephaptic transmission, disruption of sensory afferents and persistent inward currents have been implicated in the pathogenesis of neurogenic cramps
- Lifestyle modifications, treatment of underlying conditions, stretching, B-complex vitamins, diltiezam, mexiletine, carbamazepine, tetrahydrocannabinoid (THC) leveteracitam Keppra) and quinine sulfate have shown evidence for treatment.
- Prevalence rates in patients with neuropathic conditions are usually higher than those in the general population and include 44–55 % in patients with ALS [5, 6], 64 % in patients with polyneuropathy [7] and 79 % in patients with Charcot Marie Tooth (CMT) [8].
- Intramuscular nerve terminals, as well as proximal structures including the motor axon and motor neurons are among the peripheral targets implicated, vulnerable through various mechanisms to injury [18]. In patients with motor neuron disease/amyotrophic lateral sclerosis for example, damage to the anterior horn cells may result in lone fasciculations or continuous firing leading to more coordinated contraction in muscle cramps [19]. In this situation, after-discharges observed occurring after the F-wave are thought to occur from lower motor neuron bi-stability in which the cell membrane has two equilibrium levels, the higher level protecting against spontaneous motor neuron discharges. A similar low threshold state is thought to occur throughout the motor axon from direct axonal injury or demyelination, where ephaptic transmission and regional spread of firing can cause development and propagation of muscle cramps [20].



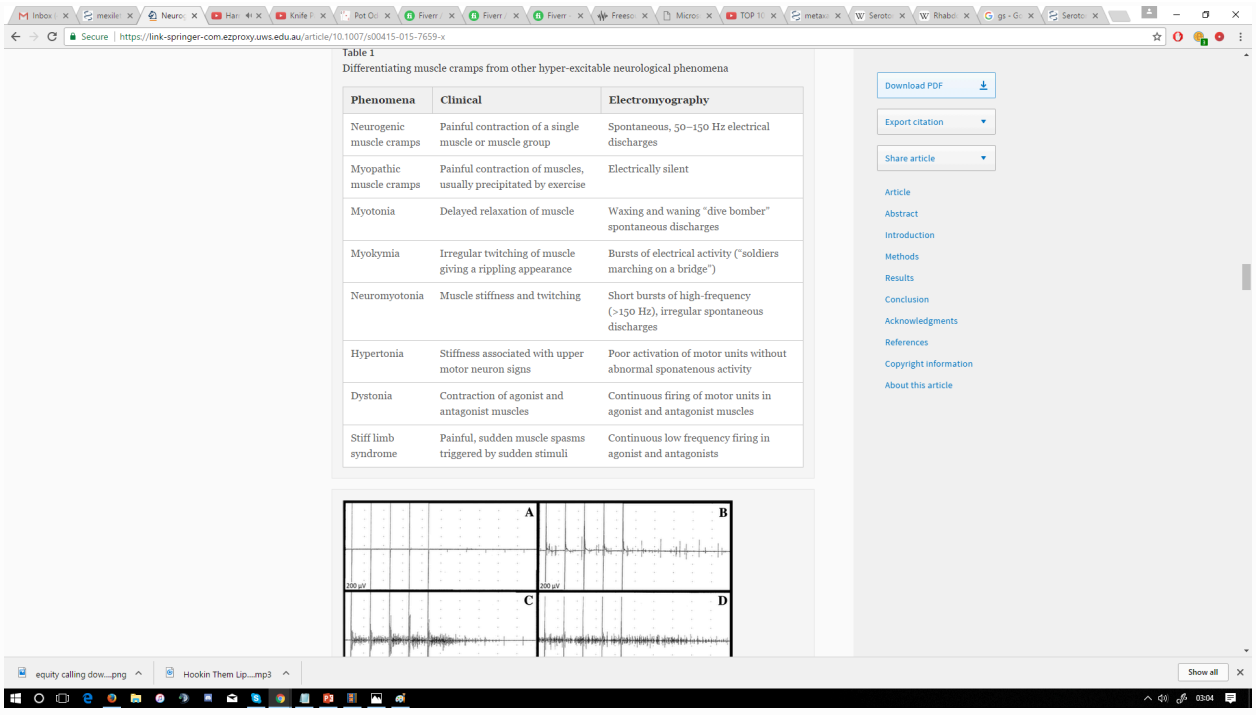
Abnormal excitability has also been shown to occur at the level of the intramuscular nerve terminal [21], and also be vulnerable to physiological effects such as changes in electrolyte concentration around motor end-plates [22]. Mechanical effects affecting the terminal endplates predispose to muscle cramps and include tendon shortening, which can occur in older age and during prolonged inactivity [23]. Central hypothesis of muscle cramps generation includes the presence of persistent inward currents, mediated by γ-aminobutyric acid (GABA), which may lead to muscle cramps by amplifying the incoming sensory input as it connects to motor neurons at the spinal level [24]. Disruption of sensory inputs themselves may also lead to muscle cramps, as these afferents have been shown to mediate the generation and extinction of motor discharges [25].

Similar to mechanisms implicated in neuropathic pain, peripheral sensitization in intramuscular motor nerve terminals occurs through interaction with

endogenous compounds and is enhanced by released substance-P and calcitonin gene-related peptide [26]. At the cellular level, disruption of chloride, sodium and potassium channels and inadequate concentrations of amino acids such as taurine have been directly implicated in the generation of muscle cramps by disrupted membrane currents [27, 28].

- Increased tone can manifest as spasms or dystonia depending on whether pyramidal or extra-pyramidal tracts are involved.

