Dr Liegner Interview conducted by Harrison Schoeneau (Disulfiram for Lyme Support Group)

The following has been slightly edited for clarity.

Harrison: Hi Dr Liegner, this is Harrison from the Disulfiram for Lyme facebook support group. We've been really excited about your recent published article, it's created a great deal of excitement in the Lyme community.

I want to personally commend you for being the first Lyme doctor who was willing to go out on a limb and deviate from the current standard of care for Lyme to help his patients with a potential new breakthrough drug, which in this case is disulfiram.

I also wanted to thank you for having the courage to publish the results to mainstream medical doctors with your first three patients. I'm sure you knew you were potentially opening yourself up to a lot of scrutiny from the wider medical establishment.

And thanks for publishing the pioneering article and for doing all that work for the benefit of other patients and Lyme doctors.
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6627205/)

Dr Liegner: Thank you Harrison. I didn't actually feel like I was going out on some kind of a dangerous limb.

But again, I never would have suggested it to my patients, it's only because my patient suggested it to me that I did it.

H: They suggested the drug to you?

Dr L: Yes, I mean I wasn't even aware of the work, well, maybe I was aware of it. It was really the Kim Lewis video that was recorded during the first Mt Sinai Symposium on Lyme Disease in the Era of Precision Medicine (Oct 2016). Which I wasn't even aware of that symposium at the time.

And this particular patient, who is a very bright guy, he was following the work of Kim Lewis for quite a while. Probably even became aware of Kim Lewis' work just a little bit after I had become aware of it.

So he was following Kim Lewis, and somehow he must have become aware there was this video on Youtube that recorded the entire conference, and particularly Kim Lewis' Keynote Speech. Towards the end of that speech Lewis referenced the work of (Venkata Raveendra) Pothineni and (Jayakumar) Rajadas at Stanford on that high-throughput screening which identified disulfiram as the most active agent bar-none (for borrelia), an agent that's FDA approved. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827596/)

H: That work by Rajadas at Stanford has been underappreciated and we're looking forward to potentially interviewing him as well in the future.

Dr L: That'd be great.

H: So basically that led me into my first question: How did you first hear about disulfiram, from one of your patients I take it, right?

Dr L: Well, I was aware of disulfiram as an agent, Antabuse. Anyone trained in medicine would know about antabuse for the treatment of alcoholism. But I'd never used it, never prescribed it, I didn't know too much about it. And when this patient asked me whether I would allow him to try it, I started doing more research into it and learning more about it.

And he was the very first patient, my guess? he is the first human known to be treated with disulfiram for tick-borne illness, Lyme in particular. And the results were so unbelievable with his case that I mentioned it selectively to a couple of other patients whose care was difficult and problematic.

And then the 2nd and 3rd had these unbelievable results that my staff and I were pinching ourselves, waiting for the other shoe to drop because it was so incredible. These patients were very well documented, they did respond to antimicrobials but whenever you stopped they'd relapse. We got into this very problematic situation of this need for open-ended treatment, as you know that is very controversial in the (medical) community. But it has been necessary unless you want to abandon patients to their fate and just let them deteriorate. To have an agent that is not actually an antibiotic in the usual sense, is relatively safe, that's as cheap as borscht, relatively speaking, and very very potent, is amazing.

H: So when was the first patient that you put on disulfiram?

Dr L: Sometime in the late fall, or early winter of '16. He brought the video to my

attention, I reviewed it and read the article by Rajadas and Pothineni out of Stanford.

My patient was very respectful, I jokingly say he twisted my arm. He didn't, he just made a simple request, I thought about it, and after I had informed myself about the drug, I thought to myself: here's an FDA approved agent, been around for 60-70 years, fairly safe, and we have all these patients, because as a physician who cares for patients with a disease that doesn't exist, "chronic lyme disease," you kind of collect these difficult cases that nobody else wants to take care of; many difficult patients, like that first patient, and some even more difficult to manage.

The first patient was able to manage with fairly simple oral antimicrobials but there are other patients… despite our best efforts using oral agents, oral agents are not adequate. So that's even more problematic, and you're talking about intravenous antibiotic therapy, intramuscular antibiotic therapy, those are not the best solutions but that's what we have had. So when this patient, he'd been trying to come off (antimicrobials), we were able to get him to a point with intensive oral therapy where his condition was fairly good. But nobody wants to remain on open ended medication, antimicrobials, it's not the greatest thing. So he actually made a number of attempts to come off, he would do ok for a little but invariably he would deteriorate and be forced to resume them.

I'd worked with this patient for 7 years, an engineer, a rational guy, so when he asked me to try disulfiram I agreed to let him try it.

H: That was 2016?

Dr L: He was started on disulfiram St Patrick's Day 2017.

H: I think you're the first doctor to prescribe this off-label for Lyme disease. Do you believe that's the case?

Dr L: I believe that's the case, but only because of circumstance. But I never would have suggested it to my patients, only because that first patient requested it of me and I didn't think it was unreasonable. And I said ok, here's the deal, stop your other drugs, because otherwise how will you ever tease out what disulfiram does or doesn't do?

He stopped his high-dose amoxicillin (we're talking about industrial strength dosing). Stopped his high-dose minocycline and high-dose Malarone. And on that regimen he had done pretty well, so long as he was on it. So he stopped that, a little bit in advance

of taking the disulfiram. And then he began disulfiram, and again at that time I had no idea what the dosing was. So I looked into the literature on the usual dosage range for someone who was being prescribed it for alcoholism. So I chose a number, 500mg a day, and I gave him a prescription for it. I also gave him a standing order for surveillance labs, telling him have the labs done on a fairly frequent basis, and send me a note every couple weeks so that we know how you're doing. He did all that.

His labs were fine and he did send me notes every once in a while (he lived at some distance and it would have been a hardship for him to get to the office which was why I asked him to send me a note regarding his status every couple of weeks). He was doing fine and then a couple months later he left a message on my office voicemail canceling his followup appointment, declaring: "I'm cured!"

He mentioned in passing that he had required a hospitalization but he didn't tell me why.

So naturally I was very curious. I called him back and spoke with him, he mentioned to me that he had required psychiatric hospitalization at the time. But he said I'm fine, I'm doing well, getting by without any psychiatric meds. I did some more research and that's when I realized that occasionally disulfiram can cause psychiatric problems itself because it affects neurotransmitters.

I called him back, I told him that, and he said to me, "Eh, I don't really think it was from the disulfiram." He had been under a lot of situational stress at the time. Then he said, "But even if it was, it was worth it! Don't fail to offer it to other people just because of that!" So he admonished me, you know?

We've been keeping in touch with him and he hasn't needed to come back in. I spoke to him in the past week, he's remaining well greater than two years out, 27 months, since stopping the disulfiram.

H: Do you know if he had bartonella and babesia?

Dr L: He had babeiosis. To the best of my knowledge, not bartonellosis, as far as I could tell.