Myotonia is a delayed relaxation of muscle which occurs in response to voluntary activation. Myokymia is often described as a “rippling of muscle” or “bag of worms” phenomenon caused by dysfunctional peripheral nerves.
Although impaired blood flow can also predispose to muscle cramps, muscle pain without cramping can also occur from vascular claudication and should be recognized as a separate phenomenon due to the distinct management including investigation with Doppler ultrasound and vascular recanalization [30].
Metabolic myopathies are characterized by electrically silent cramps, which are caused by a mismatch in the rate of ATP utilization-to-resynthesis in muscle [31].
Cramps have also been reported with acetylcholinesterase inhibitors, bronchodilators, beta-agonists, steroids, morphine, cimetidine, penicillamine, antiretrovirals, cardiotropics, immunosuppressants, psychotropic drugs, and anticancer drugs



Peripheral nerve hyper-excitability syndromes

Peripheral nerve hyper-excitability (PNH) syndromes are characterized by muscle cramps, myalgias, fasciculations or myokymia. The most benign syndrome is cramp-fasciculation syndrome (CFS), characterized by cramps and fasciculations without additional peripheral or central nervous system involvement [43]. Isaac's syndrome is characterized by continuous discharges, myokymia, neuromyotonia, cramps and hyperhidrosis. When PNH is associated with sleep disturbance, encephalopathy and autonomic disturbance, the term Morvan's Syndrome is used [44]. Voltage-gated potassium channel antibodies (VGKC) are often elevated in these conditions and in patients with central manifestations, neural antibodies such as CASPR2 and LGI1 may also co-exist [45]. An increase in the prevalence of neoplasm, the most common being thymoma, has been described in patients even with PNH, particularly in the setting of Isaac's syndrome and positive VGKC. Although no specific genetic target has been implicated in patients with muscle cramps, there may be a hereditary component in some patients as evidenced by families described with muscle cramps inherited in an autosomal dominant manner [46].

Investigations recommended:

Table 2
Recommended investigations for muscle cramps

Screening investigations
Complete blood count
Electrolytes (including calcium, magnesium, phosphate)
Liver enzymes
Creatinine, urea, urinalysis
Fasting blood sugar, 2-h glucose tolerance test, hemoglobin A1c
Creatine phosphate kinase
Urinalysis
Advanced investigations
MRI spine
Nerve conduction studies/electromyography
Slow RNS for after-discharges
Voltage-gated potassium channels (VGKC)

Calcium channel blockers:

- Gabapentin is a partial agonist so maybe not the best/first to try.

Diltiezam

- Class 3 antiarrhythmic.
- Vasodilator. benzothiazepine-type calcium channel blocker.
    -
- is metabolized by and acts as an inhibitor of the CYP3A4 enzyme which can cause it to interact with a variety of other medications.

Amlodipine

- Suggested by dermatologist. Says it helps some pts - Dr Pablo Penas by the way, GVHD skin specialist.
- Angioselective calcium channel blocker. So how it does this is confusing and disputable.

Dopamine and its pathways

Dopamine – synthesised in medulla of adrenals and also various parts of the brain (primarily s. nigra in terms of motion).

- Dopamine attaches to dopamine receptors and TAAR1. D1 – D5
    - Also dopamine like receptors are subgroup of them.
        - § Dopamine-like receptor 1 (d1-like) = D1 and D5 receptor. **Excitatory effect on target.**
            - Through opening sodium channels.
        - § D2-like = D2 – 5 receptors. **Inhibitory effect on target.**
            - Through potassium channels.
            - D2 receptors act as autoreceptors à decrease dopamine synthesis and synaptic release.

Synthesis, storage and reuptake.

- Cytosol à vesicles via VMAT2 transporter.
- Exocytosis is usually triggered by action potentials, or intracellular TAAR1.
- Hits up post-synaptic dopamine receptors, or presynaptic autoreceptors.
- After postsynaptic neuron elicits AP, dopamine is released from receptor
- Reuptake occurs via dopamine transporter or plasma membrane monoamine transporter.
- Can be broken down by monoamine oxidase or repackaged by VMAT2 for future use.

Synthesis pathways;

l-tyrosine à l-dopa (via tyrosine hydroxylase) à dopamine (via decarboxylation with DOPA decarboxylase) à norepinephrine (via beta hydroxylase)
COMT in extracellular compartment – expressed on postsynaptic neurons and glial cells.

Specific to Prefrontal cortex (PFC) as opposed to striatum.

Outside the nervous system;

Can be found in blood – purpose unknown.
Over 95% is in form of dopamine sulfate. Sulfotransferase 1A3/1A4 works on free dopamine to make it.
Bulk of this is made in mesentery – thought to reduce the toxicity of food that contains dopamine (plasma levels rise 50 fold) and is excreted in the urine.

May act on:

- Dopamine receptors in periphery
- Metabolised
- Convereted to noradrenaline/norepinephrine via dopamine beta hydroxylase à adrenal medulla.
- Vasodilator and inhibitor of NA.
- Sympathetic nervous system effect on heart = increased HR. Increases heart contraction force too.
- Increased dopamine à reduced effect of pain med
    - New classes of analgesics that have bearing on dopaminergic activity.

Actions on organs.

- Vasodilator
- Kidneys à sodium excretion, urine output
- Pancrease à reduces insulin production.
- Digestive system à reduces motility, protects mucosa.
- Immune system à reduces activity of lymphocytes.
- With exception of blood vessels, produced locally and exerts effects near it.

In skeletal muscle;

- Increases muscle tone.
    - Our results provide the first demonstration that dopamine can directly control movement by manipulating somatic motoneuron behavior and skeletal muscle tone.
    - Via D1like receptors, not D2.
    - https://www.ncbi.nlm.nih.gov/pubmed/21653722
- Can induce muscle contraction.
    -

- Tx with DA antagonist will induce preservation of muscle force production in periods of atrophy, and hypertrophy otherwise (done in rabit calf muscles)
    - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3038169/

- skeletal muscle is a reservoir of ldopa and doesn't break it down much. Excess will result in ldopa escaping into peripheral blood.

http://jpet.aspetjournals.org/content/190/1/187.short
Contains little comt/dopa decarboxylase activity.

In pain;

Types of pain:

1. Nocioceptive = via receptors in response to tissue damaging stimuli.
2. Neuropathic (NP) pain = nervous system lesion/dysfn.

a) Acute pain = term given to immediate reaction after giving rats a pain stimulus (usually formalin)

b) Tonic pain = term given to the point 15 – 20 mins afterwards

- Known to be a part – esp in the basal ganglia.
- Activation of mesolimbic dopamine in ventral striatum and nucleus accumbens à analgesia.
- Injection of quinpirole into nucleus accumbens à inhibition of persistent phase of formalin-induced nocioception . D1 agonist = no effect. This was blocked by pre-administration of d2 receptor antagonist.
- Microinjection of apomorphine/quinpirole into dorsolateral striatum à reduces formalin-induced nociocpetion. Nonselective DA antagonist haloperidol and selective DA antagonist eticloperide enhance pain. Manipulation of d1 receptors = no effect.
- D2 (and likely D3) = modulation of tonic pain, in striatum + accumbens through postsynaptic binding.
    - Formalin-induced behaviour = 2 phases. Acute and tonic.
    - In a test, morphine was given before or after early phase pain.
    - Significantly higher pain inhibition seen in injection after early phase.
    - Limited effect on late phase due to behavioural/neural changes.
    - More formaldehyde = more likely to suppress pain.
        - § (2% vs 5%) = 55% and 76% chance of suppressing early stage pain.
        - § Didn’t effect late stage pain.
- 6-OHDA = neurotoxin (6-hydroxydopamine).
    - Targets cells expressing tyrosine hydroxylase = good for evaluating dopamine lesions.