And that's the other incredible thing that these patients who have Lyme and babesiosis... their need for babesiosis treatment seemed to also be eliminated with the course of disulfiram - that's unbelievable. To be able to impact two big difficult infections? to treat with a single agent that's inexpensive and for a finite period of time -

also astounding. I didn't go into it thinking that this had any activity against babesia but it turns out it seems to. Babesiosis is also very very problematic, and even mainstream is acknowledging that our wonderful treatments against babesiosis are not very good. (see the work of Choukri ben Mamoun and others: http://www.jbc.org/content/293/52/19974.abstract)

So contrast a couple months of disulfiram versus open ended treatment with azithromycin and either atovaquone (Mepron) or Malarone. Those are very expensive drugs. The conventional wisdom is that ten days of azithromycin and Mepron, and you're cured. That's obviously false. Even Peter Krause reported on the use of azithromycin and Mepron early on and recommended ten days, he recognized there was persistent parasitemia after that treatment, and it was ignored . Well, what does that mean? Are we supposed to just ignore the persistent parasitemia? Not just persistent parasitemia - people are symptomatic. (https://www.nejm.org/doi/full/10.1056/NEJM199807163390304)

So clearly we need better methods for both diagnosis and treatment for many of these tick-borne illnesses.

H: Yeah, tell me about it.

I did want to ask, do you think the reason the first patient was able to tolerate the 500 milligrams dosage right out of the gate, was that because he had been treating very heavily with other antibiotics for a long time and his bacterial load was probably fairly low to begin with?

Dr L: That's a really good point. He was relatively well compensated (meaning the treatments he was on were keeping him relatively well, as opposed to, say, ‘decompensated’ or deteriorated.) so I'm certain he had a burden of infection, but it's a different situation than taking someone who is not well controlled or hasn't been treated and who has a high burden of infection. He actually tolerated the treatment pretty well except with psychiatric hospitalization. And neither he nor I are certain the disulfiram was related or contributory to that episode. But yes, he seemed to tolerate it pretty well.

H: Do you mind telling us a little bit about the other two patients in your published article or clinical trial? How are they doing? Some of the people in the group are quite curious to hear.

Dr. L: Sure, so after having that experience with case #1, and again, us clinicians who care for the patients are confronted with this all the time and it's very problematic, but we haven't had any options. The mainstream certainly has been so cocksure that their treatments have been perfect, so they haven't even been looking. It's only because of the privately-funded research that any progress has been made at all. There are four groups: The Ying Zhang group at Hopkins, the Kim Lewis group in Northeastern, the Eva Sapi group at University of New Heaven, and the Jayakumar Rajadas group at Stanford. Those four are the only groups that are actually acknowledging the problem of persistent infection with Lyme and trying to see if we can come up with better methods of treatment. The amazing thing is that in a relatively limited period of time they've come up with some really important hits. Not just disulfiram, but there are other agents that have activity.

The 2nd patient, his care was very, very problematic. He was a retired physician. He lived in Pennsylvania on 20 acres and had something like 4 indoor-outdoor dogs. He had been sick before he came to me, had already received a couple of rounds of antibiotics including IV antibiotics. He was really, really sick and had bullet-proof confirmation of central nervous system Lyme. You could not ask for a better documented case. And in addition to many physical symptoms that were quite severe, he had very significant neuropsychiatric symptoms.

He had been under the care of an excellent academic psychiatrist, and it turned out that he required very, very intensive treatment both medically and psychiatrically. We could barely keep his head above water.

When he was under my care we did try different regimens, including oral regimens - but he was a case in which oral therapy was not adequate. He required a long course of IV antibiotic therapy. I was not his treating physician; his local physician was treating him and, of course, I supported that treatment. With maximally supportive treatment he did fairly well where he could enjoy a fairly good quality of life, not perfect, but he could get by. He had one episode that was quite serious with life-threatening sepsis related to his IV catheter and after that the local physicians, understandably, were not interested in continuing IV antibiotics. So, because oral antibiotics were not adequate we used intramuscular ceftriaxone, which is quite a practical method. He was on that for 2-3 years and, as you might imagine, he didn't have a choice unless he wanted to deteriorate into misery. But you can imagine getting intramuscular injections. He administered them himself, again, being a physician. And he required very intensive psychiatric treatment, too.

Besides oral psychopharmacotherapy, because his depression was so dense and so severe, he had required IV ketamine infusions every month or so to keep his depression under control. Which is a pretty extreme thing to have to do.

When I reported to him the unbelievable results we had with case 1, he thought about it – again, he is a physician – and he discussed with his other physicians. He had a very fine local primary care physician and an excellent psychiatrist and an excellent neurologist locally. So he discussed it with them, I discussed it with them, and we realized that while this (disulfiram treatment for Lyme) is based on 1 single patient, not a lot of data, but everybody agreed that it was worth taking a chance. So he was the 2nd patient.

And, by the way, the first 3 patients were all 200+ lbs. The 3rd patient was 220lbs and the first 2 patients were about 200 lbs. So we did the same thing with the 2nd patient, we discussed his care with his other doctors to see what other medications he was on and this patient, unlike the 1st patient, had a very profound impact from the disulfiram - he was fairly bed-bound during the first 6 weeks of his treatment, fairly debilitated by the treatment. And at the end of the 6th week he was going around somewhere and he had a fainting spell – a syncopal episode – hit his head, had a concussion, needed to be hospitalized, and luckily did not sustain any serious injury.

But because of that his neurologist recommended to him that the disulfiram be discontinued, which was completely reasonable at the time. When I heard that he had a concussion I called him a week or so later and he said to me, “I think the treatment worked.” So he’s been followed and doing quite well for greater than a year, and not just “well” but “incredibly well.” Much better than he had ever been with his intensive IV antibiotic therapy. And, also, amazingly, he was able to wean off, with his psychiatrist, most of the intensive psychopharmacotherapy that he had been on. He was able to discontinue the ketamine infusions and he has an excellent quality of life. He was back to, what he thought would be back to baseline - a fairly normal activity level for someone his age as he was in his late 70s. Quite impressive.

He recently re-contacted us because he had sustained another tick attachment, and had asked to be treated for the tick attachment - the ‘mid-level’ in his physician’s office had declined his request. So about 10 days later he developed a small rash and he started getting sick and finally he got 21 days of doxycycline.

Meanwhile, his psychiatrist, who was very comfortable with disulfiram had put him back on disulfiram 500mg a day, even before he came back to see me. The psychiatrist had

previously adjusted his other meds to avert a DDI that we thought had caused his original syncopal episode - this time, as far as I know he has not had any problems with the disulfiram. So when he saw me he was already on that, we reassessed him and the plan was to repeat what had worked before which was for him to be on disulfiram 500mg a day for 6 weeks and then stop and observe. So, again, he was doing extremely well, so we think he got reinfected and that is why he developed symptoms. But he had been doing really well for a year prior to this and, again, this is a guy who had required intensive IV antibiotics just to keep his head above water. So, very dramatic.

The 3rd patient weighed about 220lbs. He was pretty well-functioning even though he had required fairly intensive treatment before the disulfiram. He tried 500mg a day and it just knocked him for a loop, he couldn't handle it and he wasn't able to go about his normal activities. He was the first patient on his own direction who greatly reduced the dose 125mg every other day. He found that he could tolerate that, and then he slowly ramped up the dose over about 2 months to get to the full dose of 500mg. He was on that 2 months and then stopped, enjoying what seemed to be a really great remission for the next 6 months. At the 6 months mark, he was local, so he came in and wanted to be tested which I really didn't want him to do (because he told me he was clinically well). But he insisted, and the cost of his testing was covered by his insurance.

We went ahead and did it, and he ended up having a positive Lyme PCR at a time when he told me that he was feeling well. I was upset by that because I didn't know what to make of it, I was almost disbelieving of it, but then over the next month or two he developed fairly typical symptoms of Lyme. So he just was retreated with a longer course of disulfiram.