- Lesions of striatum = significantly decrease latencies of several nocioceptive reflexes and accelerates time of onset of chronic deafferentation pain (pain after nerve injury)
  - § Deafferentation pain likely results from reorganization of the nervous system after nerve injury via processes that interact with the substrates for pain perception (the pain matrix)
  - § The pain matrix = cingulate cortex (main one. Aka brodman area 24), periaqueducat grey, thalamus, lentiform nucleus, insula, anterior cingulate and prefrontal cortex, and primary and secondary somatosensory cortexes.
  - § Anterior cingulate = involved in both acute and chronic pain. Thought to be context dependent = non-specific attentional phenomena among other things.

· Stimulation of Ventral tegmental area and substantia nigra = tonic analgesia – lesions of 6-OHDA variety here = similar to straitum lesions = harder to initiate movements = parkinsonian features.
· Lesions of VTN-SN = enhanced pain, electornic stimulation = decrease it.
· Unilateral 6-OHDA lesions = immediate and lasting latency in response to mechanical stimulation on ipsilateral side. No changes in contralateral
· Unilateral dopamine depletion = mechanical hypersensitivity. Mesotriatal dopamine establishes pain thresholds in response to mechanical stimulation.

In fibromyalgia

§ Dopamine synthesis in presynaptic cleft = decreased in FBM.
- Including thalamus, mesencephalon, insula, ACC, hippocampus.

§ Stress increases its effect.
§ In females with FM – dopamine release into striatum was disrupted.
- Therefore dopamine based tx are pretty good.

Restless leg syndrome patients benefit from dopamine tx and anti-Levadopa in peripheral system.

§ They have heightened allodynia to pin prick and touch compared ot healthy controls.
§ Tx with Levodopa (100mg) + 25mg benserazide = less RLS symptoms, no effect on pin prick pain.

§ https://www.ncbi.nlm.nih.gov/pubmed/14985260
§

Dopamine agonists;

§ Antinocioceptive effects of higher doses of apomorphine are reduced by centrally acting sulpiride but not by peripheral D2 antagonist domperidone.
    - Central receptors are important to effects of apomorphine.
§ At a low dose – it is hyperalgesiac though. Probs because it increases presynaptic dopamine à attenuate normal dopamine responses in response to stimulation.
§ Pramipexole [73] and ropinirole [74] have been used in FM à D2/D3 but not D1, 4 and 5 agonists. = significant benefits seen.
§ Pramipexole was better than ropinirole – dose = 0.25 titrated to 4.5 mg/night.
§ Bromocriptine decreases pain, while haloperidol increases them.
    - Pts on bromecriptine = lowered met-enkaphalin levels in brain and CSF. Haloperidol = opposite.
    - = good effect in tx of painful DN.

Reuptake inhbitors.

§ Nomifensine = dopamine reuptake inhibitor was an old one that increased analgesic reaction to formalin test but not to others.
§

Role of central dopamine in pain and analgesia

https://www.ncbi.nlm.nih.gov/pubmed/18457535

Duloxetine and its association with it.

- SNRIs = increased dopamine transmission in brain.
- Is, to a lesser extent, also a dopamine reuptake inhibitor.
- Increases DA in prefrontal cortex through effects on NE transporter (NET) which is used to reuptake norepinephrine (NE) and dopamine.
- Highest amount 6 hours afterwards. If taken with food = 10 hours.

Brain cognitive decline after chemotherapy;

Cognitive functions and brain regions relevant to chemotherapy-induced cognitive changes

Memory

Working memory

The ability to temporarily store and manipulate information (bilateral prefrontal and parietal regions).

Episodic memory

The ability to learn and retain new context-dependent information (medial temporal lobes and prefrontal cortex).

Remote memory

The ability to retrieve memories from the past (frontal and temporal lobes).

Modality-specific memory

Verbal memory

Memory for words and narrative material presented verbally or in writing (left hemisphere).

Visual memory

Memory for objects, faces, figures or locations presented visually (right hemisphere).

Executive function

The control system that manages other cognitive processes, including planning, rule acquisition, initiating appropriate action, inhibiting competing responses and selecting relevant information (bilateral dorsal lateral prefrontal cortex).

Processing speed

The speed and efficiency with which information is used in completing a task (distributed frontal subcortical network).

Visual, spatial and constructional ability

The ability to visualize and manipulate two and three-dimensional objects (right parietal and bilateral frontal regions).

Attention and concentration

Attention is the ability to focus on certain information or stimuli at the same time as ignoring other information or stimuli. Concentration refers to the ability to maintain attention without being distracted by competing stimuli (distributed frontal subcortical network).

Reaction time

Simple reaction time is the time it takes for a person to react to a stimulus (for example, pressing a button when a light goes on), whereas complex or choice reaction time is the period of latency before a decision is made regarding a stimulus (for example, deciding if a sequence of letters represents a word) (distributed frontal subcortical network).

Motor speed and dexterity

The speed and accuracy with which a person can perform simple motor tasks and manipulate objects (for example, placing pegs in holes on a board) (bilateral frontal and pyramidal and extrapyramidal motor systems).

- Chemo direct damage. Many cross BBB, so it's probs happened to me.
- Genetic variations in the MRDP1 gene which encodes P-Gp (P-glycoprotein)/polymorphisms are associated with higher transport of chemo out of brain cells. More of this protein = more transport out.
    - C3435 in exon 26
        - § T allele = lower P-Gp therefore higher chemotoxicity.
        - § T allele also associated with higher levels of vincristine and steroid hormones after peripheral administration.
- Telomere shortening
    - Most neuronal cells are post-mitotic; however, certain cells, such as glia in the CNS, remain mitotic and are susceptible to telomere shortening
- Oxidative stress = damage.
- Il2/interferon a immunotherapy pts were associated with depression, weakness, fatigue and cognitive disruption.