I had intended him to be on 750mg a day, figuring maybe that would be better for his weight of 220lbs, but he found that he couldn't handle 750mg per day, so what he did was 750mg per day for 2 days on, and nothing on the 3rd day. Which actually ends up being the exact same dose that he was on when you total it up for the month as 500mg per day, but he was on it longer, he was on it for 3 months. He came off it in July and we've just been in touch with him and he is going to be seeing me later this Fall.

According to my nurse, he is doing extremely well, you know, having done that second course. But the ultimate outcome, we're not sure and also he might have relapsed, that's a possibility, but also you cannot completely exclude the possibility that he was reinfected. He's an active outdoors guy, but he didn't think he had a tick attachment after that 1st round.

So that's where we are with those first 3 patients.

H: In summary it sounds like all 3 are doing fairly well. Either in remission or…

Dr. L: I don't even want to say the word "cure" because I don't know whether people are cured and we don't even have the means to say people are cured. We don't have very good tests to know that, but case 1, 27-months out is doing extremely well. Case 2 was doing extremely well for greater than a year, and then had another tick attachment and we think he got reinfected. Case 3 may have relapsed, regardless of whether he was reinfected, and was retreated. So far, from July until September, he at least states that he's doing extremely well.

And the other thing is that all 3 of these people also had babesiosis, and the babesiosis was also very problematic.

H: What about bartonella? Did they have bartonella?

Dr. L: To the best of my knowledge, none of those 3 had bartonella, as far as I know.

H: So the 3rd one, how long did he stay on the 500mg dose per day during that first round of treatment?

Dr. L: He was on it for 2 months, once he worked up to the full dose of 500mg a day. He was on it altogether for 4 months, the first 2 months was a ramp up and the second 2 months was 500mg a day every day.

H: So in his case you said that the PCR was positive?

Dr. L: The PCR that was obtained in November. So he finished treatment Memorial Day of 2018. He was then seen in follow-up November of 2018 and that's when he asked to have a fairly thorough reassessment. This was when we detected the positive Lyme PCR. I was trying to rationalize what that meant, because I had been going by the notion that a positive PCR implies that there was active infection up until maybe a month or so before, because when you detect DNA you don't know if it's living borrelia or dead debris.

The work of Reinhard Straubinger at Cornell indicated that when you administer heat-killed borrelia to dogs that were not infected it took about 3-4 weeks for the DNA to

be completely cleared by the system. And that's what I've been going by, but maybe the situation is different from someone who has been harboring Lyme for decades. Maybe there is a longer wash-out period from niche reservoirs like the eye, or the brain. Because at the time it was detected he told me he was clinically well. I'm thinking, well maybe my assumptions about how long it takes for borrelia DNA to clear the body are mistaken. But in retrospect it turned out that that the test result did indicate in his case that he was dealing with an active infection, either it was reinfection, or residual that wasn't eliminated by disulfiram.

H: It did indicate that he was dealing with an active infection?

Dr L: Yes. Because he clearly became symptomatic in the subsequent month or two. And that caused us to go ahead and offer him another course of disulfiram. I'd intended it to be at a higher dose for a longer period of time, but it turned out that he couldn't tolerate the higher dose. He ended up at basically the same dose he was on but at that full dose for 3 months instead of 2.

H: So you have at least one case where the patient took a full two month course at the 500mg per day that did have a reaction, relapse in symptoms from the borrelia?

Dr L: Yes, I'm assuming that it was a relapse although it's been pointed out that I can't be 100%. You know he might have been reinfected. He didn't think he was reinfected.

H: But you're pretty confident he was compliant with the 500mg per day dosage for the full two months?

Dr L: I'm pretty sure, but he's a very independent minded guy. Like I said, I intended him to be on 750mg every day but he couldn't tolerate that. 750mg two days in a row, and he took a holiday on the third day: total the dosing and it's the same as if he did 500mg every day. He was on it a full 3 months at that regimen. So we'll see if he has a more enduring remission.

But as he said to me: "Doc, if I had to do disulfiram and repeat it every couple of months, or twice a year or once a year, how much more beneficial is that or acceptable is that than having to go on IV or IV ceftriaxone and gobs of medications"... he was not able to be kept well with the standard dose of atovaquone and mepron. He needed double and triple doses of atovaquone, 3 teaspoons, 2x day, in order to keep his babesiosis under control otherwise he'd have drenching night sweats. And he was

fortunate because of his circumstances that this was covered by his plan. That's $1000 a bottle - bottle lasts a month - at triple dose that's like $3000 a month, that's ridiculous.

H: And he's finding equally as good results with the disulfiram for his babesiosis?

Dr L: Better! Way better.

H: That's really impressive.

Dr L: It is.

H: Do you have any other noteworthy patient stories that you'd like to share?

Dr L: Well here we have this agent that's a tool that we didn't have before. We have this new tool and we're trying to figure out what's the best way to use it, the wisest way to use it. How can you use it to extract the maximum benefit and minimize adverse reactions? Again, the dosage and duration that I used with these first few patients was quite arbitrary, but I'm learning from them and I'm learning from my other patients of course. At this point we have or are utilizing it in a total of about 50 individuals, 30 of whom have completed it, and 20 of whom are in the midst of it.

I will be giving a talk at ILADS in Boston, in late October/early November. And also giving a talk to the same folks at the Mt. Sinai School of Medicine who hosted that first symposium. When my article was first published, I forwarded it to them and told them that if they would like me to speak I'd be happy to. So I'll speaking there on October 19th.

In lieu of that, I've asked my office nurse to try to review all the cases, to try to categorize what the outcomes have been, what kind of adverse effects we've seen, who has seemingly enjoyed an enduring remission, who had a remission then relapsed, who didn't benefit from it, what some of the adverse effects were. We're trying to roughly tabularize that, and again I'm not a guy who does clinical trials, it's not my background and training. I don't even know how to do Excel (which I should learn).

So we're doing it the old-fashioned way, reviewing charts, trying to categorize them. Whatever we have is still going to be on an interim summary. There's 20 patients right now who are still in process.

H: So out of the 30 who have completed therapy, how many would you say are in remission?

Dr L: I don't exactly have a number, there's a sizeable portion who seem to be enjoying an enduring remission. I don't even know the numbers, but it's enough for us to be very impressed because we haven't seen this with other treatments. And again, I want to emphasize, it's not a panacea, it's not a silver-bullet, I don't think everybody is going to enjoy that kind of outcome. Most of the patients who've been on it report feeling that being on it was beneficial - net beneficial to their status. There are some exceptions of people who did not find it beneficial.

H: So out of the patients who are not responding to treatment, do you have any idea why they might be failing this treatment?

Dr L: The patients who seem to respond well are the patients where there is a track record of them actually being antimicrobial-responsive. In other words, first of all, I have a pretty good handle on what they have because I have the documentation clinically, labs of their diagnoses. And they've demonstrated that they respond to treatment but relapse.

One of the patients who didn't respond, I was pretty confident he had Lyme given his history and some reasonable laboratory support. Very nice young man, we really tried everything in our bag of tricks for antimicrobial therapy, but he just never seemed to have a convincing response. And we were hopeful that maybe disulfiram would be helpful where the other (treatments) were not.

He did the disulfiram course, and he was quite compliant. Unfortunately... he was honest like we encourage our patients to be, and he really didn't see any benefit. At that point I really encouraged him to get additional consultations to figure out the mechanisms that were interfering with his ability to have a normal life. Autonomic dysfunction, maybe he needed to have that addressed. Maybe he needed some other kinds of treatments. So I've asked my nurse to get some late follow-up on him.

There was another patient with positive Lyme PCR in the spinal fluid, and had quite a bad neuropathy from Lyme, even before anything to do with the disulfiram. He got an initial course of treatment which he had a very good response from, but he had a little bit of emotional instability so it was stopped - kind of prematurely. He enjoyed a couple of weeks of incredible well-being that he hadn't experienced before, and because of that emotional instability we made sure he'd be consulting with a psychiatrist going forward.

We then retreated with a longer course and a bit of a higher dose than he was on previously. With that, he had a pretty bad neuropathy from the disulfiram, superimposed on top of his Lyme neuropathy.

Unfortunately he was not able to report feeling any net benefit and still had to deal with the neuropathy from the disulfiram which is somewhat better, but still not too pleasant. We didn't really embark on too much in the way of standard antibiotic therapy because he had one shorter course of oral antibiotics, and then we were discussing whether to do IV ceftriaxone, or intramuscular ceftriaxone. And that was at a time we were starting to see such impressive results with the disulfiram. We talked about it very carefully, with him, his spouse, so we decided to do the disulfiram. Unfortunately, our staff just spoke to him recently to try to determine whether he had received any benefit at all from going the disulfiram. He felt it was not net beneficial.

H: Off the top of your head, how many patients exist that had literally zero benefit from the treatment? Out of the 50 you've tried it on so far?

Dr L: It's a fairly small number. Out of the 50, maybe three, four, five didn't seem to derive any benefit whatsoever. Most of the patients have recorded benefit, and some of them enduring benefit.

H: And out of those 5 who didn't report benefit, did they ever go on to benefit from other antibiotics by any chance?

Dr L: Well that person who I described with the neuropathy, he was interested in exploring hyperbaric therapy. Which I had no objection to, I encouraged him to wait a bit so we could see what the disulfiram did or didn't do. He did wait. And then he heard about hyperbaric oxygen and had found a competent practitioner who did that. Did that for a little while, then he learned of the work of another practitioner out on the west coast who had a bit of a different approach. I think he's pursuing that right now with the use of Alinia - which is not something in the scope of what I've used. He's finding Alinia is having an impact, but I'm not sure of the outcome. Hyperbaric oxygen, he didn't do it that long so I'm not sure whether it conferred any benefit.

I think the patients have to find the right help. If the right help is me, that's fine, or what I have to offer, and if it's not, if they can't get better with what I have to offer they should definitely try to find whatever venue they can to get help and get better.

H: I've actually done hyperbaric oxygen, I did do it while I was on antibiotics as a supplement. I think I got some improvement, felt a little bit more stable. Felt I could consider it in remission, but the second I got off it within a few months everything was coming back. I didn't feel it was a very effective use of my money personally. But I have heard of Alinia and there are some people that seem to be saying good things about their experience with that. But you haven't used it personally?

Dr L: No, at the patient's request I did speak to the practitioner who's treating him. He maintains the reason he uses Alinia, it's kind of paradoxical, it's not for its anti-parasitic effects according to that doctor, he believes the Alinia is very effective in degrading biofilms. And that's the rationale for it, that was new to me. But I don't have any experience with Alinia, but I know that colleagues of mine have been using it and patients have been reporting that it's been used. I don't know too much about it. If someone who's using it could report on it in a published fashion so people could evaluate it, that would be helpful.

H: I have a few more things I want to run by you about the current patients. Out of the patients you've treated how many have had to repeat the protocol? One or two? They did the 2 full months and they had to repeat it?

Dr L: It's a limited number. One of the patients I treated, a very nice woman who lives in Dutchess County, had definite Lyme, good evidence of bartonellosis. And we really thought she had babesiois given her symptoms and response to Malarone. I think she was one of the first disulfiram patients I knew had bartonella, and I let her know I didn't have any data on what disulfiram did or didn't do for bartonella because, far as I know, the first three patients did not have bartonellosis.

She perceived bartonella was an important part of her syndrome, and she was being treated with azithromycin and rifampin. She was reluctant to go off that treatment while she was treating with disulfiram. In her case I allowed her to stay on that combination, that is to say - azithromycin, rifampin, and disulfiram - throughout the course of her treatment.

She was monitored carefully, fortunately, she tolerated it very well, there were no derangements on her surveillance labs. She definitely perceived benefit, and her symptoms of Lyme and babesiosis - again we didn't prove that she had babesiosis - but clinically I felt confident she had it. She definitely benefited. I believe she feels that Lyme and babesiosis are presently not an issue. But bartonella remains an issue, I'm trying to think whether she tried going off her zithro/rifampin… by the way I encouraged

her to consult a colleague of mine who does a lot more work with bartonellosis than I do. So she's done that, she's being seen at that practice as well as by me.

So that's one case you would think if this were effective for bartonella, that she would not require ongoing treatment for bartonellosis - which she does. It's not a lot of data, it's one patient, but that's why I have expressed that I'm somewhat doubtful it's an effective therapy for bartonellosis. But I have some colleagues who are thinking that it may have activity against bartonella for some patients, but the jury is out on that.

H: It's pretty safe to say, even if disulfiram has no effect on bartonella, we should be extremely excited. The fact it works on borrelia alone is an enormous breakthrough. But having activity against babesia is a huge plus. To expect to kill all three, it's a little bit too high of expectations.

Dr L: Well I joked and said to one of my colleagues that hey, if it knocked out borrelia, babesia, and bartonella we would have really hit the Trifecta.

H: Do you have a preferred method to treat bartonella that you typically see the best results with?

Dr L: Again, I don't consider myself an expert on bartonella at all. A lot of other people have more depth with it. I use either a tetracycline agent or an azolide, clarithromycin, azithromycin with rifampin. That's what I usually do. And I know there are other regimens out there, some people incorporate bactrim. Dr Robert Mozayeni has a lot of expertise with bartonella, often uses rifabutin. That's a drug I haven't used.

I think the same thing with bartonella, there is a lot we don't know. There is definitely room for improvement in methods of treatment for that. And that should be a big focus of research too.

H: Have you heard anything about these two new compounds patients are talking a lot about: methylene blue, and this is more on the fringe, and not standardly accepted, some people are talking about gallium nitrate which I believe is a heavy-metal given to horses for some reason. But apparently has some benefit on bartonella. Have you heard anything on those two?

Dr L: I've heard people on your Facebook group mention that. But I don't actually know anything about it.

H: Ok. The methylene blue in vitro study (on stationary phase bartonella) seems to have been done by Dr Zhang at Johns Hopkins, he was the one that did the study on compounds that seemed to have activity on bartonella. There wasn't a breakthrough compound like there was with Lyme. Nothing was 100% effective unfortunately, high efficacy but no cure in sight at the moment for bartonella, chronic bartonella that is. It seems bartonella might even be more problematic than borrelia is for some patients. (https://www.ncbi.nlm.nih.gov/pubmed/31035691)

H: What is your current approach with disulfiram? Your dose, duration, for new patients? Do you have a standard protocol you follow? That you could give a quick summary of?

Dr L: This a new agent, a new tool. I'm figuring out how to use it, I told you about the first three patients where I kind of just picked a dose, somewhat arbitrary duration. I'd been so accustomed to prescribing long-term antibiotics, like 3 months at a clip, so that's why I allowed that first patient to be on the disulfiram for about 3 months.

It depends what your objective is. One objective, obviously, is to try to induce a remission if you can. That's one way to design the treatment. The other is forgetting about trying to secure remission, is there some dosage regimen of treatment that is a treatment without trying to secure a remission, or can you combine the two approaches. And also because of that, case #3, who found it intolerable at 500mg a day, on his own advisement cut the dose, and did it every other day.