- Higher levels of il6, 8 and 10 seen in paclitaxel/docetaxel pts
    - Though no direct link seen to cognitive fn, breast cancer ptswith fatigue have higher levels of all of the above.
- In AML pts, higher levels of IL1, IL1 receptor agonist (IL1RA), Il6, IL8 and tnf-alpha seen. Il6 in particular was significant. This is pre-tx. Not enough people for data post tx.
- Direct mechanisms of actual damage à excitotoxic glutamate receptor-mediated damage and oxidative stress[63]
- Indirect mechanisms = cytokine related micronutrient deficiency, impaired sleep

Cramps more likely after cramps.

https://www.ncbi.nlm.nih.gov/pubmed/28063158

Tetany;

- Involuntary contraction of muscles.
- May be caused by diseases that affect action potentials in muscles.
- Due to lack of inhibition.
- Low calcium – hypocalcemia = main cause.
    - Low levels in ECF = increased permeability of neuronal membranes à depolarisation à higher chance of AP.
    - If lower than 50% of 9.4 (normal value) – AP can spontaneously generate.
- Can be caused by high phosphate.
- Underfn of parathyroid gland.
- Low CO2.
- Low magnesium.
- Trousseau sign of latent tetany à squeeze brachial artery and if that induces cramps = this.
- Chvostek sign. à tap anterior to ear = calcium deficiency.
    - EMG studies reveal single or often grouped motor unit discharges at low discharge frequency during tetany episodes.

Multifocal motor neuroapathy.

- Immunoglobulins help.
    - Worsened symptoms when off it.
- https://www.ncbi.nlm.nih.gov/pubmed/28320129

Genetics of neural repair.

- Apolipoprotein E = distribution of lipids. Important part in repair after injury.
- Defects in APOE result in familial dysbetalipoproteinemia aka type III hyperlipoproteinemia (HLP III)
    - Impaired clearance of chylomicron, VLDL and LDL remnants = higher plasma triglicerides.
- Coded by a 4exon allele à chromosome 19.
    - E2, e3 and e4 most important.
        - § E2 = 7% of population. E2/e2 allele = harder to clear dietary fat = higher risk of vascular disease, genetic disorder
        - § 98% of people with familial genetic type 3 hyperlipiporeinaemia are E2/E2, but only 2% of cancer pts = this.
    - E3 = neutral.
    - E4 = more likely to have brain affected after chemo and other events like stroke etc.
        - § Even carriers can have this.
        - § Mechanism is unclear.
        - § Carriers possibly have morphological changes in the brain à lower hippocampal volume, atherosclerosis, alzheimers, impaired cognitive fn, faster disease progression in MS, faster telomere shortening, sleep apnoea but higher levels of vitamin D.
    -
- Brain derived neurotrophic factor. Another important one but no studies currently link it to chemotherapy.

Oestrogen/testosterone.

- Neuroprotective effects of oestrogen are known.
    - Also help in keeping telomere length long.
- Neuroprotective/antioxidant effects of testosterone is also good.

Polymorphism of COMT

- Breaks down catecholamines through methylation of DA and NA
- Common functional polymorphism – single change of G to A at position 472, changes a valine to methionine
    - Impacts efficiency of COMT.
    - COMT is 4x more efficient when valine present.
- COMT is important in frontal cortex.
- Valine = more rapidly processed so dopamine broken down too fast.
- Pts homozygous for valine = poorer performance in tests.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329763/

Prolactin

- Inhibits dopamine.
- Receptors present in a lot of tissues including (ofc) mammary glands, liver, pancreas, skeletal muscle.
- When it binds à dimerises with another receptor. à activates janus kinase 2. à jak/stat pathway activation. à map kinase/src kinase.
- Produced by anterior pit, prostate, lymphocytes.
    - Estrogen à increase prolactin. Suppress dopamine.
- Peaks in REM sleep and early in morning.
- Levels rise after exercise, high protein meals, surgical procedures, seizures or stress,

Muscle contractions

1. AP along nerve.
    a. Resting membrane potential.
    b. Some voltage gated ion channels open and Na+ is allowed in. (til threshold potential reached)
    c. Opening of more Na+ channels à further depolarisation (rapid upstroke)
    d. Reaches peak levels
    e. Direction of Na+ concentration reversed.
        i. Na channels close rapidly.
        ii. K+ channels open – repolarisation.
        iii. Slow closing of K+ channels. (after hyperpolarisation occurs)
    f. Return to resting MP.
2. ACh enters synaptic cleft.
3. Binds to receptors.

- Calcium binds to ccalmodulin.
- Activates Myosin LC kinase
- Phosphorolates myosin light chain at serine residue 19.
- Myosin crossbridge.
- In skeletal muscle, tropomyosin will block the attachment site for the myosin crossbridge until calcium changes its conformity to allow it to attach.
- Smooth muscle doesmt have this. So Myosin LC Kinase is only regulating step.

Dopamine effect on blood flow in skeletal muscle.

- Depresses blood flow after muscle effort.
- Not alleviated by propanalol (alpha and beta adrenergic receptors.)
- Low doses of DA after propranolol = effect.

Dopamine agonists;

HEAPS of side effects. NOT preferable. NOT an option in me.

- Se =
    - Euphoria
    - Weight loss
    - Anxiety
    - Insomnia
    - Dizziness
    - Blackouts
    - Orthostatic hypertension.
    - Hallucinations
    - Hypersexuality.
- Apomorphine (Apokyn – used to treat Parkinson's disease/Restless leg syndrome) – G-protein bias at the D1 receptor.[4]
- Bromocriptine (Parlodel – used to treat Parkinson's disease/Restless leg syndrome)
- Cabergoline (Dostinex – used to treat Parkinson's disease/Restless leg syndrome) – d2 receptors.
- Ciladopa (used to treat Parkinson's disease/Restless leg syndrome)
- Dihydrexidine (used to treat Parkinson's disease/Restless leg syndrome)
- Dinapsoline (used to treat Parkinson's disease/Restless leg syndrome)
- Doxanthrine (used to treat Parkinson's disease/Restless leg syndrome)
- Epicriptine (used to treat Parkinson's disease/Restless leg syndrome)
- Lisuride (used to treat Parkinson's disease/Restless leg syndrome)
- Pergolide (used to treat Parkinson's disease/Restless leg syndrome) – previously available as Permax, but removed from the market in the USA March 29, 2007.[12]
- Piribedil (Pronoran and Trivastal – used to treat Parkinson's disease/Restless leg syndrome)
- Pramipexole (Mirapex and Sifrol – used to treat Parkinson's disease/Restless leg syndrome)
- Propylnorapomorphine (used to treat Parkinson's disease/Restless leg syndrome)
- Quinagolide (Norprolac – used to treat Parkinson's disease/Restless leg syndrome)
- Ropinirole (Requip[13] – used to treat Parkinson's disease/Restless leg syndrome)