My current general approach for most everybody is to start with a low dose. Typically half of a 250mg tablet. I've been starting out with every third day. 125mg every third day in some people who are very sensitive, or if there are special reasons we that we want to be cautious, for example they have a baseline neuropathy. We want to be careful not to exacerbate things, and again some of the patients who are on another chat group, Kristina Petterson Bauer, some of the patients have reported starting on a quarter of the treatment, 62.5mg. I think you can't be too careful.

Some of the patients' conditions have been very precarious to begin with, we want to be careful not to push them over the edge. We started with these low doses and were actually amazed at how potent even these tiny doses are in securing clinical benefit in some of these patients. And this is even in people who are large people! One of the patients weighed 260lbs, had a very difficult clinical picture, and they were on 125mg every fourth day only. Within a couple of weeks he was doing incredibly better. Unbelievably better!

Another patient of mine was very very sick. Those kinds of doses… first of all using those low doses you're much less likely to provoke a severe Jarisch Herxheimer type of situation (https://en.wikipedia.org/wiki/Jarisch–Herxheimer_reaction). So it makes it more tolerable. There is some Herxheimer, first couple days, week or two, but after that, the patients were enjoying really improved status, functioning, life. It's nice to have a plan, but I think each clinician and patient really need to individualize the treatment approach. I don't think it should be some rigid formula, and I also think it's important that clinician and the patient be in regular communication with one another, or be able to be in regular communication because the plan may need to be changed.

It's good to have a plan, but you might have to modify it depending on circumstances, of whether there's either the patient experiencing a lot of benefit then you might want to stretch out a certain dose for a longer period of time. Or they are having toxicity, then you might have to decide to change the regimen, or even suspend treatment if it's necessary.

H: So you've had patients that have seen enormous benefit even from the 125mg every three days?

Dr L: That's right. Every four days even.

This is potent. This is a potent agent. Mind you, I am not using this drug as a first line treatment for people who've never been treated before. Usually I've been using it in people whose care is problematic and who've already been around the block several times, and gone through long-standard treatments.

Then you might ask yourself, why not use this right up front. But I'm generally not doing that right now.

H: Is that out of being conservative? following the standard of care?

Dr L: Yes, exactly, being conservative. And also as you know you don't know what people have when they first come to you. As I've said before, I made a comment on your group, or other groups, I have no idea what disulfiram does or doesn't do for ehrlichia or anaplasma. When somebody comes with a new case of Lyme and you don't really know what they have, would I use disulfiram as a first line agent? to treat Lyme, babesiosis, potentially ehrlichia, anaplasma, god knows what else? I don't think so.

H: So what would be your go to antibiotics in the standard acute care of Lyme?

Dr L: Well, for a new case, a lot of us, even though we know that doxycycline has problems, or minocycline has problems, it kills the spirochaetal form, but it may shift things into the cystic phase. I would still use that when you're confronted with a new case of Lyme, maybe someone has erythema migrans for the first time, or an acute case of Lyme. I don't think I'd be brave enough to use disulfiram in that setting, even though it theoretically might be superior for Lyme and babesiosis, but I don't know what it would do for the other tick-borne illnesses. I would probably use what would be considered the more standard treatment.

H: Doxycycline?

Dr L: Yes a lot of people use doxy, and I used to use amoxicillin a lot. But it doesn't cover babesia, doesn't cover ehrlichia, doesn't cover anaplasma. So although I often would use amoxicillin in patients for Lyme disease, I abandoned using it as first line agent by itself for a new case of Lyme.

H: I don't know if you saw Kim Lewis apparently did some studies that showed vancomycin was the most effective antibiotic, that was underneath disulfiram, but broad-spectrum the most effective antibiotic against borrelia. Did you see that study?

Dr L: Well I was aware of the work of Alan Barbour and one of his collaborators that vancomycin has good activity against borrelia. I will sometimes use vancomycin, but again, you're dealing with IV agents. You need a central line if you use vancomycin - that can be problematic.

H: The best oral is probably doxycycline as your first line of treatment, and then you could maybe consider bactrim or cefuroxime. What else? Those are the main ones I can think of…

Dr L: I don't use bactrim for erythema migrans. I don't use bactrim very much at all. But I know people use it for bartonella. But you know, the usual first line agents, the thing is cefuroxime has the same problem as amoxicillin, it may treat Lyme but it doesn't treat the coinfections. So with a new case, again, many people would use doxy. I published the second article in the world literature describing the use of minocycline for Lyme disease. That, like doxy, would cover ehrlichia and anaplasma, but does not cover babesiosis.

For an early case of Lyme disease, or even a tick bite, often I will offer people minocycline or doxycycline, then if they want to, realizing there is no published literature on this at all, I would often offer them the option of being treated with Malarone as well to try to abort babesia infections. Again, there's been no published literature on using Malarone as a prophylactic type of treatment, but it seems to me if you're going to use doxycycline to treat early Lyme why wouldn't you cover - and that covers most of the treatable tick-borne diseases - why wouldn't you also offer them treatment with something that you would hope might avert establishment of babesiosis. Again, I'm not aware of any articles in the literature that even broach that question, which is kind of silly. You'd think by this time people would be questioning can you treat preventively, either for erythema migrans, or just a tick bite, to avoid people becoming infected with babesiosis. I'm the only clinician I know of that would offer malarone for tick bite or early erythema migrans before the disease diagnosed or established. Why wait till it gets diagnosed and established when babesiosis can be every bit as problematic Lyme in terms of eradicating it with our current, not very good treatments (again, see the work of Chourki ben Mamoun and others).

H: So both doxy and minocycline are not able to address babesiosis at all?

Dr L: As far as I know they are not effective against babesiosis.

H: You think those are the best two first lines of treatment, even though they might not be the strongest against borrelia, but because they have the broadest spectrum of coverage, minus babesia, they're probably the best option?

Dr L: That's what I offer for tick bite, if people want treatment for tick bite, minocycline and Malarone for a month or so, or for an early Lyme with erythema migrans we usually do that initially. Cefuroxime, like amoxicillin, it only treats Lyme, and those are not particularly effective for ehrlichia, anaplasma, babesia, or as far as I know bartonella either.

H: Are minocycline and doxycycline basically the same drug to you, in terms of their effects or efficacy?

Dr L: Yeah, they're very similar. To me minocycline has certain advantages, easier on the stomach, usually not sun-sensitizing, well-absorbed, gets everywhere, including the nervous system at any dose. I often prefer that. Some of my colleagues prefer plain old tetracycline, which I'll occasionally use in patients, some think it is superior to doxycycline or minocycline - plain old garden-variety tetracycline.

H: How do you typically ramp up from the initial 125mg disulfiram dosing every three days? Do you go 125mg every two days? Or just eventually from 125mg every 3 days to 250mg every 3 days?

Dr L: I've been doing it gradually with the idea of making the treatment as tolerable as possible for the patients. And that slow ramp-up makes it tolerable, but then I also wonder what's the best approach? I actually don't know what the best approach is. If you do a very gradual ramp-up over months, say 125mg every third day, then 125mg every other day, then 125mg every day. Then you go to the next level, 125, 125, 250, then 125, 250, then 250 every day… by the way I'm usually giving people 10-14 days at any given dose to let the drug equilibrate before ratcheting it up, depending on how slowly you do it.

You can drag it out, the question is how necessary is it to be that gradual, or do it more quickly. You're also exposing the patient to the disulfiram over a longer period of time, and is that going to result in more toxicity than if you sucked it up and started at a higher dose right at the get go and had gotten it over within 6 weeks? I don't know the answer to that, what is the best approach, I'm not sure.

With antibiotics typically I'll gradually ramp it up, so it's a similar approach I'm adopting with disulfiram, but are you going to end up with more toxicity because the patient is on the drug for a longer time, taking longer to get up to the full dose. Anyway, my general approach for most people would be to start slowly, ramp it up over a period of time which would be a couple of months to get to the target dose. And I'm trying to figure out what that target dose ought to be. I'm figuring it should be like most drugs, most drugs are based on dosage per weight. And then once you get that target dose, have the patient on it for somewhere between 6-12 weeks. I'm not having anybody on a quote "target" dose longer than 12 weeks so far. And then suspend treatment and observe for a period of time and see how they do, realizing it takes at least two weeks for the drug to wash-out. Then you really need a period of equilibration of probably a couple months to know where you are, what you have or haven't achieved.

I usually have an assessment with the patient, because some people are eager to ramp-up sooner rather than later. If one wants to be gradual, what I've been doing is 125mg every third day, then 125mg every other day, then 125mg every day, and that can stretch it a number of weeks of course. Then going 125 125 250, then for a while, 125mg "_____." Is that too gradual? again I don't claim to have this all worked out. Also, I'm proceding in a consensual approach with the patient, letting them know what my

experience has been, letting them know what I don't know. We're figuring this out as we go along. Also I'm not only learning from my own patients, but learning from the experience of the patients who are in your group and in some of the other groups. We're all learning together, I'm trying to provide my insight but I'm also very much learning from the patients. Many of the patients are posting excellent articles from the literature, some of which I wasn't even aware of. It's definitely a learning curve.

H: How often do you have to pause the treatment in the middle of it, and what would be the symptoms or the reasons that you typically pause treatment?

Dr L: I wouldn't say so much to pause so much as to suspend treatment if we think the patient is experiencing significant adverse effects; emotional instability, or they're clearly developing a neuropathy from the treatment that's distinguishable from their baseline neuropathy from Lyme. It gets to be a judgment call, where you have to weigh risk vs benefit. If you think that the course of disulfiram may be able to induce remission, is it worth it to risk of sustaining neuropathy from the disulfiram? if you think at the end of the day you can induce remission, realizing that in many instances, but I can't even say every instance, the disulfiram induced neuropathy improves or resolves once you discontinue the agent.

It's a judgment call, in that situation one would like to engage in what one calls shared decision making with the patient. Realizing that there remains a degree of uncertainty, it's not all cut and dried.

H: So you typically suspend permanently, you don't typically suspend for a few days and resume...

Dr L: You might. If it seems it's not really an adverse reaction but the disulfiram is provoking too intense of a Herxheimer for example, certainly then yes you might want to suspend or slowly "____" and so that's a little bit different than having a clearly toxic or adverse reaction.

H: Have you seen anything where, just so patients are aware in the group, any experiences or reactions that you would think are justification to immediately stop? Is there anything you might want to warn people about if it happens to them?

Dr L: Yes. I had two patients who had modest, but enough of a liver dysfunction situation, where their liver function tests were high enough, and not only that but on exam one of the patients, when you exam the patient's abdomen and they take a deep

breath with your hands folded over their ribs, and that caused discomfort. What they call a positive Murphy sign, it's a term that people use often when you're evaluating a patient for gallbladder symptoms. If they take a deep breath and you're fingers are over the ribs, and when they take a deep breathe it induces pain, so that was one particular patient where not only was there these liver enzymes which were high, they were elevated enough they got my concern, but on top of that the person has a positive Murphy sign… they happened to be near the end of their course of disulfiram treatment, they'd already exceeded the minimum recommended duration at full dose, so we were at a point where we were deciding, maybe they were at 8 weeks, we trying to decide whether we would do 10 weeks, 12 weeks. Well that was the decider, it was time to stop. Those liver function tests resolved. So that's one example.

And I am following liver function tests very carefully, especially early on. Luckily in our cohort of patients we've not seen any serious liver injury, but from the literature we can see that there are some rare cases of very severe liver injury. And you don't want to miss that. And you know that it takes at least two weeks for the drug to get out of the system, so even if you stop it you can't guarantee there won't be on-going injury for a while.

H: How frequently do you test liver enzymes once someone starts the protocol?

Dr L: I give them a standing order for up to weekly general labs, which includes liver function tests. So I've been having patients at end of week 1, 2, 4 and every two weeks after. Maybe that's overkill, again, considering this is novel use of this agent, I would rather be safe than sorry. And you can't be too careful. Maybe that's excessive, every two weeks, after the first month. And the patients are not always as compliant as I would like, and "knock wood" in these first 50 patients we have not seen anything dangerous, life threatening. No irreversible injury, but we're very mindful of that potential and that's why we follow these patients very carefully.

We had these dramatically favorable results, and I prepared this manuscript, and I felt obliged to scour the literature and include a manuscript as a warning to patients and those clinicians who might use disulfiram to be very aware of the potential adverse effects, some of which can be quite serious. So that hopefully they can see it coming and discontinue treatment before some irreversible injury occurs.

Overall, with all of this monitoring that I've done in these patients, I'm impressed how benign this agent is overall. It's been very well-tolerated by most people and we have

hardly seen any derangements on these labs with rare exceptions. But obviously it's important to do this monitoring.

H: The main three side effects that people are concerned about are liver damage, which we just discussed. You've only had two patients who had elevated liver enzymes and that went away and they had no lasting effects. Liver damage hasn't been an issue for you. What about the neuropathy side effect, has it reversed?

Dr L: It's common enough it's gotten my attention. Still not that many, maybe 10 or 12 patients. But it's enough that it made me want to research what the mechanism is, number one, and also made me more mindful of being conservative in the dosage that I used. And trying to adjust the doses to weight in an effort to minimize the neuropathy and also to be mindful that duration of low dosage may be important. That's why I'm questioning myself, are you better off ramping it up over many months and getting to the target dose, so then the whole duration of treatment is longer? Or are you better off hitting people with the full dose, realizing they're going to have significant Herxheimers, and limit their activities, have support, and get it over with and not drag it out. What's the better strategy? At this point I'm not sure.

H: I can say firsthand when I first treated my Lyme with doxycycline I had severe neuropathy develop. So how can you be sure that out of those 10 that they're all suffering neuropathy from the drug's side effect rather than the Herxheimer itself?

Dr L: You mentioned doxy, did you mean doxy, or did you mean disulfiram or doxy?

H: I meant doxycycline. When I was first diagnosed in 2016 that was my first treatment drug and I had extremely severe neuropathy develop throughout the body. I even had my teeth go numb. I'm just wondering if that had happened to me on disulfiram, I could easily have said "oh man this has ruined my nerves." That took months to recover from but it eventually all reversed.

Dr L: It's a good question. Did the disulfiram provoke neuropathic symptoms because it was a Herxheimer of the borrelia in the peripheral nervous system that the drug provoked, versus strictly a disulfiram induced neuropathy? It's a good question.

I told you about that one patient who had a well established neuropathy from Lyme… I guess that's a good question, is the neuropathy that it provoked disulfiram-neuropathy, or was it just a provocation of his preexisting Lyme neuropathy? Good question that you raise.