- Rotigotine (Neupro – used to treat Parkinson's disease/Restless leg syndrome)
- Roxindole (used to treat Parkinson's disease/Restless leg syndrome)
- Sumanirole (used to treat Parkinson's disease/Restless leg syndrome)

Partial agonists;

- Aripiprazole (Partial agonist of the D_2 family receptors - Trade name "Abilify" in the United States; atypical antipsychotic)
- Phencyclidine (a.k.a. PCP; partial agonist. Psychoactivity mainly due to NMDA antagonism)
- Quinpirole (Partial agonist of the D_2 and D_3 family of receptors)
- Salvinorin A (chief active constituent of the psychedelic herb salvia divinorum, the psychoactivity of which is mainly due to Kappa-opioid receptor agonism; partial agonist at the D_2 with an Intrinsic activity of 40-60%, binding affinity of K_i=5-10nM and EC_{50}=50-90nM)[11]

Other movement disorders;

- https://en.wikipedia.org/wiki/Progressive_supranuclear_palsy
    - Volumes of brain deplete. = issues.
- MSA – multiple system atrophy.
    - Progressive loss of certain areas of brain à substantia nigra, striatum, inferior olivary nucleus, and cerebellum.
- ***Dystonia***
    - Repetitive twitching/tremors/contractions.
    - Can be reaction to neuroleptics.
    - I had cramps in first transplant though.
    - Less likely
    - Tardive dystonia = dystonia caused by neuroleptics amongst other meds
        - § Symptoms include lipsmacking, tongue movements, grimacing, excessive blinking which I don't have.
- ?cerebellar dysfunction. à Na/K pumps of purkinje fibres are important and if blocked cause ataxia/dystonia in mice.
    - Examination of me.

Dopamine rececptor implications in writers cramp

- 11C-racloporide (synthetic dopamine receptor agonist) binding to d2/d3 receptors at rest = reduced in writer's cramp pts.
- Lowered dopamine release in left striatum in tapping task.

Dopamine in FM patients;

Dopamine D2/D3 receptor availability at rest and its association with individual pain perception was investigated using the [(11)C] raclopride PET-method in 24 female Fibromyalgia (FMS) participants with (FMS+, N=11) and without (FMS-, N=13) comorbid depression and in 17 healthy women. Thermal pain thresholds (TPT) and pain responses were assessed outside the scanner. We compared the discriminative capacity, i.e. the individual′s capacity to discriminate between lower and higher pain intensities and the response criterion, i.e. the subject′s tendency to report pain during noxious stimulation due to psychological factors. [(11)C] raclopride binding potential (BP), defined as the ratio of specifically bound non-displaceable radioligand at equilibrium (BP(ND)) was used as measure of D2/D3 receptor availability. We found significant group effects of BP(ND) in striatal regions (left ventral striatum, left caudate nucleus and left nucleus accumbens) between FMS+ and FMS- compared to healthy subjects. Correlational analysis showed negative associations between TPT and D2/D3 receptor availability in the left caudate nucleus in FMS-, between TPT and D2/D3 receptor availability in the right caudate nucleus in FMS + and positive associations between TPT and D2/D3 receptor availability in the left putamen and right caudate nucleus in healthy controls. The response criterion was positively associated with D2/D3 receptor availability in the right nucleus accumbens in FMS - and negatively with D2/D3 receptor availability in the left caudate nucleus in healthy controls. Finally, no significant associations between D2/D3 receptor availability and discriminative capacity in any of the groups or regions were determined. These findings provide further support for a disruption of dopaminergic neurotransmission in FMS and implicate DA as important neurochemical moderator of differences in pain perception in FMS patients with and without co-morbid depression.

DOPAMINE IS IMPORTANT à lowered in brain/basal ganglia

In vivo administration or in vitro application of dopamine or of dopamine receptor agonists induce vasodilatation in the cerebral, coronary, renal and mesenteric vascular beds and cause hypotension. Moreover, dopamine stimulates cardiac contractility and induces diuresis and natriuresis. Peripheral

(cardiovascular and renal) dopamine receptors belong to the D1-like and D2-like receptor superfamilies, thought to be located post-junctionally and pre-junctionally respectively. Stimulation of vascular D1-like receptors causes direct vasodilatation and reduction of vascular resistance. Stimulation of vascular D2-like receptors causes indirect vasodilatation, resulting from inhibition of sympathetic vasoconstrictor tone. Combined radioligand binding assay and light microscope autoradiography have investigated the anatomical localization of cardiovascular and renal dopamine D1-like and D2-like receptors in different animal species including humans. The application of molecular biology techniques to dopamine receptor research has shown that the picture of dopamine receptor subtypes is more complicated than it was suggested in the past, with at least 5 subtypes belonging to the dopamine D1-like (D1 and D5 receptors) and D2-like (D2, D3 and D4 receptors) superfamilies. The development of antibodies raised against selected sequences of dopamine receptor subtypes has allowed a more detailed characterization of the density and pattern of peripheral dopamine receptors. Dopamine receptor protein immunohistochemistry confirmed the localization of dopamine D1 and D5 receptors in the tunica media of systemic arteries and of prejunctional dopamine D2-D4 receptors closely associated with sympathetic neuroeffector junctions. The distribution and the density of prejunctional dopamine D2-like receptors was different in various vascular beds investigated. The kidney expresses the 5 different subtypes of dopamine receptors, displaying a not homogeneous vascular and tubular localization. Dopamine acting as autocrine or paracrine substance is probably involved in the regulation of immune activity. Human peripheral blood lymphocytes contain dopamine and express plasma membrane and vesicular dopamine transporters as well as dopamine D3, D4 and D5 receptors. Another recently characterized peripheral dopaminergic system is located in the lung. Dopamine D1-like receptor immunoreactive structures were found in a small percentage of nerve fibres contained in pulmonary nerve trunks. D1-immunoreactive nerve fibres were approximately 2-3% of total fibres, whereas D5-immunoreactive fibres accounted approximately for 5-6% of total fibres. Also dopamine D2-like receptor immunoreactive fibres were found in pulmonary trunks. D2-immunoreactive fibres accounted for approximately 3-5% of total nerve fibres, D3 receptor-immnunoreactive fibres accounted for about 8-10% of total nerve fibres, whereas only rare profiles of D4 receptor protein-immunoreactive fibres were observed. Dopamine recepetor protein immunostaining was also found in neurons of nodose ganglion, that display immunoreactivity for different neuropeptides.

Based on the correspondence between the number of dopamine receptor immunoreactive pulmonary nerve fibres and of vagal ganglionic neurons immunoreactive for dopamine receptors it is possible to hypothesize that these receptors are located on pulmonary afferents. In spite of the heterogeneity of peripheral systems expressing dopamine receptors, analysis of their localization with appropriate microanatomical techniques may contribute to investigate their role in health and disease.

è Thery're important.

è They work by inhibiting other things possibly.

Physiotherapy/electornic stimulation

Electronic stimulation to increase cramp threshold - showed significant improvements in this RCT:

CTF had significantly ($p<0.001$) increased in CT calves from 23.3±5.7 Hz to 33.3±6.9 Hz, while it remained unchanged in nCT (pre: 23.6±5.7 Hz, mid: 22.3±3.5 Hz) and in both legs of the CG (pre: 21.8±3.2 Hz, mid: 22.0±2.7 Hz). Only CT saw further insignificant increases in the CTF. The applied stimulation energy ($mA^2 \cdot \mu s$) positively correlated with the effect on the CTF ($r=0.92$; $p<0.001$).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3984281/

https://drive.google.com/open?id=1CN_q24s5wPN8895quertezixRce8RYStmKMCf6mQmkE

What to ask in me:

- Phenyl alanine urine test.

Untreated PKU can lead to intellectual disability, seizures, behavioral problems, and mental disorders. It may also result in a musty smell and lighter skin.

- Troponin à trop T test (muscular inflammation.
    - Troponin I test.
    - CTnT/CTnL too – cardiac muscle injury. (less likely) .
- Calcitonin levels. All hormones.
- MLCK (myosinlight chain kinase) levels à 2 = skeletal muscle.

- PKA?

- COMT inhibitor? DOPA decarboxylase in me?

Potential drugs that may work - my case for them:

COMT inhibitors.

- Peripheral most likely. Important centrally too à in frontal cortex important for dopamine fn. See above.
- Opicapone = new one coming through.
    - Well tolerated. Dyskinesias = most common side effect.
    - https://www.ncbi.nlm.nih.gov/pubmed/28234566
- Examples
    - Opicapone
        - § NMS (severe reaction to antipsychotics) and non traumatic rhabdomyosis = contraindications = I don't have that.
    - **Entacapone**
        - § Reversible inhibitor. Selective.
        - § Liver fn testing is important.
    - Tolcapone = liver toxicity. Also centrally acting = no good.

Dopa decarboxylases

- Dopa decarboxylases.
    - § **Benserazide** = peripherally acting only.
        - Given with L-Dopa.
        - Vasoconstriction, arrhythmias etc are minimised.
        - Cannot stop dopamine effects particularly dyskinesia.
    - § Carbidopa = peripheral acting too.
        - Has interactions with serotonin.
    - § Methyldopa = heaps of contraindications, reduces total dopamine in the body = bad. = opposite of the above conditions.
        - Competitive inhibitior.
        - Converts to a-methylnoreipinephrine which reduces sympathetic nervous system effects.
        - Sae mechanism for clonidine.
        - Liver bad. Very bad side effects.

- Symmetril - = antiviral that is thought to work by making presynaptic dopamine easier to release.

Dopamine agonist.

  - Also by binding to glutamate receptors in subthalamic nucleus = balances dopamine/glutamate.

Anticholingerics

- Artane/cognetine = anti-cholingerics.
  - Restore balance between ach and dopamine.
  - Reduce tremor and stiffness in muscle.
  - Side effects = blurred vision, urinary retention, dry mouth. Delirium. Increased heart rate. Higher rates of death.
- Procyclidine – improves tremor but not rigidity/bradykinesia.
- Biperiden – parkinson's, reducing swelling in methadone users, relieves muscle rigidity, abnormal sweating, tremor,
  - Interacts with quinidine, alcohol, metoclopramide, antispasmodics, antipsychotics.
- Cycrimine – muscuranic receptor M1

Antimuscuranics -

Methylatropine

Atropine methonitrate- lacks CNS mechanism.

- Fibrillation
- Tachycardia
- Potentially confusion and thingy.
- That's atropine. Not methonitrate.
- Indeed is a peripherally acting drug exclusively.
- https://www.ncbi.nlm.nih.gov/pubmed/11224265
- Methylatropine nitrate = 0.3% chance of causing renal failure.
- anticholinergic, parasympatholytic agent
- Atropine methonitrate = good bronchodilator too.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC471418/

- Quaternary ammonium analogues of metaxalne = unable to cross BBb
- Currently, methylatropine is the most popular and potent of these quaternary derivatives; however, it is expensive and produced in limited quantity.
- ethylatropine bromide = inexpensive alternative perhaps.

https://www.ncbi.nlm.nih.gov/pubmed/28044440

- Microwave irradiation an induce crossing into central system through BBB though
- https://www.ncbi.nlm.nih.gov/pubmed/3961098

- Lidnocaine. Metaxalone

Beta blockers

- Propranolol and oxprenolol

Carbamates.