H: My neuropathy was in the standard areas: legs, throughout the body, so I could easily imagine thinking this is a side effect of disulfiram. And I just wonder, 10 out of 50, seems fairly high, 20%. And if there were 20% of people developing neuropathy with the drug, you would think there would be more evidence in the literature saying, hey, this is an extremely common side effect. Which there doesn't appear to be anything saying that from my understanding, is there?

Dr L: There's quite a few articles on neuropathy induced by disulfiram in alcoholic patients, there's a sizeable literature.

H: But do you think the frequency is anywhere near 20%. That seems very high to me.

Dr L: I don't know the answer. But again, because I've been seeing that, and it seemed to resolve when the disulfiram was discontinued in most patients, I'm assuming in many cases it really is disulfiram related and not a type of a herx effect of the nervous system. People may have a subclinical lyme-related neuropathy that was then provoked by the disulfiram. This really requires careful study by people who have expertise in evaluation of peripheral neuropathy.

H: But is the understanding of the mechanism of action that somehow the copper is being chelated out of the body into the nerves, potentially, or into the blood? Potentially damaging the nerves temporarily?

Dr L: There were a number of articles posted in your group this morning, by one of the patients that raise a lot potential different mechanisms. But after seeing that, I did some research and came across a series of articles out of Vanderbilt. They were taking the position that the peripheral neuropathy of disulfiram was due to one of its breakdown products, something called DEDC, diethyldithiocarbamate. It
binds with copper and that combination with DEDC-copper migrates, because it's lipid soluble, migrates into the nerve bringing with it the copper. They asserted that it was the copper *per se* that was damaging the myelin in the peripheral nerves. And also that DEDC-copper also migrates to the central nervous system, they were stating it was the copper damaging the myelin and that when you discontinue the disulfiram that eventually it leached back out of the nerves and enabled the nerves to recover.

That series of articles also pointed out that the washout from the CNS of the DEDC-copper was much more delayed. And you have to wonder, some of the toxicity that people experience, and even the neuro-psychiatric symptoms, is it related to the

effects of disulfiram on the neurotransmitters per se, or does the DEDC-copper itself produce some type of nerve toxicity that's separate and apart from neurotransmitter related neurotoxicity? Good questions that I don't know the answers.

There may also be other mechanisms of peripheral neuropathy besides the one that the Vanderbilt group identified.

H: But it would probably be safe to say that one should not be supplementing with copper unless medically advised while taking this drug?

Dr L: I would imagine. Patients are raising all kinds of questions intended to minimize the toxicity, but I don't know if that is advisable. Whether that be a good or a bad thing?

H: The psychosis is the other major side effect that people have been concerned about. From your understanding psychosis is not necessarily caused by the copper but how it affects dopamine in the brain.

Dr L: Right. The main argument has been that disulfiram inhibits dopamine beta-hydroxylase, and again one of my colleagues who was hysterical about how dangerous disulfiram is and how everyone would end up in the loony bin had tried to convince me of that. But in the literature between 1996 and 2016 he came up with a total of 8 reports in the literature of disulfiram-induced psychosis. Not that every case gets reported, but that ended up sort of countering his own argument, because that's not a lot of cases. But yes, certainly it's within the realm of what can happen with disulfiram.

In our 50 or so patients, we had 1 patient who developed a hypomanic state of enough concern to that patient's mental health practitioner that they contacted me. The patient had already been on treatment for a while, and we agreed that that was a definite indication to discontinue it. Things did clear up. A small number of patients are experiencing what I'm describing as a poorly characterized state of emotional distress; not psychosis, not depression, there is an element of anxiety. Again, that's a limited number, but I'm beginning to perceive a sort of a syndrome related to disulfiram use. It sort of mandates that you discontinue the treatment. It was not psychosis, but it was uncharacteristic for these patients, a state of emotional distress that I'm pretty convinced is related to the disulfiram and would be a reason to discontinue it.

H: Permanently. Or consider a lower dose?

Dr L: Certainly for that go around of treatment. Because it can take a while for that to clear from the system. It might be even more than two weeks to clear from the CNS. One of the patients where it happened, that person took a break and resumed it, and it didn't go well on the resumption. We both concluded that they needed to discontinue it and take a good long break before considering resuming disulfiram.

H: Do you think there is any merit if someone is already predisposed to psychosis, and this is being caused by the fact that disulfiram is blocking the breakdown of dopamine, to potentially take a dopamine inhibitor to counteract the buildup of dopamine that might be caused by this drug?

Dr L: Put it this way, I think it's overkill to have every patient going on disulfiram to have a psychiatric evaluation. On the other hand, if the person is already dealing with psychiatric issues they're probably already working with a mental health practitioner if they're having those issues. But it might be in individual cases prudent to have the patient consult with a psychiatrist in advance of starting disulfiram.

Another thing I wanted to mention, because this is a novel use, even though it's an FDA approved drug, before I ever prescribe disulfiram, I have a boilerplate letter which I modified for each patient. I ask the patient to provide me with the full contact information of all the important clinicians, physicians, other practitioners that are involved with their care. I send out a letter to those practitioners in advance of prescribing so that they are aware of what we're doing, why we're doing it. And also so that they're informed so they can be vigilant in case there is anything adverse that's happening. It's probably not mandatory to do that, but probably a good thing to do given this is novel use of this agent. Also, if the patient does have an adverse reaction of one kind or another it's not really fair to the primary care physician to embark on this and have a problem, and inform them after the fact, instead of informing them in advance. That's what I do, even though it is time-consuming and a bit more effort, it's good procedure to follow good practice of medicine to inform the other practitioners involved in the case.

H: That makes a lot of sense. Just to be clear, is it the dopamine breakdown that's being blocked by disulfiram?

Dr L: I'm not a psychopharmacologist. One of my colleagues, Dr Jane Marke, she's in Manhattan, very bright, very involved in the Lyme endeavor. She and I are in another group, Dr Robert Bransfield's group, MMI. Microbes and Mental Illness. I know she's posted there with her thoughts on different mechanisms of action. Again I'm not a psychopharmacologist, outside of my skill set.

H: When I first did my first experimentation with disulfiram I started very early on when there wasn't much information, when there wasn't much information on the dosing. I started pretty high, 250mg daily. And I didn't realize the topical alcohol containing products could be an issue, so I was still using a few of those. I might have even used an alcohol containing tincture once. I was bedridden, couldn't do anything, low motivation, low energy, I thought if anything my dopamine seemed to be down, not up. Because high dopamine is something you get from cocaine or methamphetamine, a lot of energy, not an insufficiency of energy. I definitely went in the other direction, but that may have been a side effect of the acetaldehyde build-up.

Dr L: Sounds like you might have been having D.E.R., disulfiram ethanol reaction. That's another thing, I don't know what to say about supplements, herbs, what not. But a lot of the herbs are in alcohol tinctures, those have to be eliminated.

H: Right. I describe myself feeling like I was drunk, partially. I'd get up, stumble a bit, not solid on my feet. I definitely think it was probably alcohol related…

How extreme do you recommend patients go as far as avoiding alcohol? Anything topical as well as anything oral with alcohol you suggest avoiding?

Dr L: Obviously any ingested alcohol for sure. Some of my patients may be very sensitive, even getting skin swab for blood draw with isopropyl alcohol, they reported having a mild D.E.R. Some surprising things have come up that you wouldn't have expected, or even been aware of. One of my patients apparently experienced a disulfiram ethanol reaction after eating a slice of pecan pie. Which was surprising, but then it turns out pecan pie has molasses in it, and at room temperature molasses can ferment. Things that you wouldn't expect.