- **Carisoprodol** – soma.
    - Sedative, muscle relaxant, euphoria, analgeisai = uses.
        - § Side effects lessen. Mild.
        - § Euphoria – short burst = common.
    - Potentiates/interacts with opioids
    - Withdrawal is severe.
    - Tybamate = similar.
    - Meprobamate = metabolite and a medicine In itself.
    - Lorbamate is another one.
- Acetylcholinesterase inhibitors.
    - Inhibits enzyme from breaking down Ach. = more Ach.
    - INCREASES NMJ function – not what we want.
- Eldepryl = MAO-B inhibitor.
- Sifrol/dopamine agonists as tx for the depression.
- **Diphenhydramine** - antihistamine and anticholingeric
    - Inverse agonist of H1 receptor. = opposite effect of inducing histamine release.
        - § Also affects central H1 = drosiness. Crosses bbb
        - § Is anti-muscuranc
        - § Affects serotonin too.
    - Benadryl.
    - **Physostigmine** used to tx od/anticholingeric syndrome.
    - dry mouth and throat, increased heart rate, pupil dilation, urinary retention, constipation, and, at high doses, hallucinations or delirium.
    - Flushed skin, ataxia, no accommodation in vision, erectile dysfn.

Antihistamines = play a role

Hydroxyzine

Naftidrofuryl

- vasodilator. May be effective in relieving muscle cramps. Attaches to 5ht2a receptors – inverse agonist. = opposite effect.
- 5h2a receptors can downregulate with SSRIs and is involved in depression pathogenesis.
- Can cause liver failure.

Also treats tinnitus.

https://en.wikipedia.org/wiki/Naftidrofuryl

Benzos

- Clonazepam = works in me. Addictive tho.
- Increases effect of GABA on GABA receptors.
- Lorazepam.
- Any way to make this non addictive?

Tizanidine = a2 adrenergic agonist – centrally acting

- Liver damage
- 5% of pts get it.
- Must monitor regularly for first 6 months.
- Concommittant use with antiarrhythmics or CYP1A2 inhiitors (mexiletine for eg. Is sodium channel blocker)
- Can cause increased spasms, as well as hallucinations and a range of other side effects like depression etc.

Barbituates = last resort.

Amantadine = Antiviriral that increases central dopamine in nigrostriatal system.

Tolerance:

- Develops over time.
- Makes your brain more receptive to glutamate.
- There is cross tolerance between alcohol, the benzodiazepines, the barbiturates, the nonbenzodiazepine drugs, and corticosteroids, which all act by enhancing the $GABA_A$ receptor's function via modulating the chloride ion channel function of the $GABA_A$receptor.[27][28][29][30][31]
- Changes t

- Decrease in NA, ACh, 5ht and DA dopamine seen in benzos. Withdrawal will therefore induce decreases in these. Excitotoxicity occurs in withdrawal.
- Benzo receptors also change. Some upregulated some downregulated.
- Persistent neuroadaptations can occur in withdrawal.
- Emotional blunting and suicide too.
- The pharmacological mechanism of benzodiazepine tolerance and dependence is the internalization (removal) of receptor site in the brain and changes in gene transcription codes in the brain.[40]

- Flumazenil is being studied as a potential treatment to reduce withdrawal symptoms.[62] As its use may result in seizures this should only be done within hospital in areas experienced with the procedure.[63]
-

Adrenergic receptors.

How uptake works –

There are 2

1. Uptake presynaptically. Takes it out of cleft.
2. Uptake post synaptically – stops it from affecting lateral muscles.

Dopamine works on all 5 adrenergic receptors.

- Alpha 1
  - Vasoconstriction
  - Decrease motility in GI tract.
  - Constriction of smooth muscle.
    - § Eg = ureter.
    - § Hair
    - § Uterus.
  - Gluconeogenesis from adipose tissue.
  - Glycogenolysis in liver.
  - G coupled protein receptor. PLC mediated downstream effects à reelease calcium whatevs.
- Alpha 2
  - Alpha 2 = negative feedback affected. So NE attaching = less response to NE next time.
  - Inhibits insulin.
  - Inducts glucagon release
  - Contracts sphincters of GI tract.
  - Thrombocyte
- Beta1
  - Increases Cardiac output. Works on increasing HR, conduction velocity and stroke volume (contractility increase)
  - Renin release from juxtoglomerular cells of kidney.
  - Ghrelin from stomach.
- Beta2
  - Adrenalin binding.
  - Smooth muscle relaxation.
  - Lipolysis.
  - Anabolism.

    - Relaxes detrusor.
    - Dilate arteries in skeletal muscle.
    - Inhibits renin secretion in kidney.
    - Inhibits hisamine from mast cells.
- Beta3
    - Enhances lipolysis.
- DBS (deep brain stimulation) if all else fails?

http://search.proquest.com.ezproxy.uws.edu.au/docview/1501884219?accountid=36155&rfr_id=info%3Axri%2Fsid%3Aprimo

Calcium channel blocker.
Amlodipine

Minocycline - antibiotic with some neuroprotective effects. Attenuates tnf alpha.
https://en.m.wikipedia.org/wiki/Minocycline

Scleroderma

Wound healing steps

Myofibroblasts;

- Myofibroblasts can contract by using smooth muscle type actin-myosin complex, rich in a form of actin called alpha-smooth muscle actin. These cells are then capable of speeding wound repair by **contracting the edges of the wound.**
- Fibroblasts can xform into myofibroblasts in photobiomdoulation - low power laser therapy.
- Apoptosis SHOULD occur but doesn't always and it's suggested that in several fibrotic diseases (for example liver cirrhosis, kidney fibrosis, retroperitoneal fibrosis) that this mechanism fails to work, leading to persistence of the myofibroblasts, and consequently expansion of the extracellular matrix (fibrosis) with contraction.
- Bmp antagonist noggin, or low bmp receptor presence preventended adipocyte formation
- actively growing hair follicles, which are critical for myofibroblast-to-adipocyte reprogramming, strongly express BMP2 and BMP4 (14)

- Wnts are known inhibitors of adipocyte differentiation, we also examined K14-Wnt7a mice and discovered a lack of fat regeneration, despite an increased number of new hair follicles after wounding
- Coculture of human keloid fibroblasts with human scalp hair follicles also induced their adipogenic conversion
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5464786/

Myofibroblasts vs fibroblasts in gvhd - local and donor derived;

- In this study - it was seen that myofibroblasts generated from original donors were present in wounds.
- Fibrocytes (circulating in blood) can have an impact, via TGF beta and connective tissue growth factor CTGF, on fibroblast activity, but it likely isn't direct as opposed to paracrine in nature.

Pirfenidone

In idiopathic pulmonary fibrosis - most trials seemed to have it help the lungs. Done on, cumulatively, thousands of patients. Seems to be more effective than placebo and steroids in this; but hasn't received approval by FDA yet.
https://en.wikipedia.org/wiki/Pirfenidone#Adverse_effects

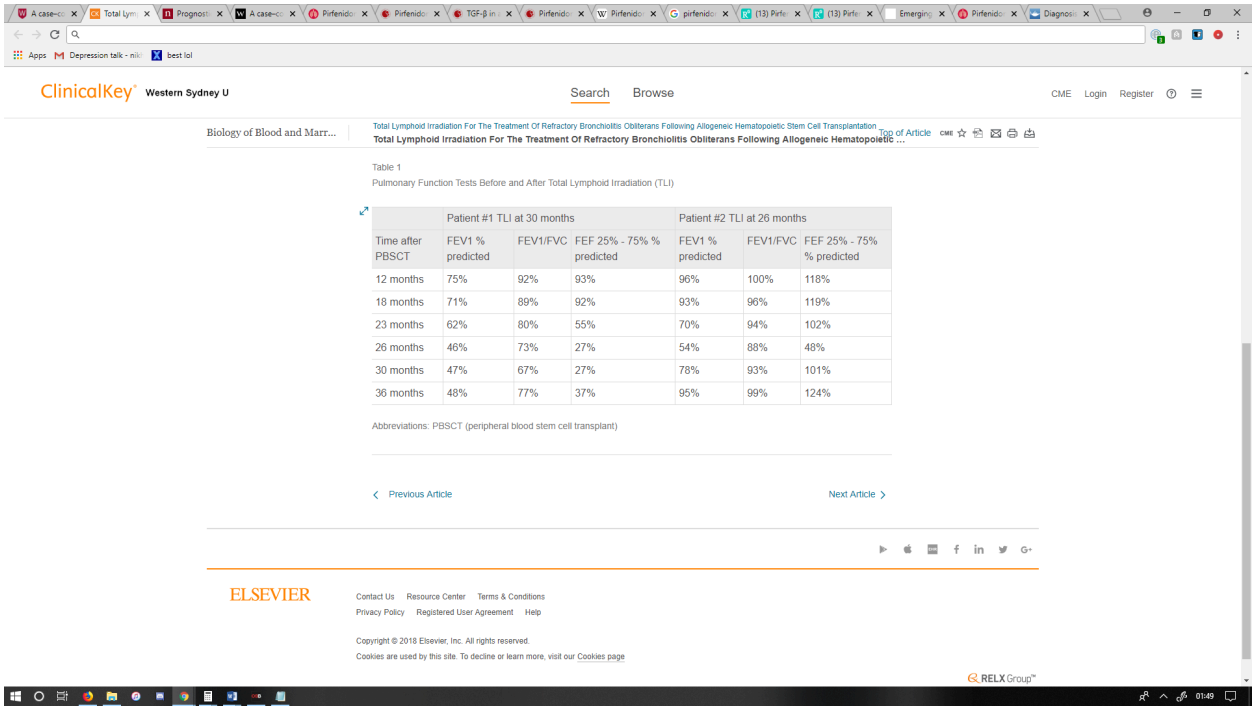
Ameliorates TGF-beta stimulated collagen production
Clinical trial taking place in 30 patients with BOS post GVHD - recruting
https://clinicaltrials.gov/ct2/show/NCT03315741

Pirfenidone
Mouse models = good.
Early trial in 5 patients = good, with only 1 coming off it for nausea/other GI effects
http://www.bloodjournal.org/content/129/18/2463

NLRP3 may also be implicated in its MOA
https://www.sciencedirect.com/science/article/pii/S108387911630386X
Pirfenidone treatment in patients with bronchiolitis obliterans syndrome following allogeneic hematopoietic stem cell transplantation

http://erj.ersjournals.com/content/48/suppl_60/PA3923

More drastic;
Total lymphocyte irradiation
After 12 months or so, both patients trialed had good results with improvement in LFTs.



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Biology of Blood and Marr...

Total Lymphoid Irradiation For The Treatment Of Refractory Bronchiolitis Obliterans Following Allogeneic Hematopoietic Stem Cell Transplantation

Total Lymphoid Irradiation For The Treatment Of Refractory Bronchiolitis Obliterans Following Allogeneic Hematopoietic ... Top of Article

Table 1

Pulmonary Function Tests Before and After Total Lymphoid Irradiation (TLI)

	Patient #1 TLI at 30 months			Patient #2 TLI at 26 months		
Time after PBSCT	FEV1 % predicted	FEV1/FVC	FEF 25% - 75% % predicted	FEV1 % predicted	FEV1/FVC	FEF 25% - 75% % predicted
12 months	75%	92%	93%	96%	100%	118%
18 months	71%	89%	92%	93%	96%	119%
23 months	62%	80%	55%	70%	94%	102%
26 months	46%	73%	27%	54%	88%	48%
30 months	47%	67%	27%	78%	93%	101%
36 months	48%	77%	37%	95%	99%	124%

Abbreviations: PBSCT (peripheral blood stem cell transplant)

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https://www-clinicalkey-com-au.ezproxy.uws.edu.au/#!/content/playContent/1-s2.0-S1083879109008726?returnurl=null&referrer=null

Inhibits tgf beta
It does impact this in mice, and is thought to be the main way this works. Also inhibits il17, it was seen.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5418639/

Another study showing it reduces il17 and tgf beta
https://www.ncbi.nlm.nih.gov/pubmed/27715339

Didn't inhibit il17 in in vitro study in idiopathic fibrosis
http://erj.ersjournals.com/content/42/Suppl_57/P2334

Il17 inhibitor - mab called secukinumab

https://www.sciencedirect.com/science/article/pii/S1083879114000949
Shown to be insturmental in gvh

Il17 leads to il6, tgfbeta and other cytokines such as IL-6, G-CSF, GM-CSF, IL-1β, TGF-β, TNF-α), chemokines(including IL-8, GRO-α, and MCP-1), and prostaglandins (e.g., PGE_2) from many cell types (fibroblasts, endothelial cells, epithelial cells, keratinocytes, and macrophages)
https://en.wikipedia.org/wiki/Secukinumab

Helps in mice - scleroderma
https://www.ncbi.nlm.nih.gov/pubmed/27862942
Postulated that it helps in bo too

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5470889/
Pirfenidone may impact thisp athway - but it's only being looked into rn
https://www.researchgate.net/publication/316717730_Pirfenidone_A_breath_of_fresh_air_for_cGVHD