H: What's your take on some of the acetaldehyde containing foods?

Dr L: I think people are trying to avoid fermented foods. I guess vinegar has some alcohol in it. People are pointing out a lot of condiments, mustards, can have some alcohol in it. It's a learning curve. One of my patients went out to a pub, but not to drink, had shepherd's pie, and had a pretty significant disulfiram ethanol reaction and told me in shepherd's pie they use worcestershire sauce. I gather that has alcohol products in it. You do what you can to avoid anything with alcohol.

H: So patients are aware in the group, what are the typical signs of the disulfiram ethanol reaction that they should be aware of?

Dr L: They feel horrible fairly quickly; nausea, vomiting, headache. Severe DER can be life-threatening. Take a sizeable amount of alcohol when you're on disulfiram, it can drop your blood pressure. There are reports of people getting myocardial infarctions because the blood pressure is so low. It's good to know how that presents, there's a whole emergency thing you're supposed to do if you have that, but the main thing is to avoid in the first place. If it's bad, go to the emergency room.

H: If they do find themselves in a situation where they accidentally ingested something containing alcohol or acetaldehyde, you suggest if it's getting bad go to the ER? Is there anything they can do to offset it if it's a mild situation?

Dr L: I'm not sure, obviously you go to the ER if the situation is alarming. I'm sure if you go to the package insert there's a recommendation of things you can do if you experience it. I've not been faced with something that severe, but the main thing to do is avoid it in the first place obviously, and suspend the disulfiram if you're going through it.

H: Don't you find it interesting that after something like seven decades of use they didn't realize this drug had any effect on borrelia at all? After how many tens of thousands of people have used it around the world, of which I'm assuming some had Lyme disease. And probably had to stop the treatment because they probably had such bad Herxheimer reactions (in some cases, I'm assuming).

Dr L: That raises an interesting question, could somebody do a retrospective analysis of people being treated with alcoholism who had Lyme disease. One of my colleagues told me that one of his patients who was using disulfiram for their alcoholism was having such an incredibly difficult time handling the disulfiram. It turned out, the psychiatrist figured out the patient had undiagnosed Lyme disease along with their alcoholism.

So that would be an interesting thing to look at.

H: I have to assume that the patients who unknowingly had Lyme, untreated, undiagnosed, probably failed to stay on this treatment because they reacted poorly to the drug, and said hey, this is just not for me. I'm assuming that's probably what happened with many of them. And I'm assuming there's a handful of people who made it through, who had previously been treated for Lyme but hadn't cured it, and maybe ended up curing it and didn't even realized they had cured it. It just seems remarkable

that no one would even notice anything, and never commented about their reaction to the drug, with Lyme disease. It's probably not that common that you're on the drug for alcoholism and that you have Lyme disease and know it at the same time.

Dr L: My understanding is that people being treated with disulfiram for alcoholism usually handle the drug pretty well. Unless they drink. As a matter of fact, I have a family I'm caring for, all the members have Lyme. One of the family members had a problem with alcohol and was treated with disulfiram on a number of occasions for the alcoholism. Of the three family members, that family member is doing best of all. This is before anybody knew anything about disulfiram and Lyme. It's interesting, a little local anecdote.

H: What is your standard, do you have a mg per kg dose that is your target calculation for individuals?

Dr L: It's very rough. But I'm figuring why would you give someone who is 100lbs the same dose as someone who is 200lbs? It turns out 500mg a day for a 200lbs person seems to be appropriate. For a 100lbs person I'm thinking 250mg should be the maximum dose. In between, maybe 140-50lbs person, 375mg. It ranges, but because of what I've seen with the peripheral neuropathy, there was a time I'd give people 250mg, 500mg. I had one patient who is 140lbs, where giving them that leeway to go to 500mg… as you know patients are very zealous of getting rid of the infection, they are happy to explore the higher dosages. I'm realizing, whoops, they're more likely to get toxicity with those doses. That's made me rein in the doses a bit.

H: Is there any case where exceeding 500mgs is recommended? Probably not?

Dr L: One of my patients weighed 230lbs, I think we did 500mg or we might done 750mg a day for that person. They did well, and then relapsed, I think we did either 750mg, but we might even have done 1gr. That's the highest dose I ever used. They were doing well, but then overnight they developed severe neuropathy. It wasn't like it came on gradually, it came on abruptly. Of course they discontinued the treatment, and then neuropathy was pretty problematic, we needed to prescribe gabapentin. The neuropathy was bad, that's been resolving but otherwise they were doing great in terms of their symptoms. But the neuropathy was very alarming, it didn't gradually come on, they were handling the dose and then it came on fairly abruptly. We didn't see it coming, but clearly when that happened they very shortly discontinued the dose. But they've been doing very well otherwise, other than that.

H: Do you have a way in these types of cases to differentiate the side effects from the drug from the Herxheimer effects?

Dr L: Again, this in a patient who did not have any significant neuropathic symptoms from Lyme, it seemed to be induced from the disulfiram.

H: We were wondering are there any symptoms that you can describe that that patient experienced in regards to the severe, abrupt neuropathy, so patients are aware of what to look out for.

Dr L: It was a severe burning type of discomfort, and this is a person who is not a wimp. It was quite alarming.

H: And does that overlap with the other type descriptions of disulfiram induced neuropathy that you've heard from other patients? Burning, does that seem to be the common one?

Dr L: That's probably the most distressing, because it's painful. That is improving as the patient stopped the drug "_____," but it is improving. Aside from that, she is doing very well and we are hoping to see if she is able to enjoy an enduring remission.

H: Do you ever use herbals, herbal remedies with your Lyme patients? As a supplement?

Dr L: I'm not trained in herbal approaches, I have nothing against them, in fact I admire the work of Stephen Buhner who is very knowledgeable. He's a master herbalist, and he really knows Lyme. I was influenced by the work of Dr Richard Brown, the book that he published, related to ginseng (The Rodiola Revolutions by Richard Borwn and Patricia Gerbarg).

So occasionally, but I'm not very well versed with herbals so I leave that to other people. And for people who want to pursue that I encourage them to look for somebody with deeper experience in herbals - some of the naturopaths are well trained in that. I often mention Stephen Buhner's books, starting with Healing Lyme: Herbal Approaches.

H: This is a question about the safety and side effects. What markers outside of the liver enzymes do you typically test for and how frequently do you test for them?

Dr L: I have a standard set of quote “surveillance labs,” not just for disulfiram, but for other treatments. And that usually consists of blood count, liver function tests which consists of AST, ALT, GGT. That’s important, not everyone gets the GGT. Total bilirubin, BUN (Blood Urea Nitrogen), creatinine, CPK, and a urinalysis. That’s usually what I consider my quote “minimal” surveillance labs. Sometimes I’ll give patients a standing order for liver function tests alone.

H: Do you continue those testings throughout the entire duration of treatment? Or only a couple times in the beginning?

Dr L: I do it throughout.

H: What are the most common major side effects you’re seeing with your patients?

Dr L: A lot of people are experiencing Herxheimer reactions. That’s another reason why I’ve found it desirable to introduce disulfiram cautiously and gingerly, and then gradually build it up. Some patients tolerate it pretty well, but many patients do report significant Herxheimers. They’re impressed with what they perceive to be the potency of disulfiram compared to other treatments.

H: One member of the group was asking if having a sulfa allergy is an issue for disulfiram use?

Dr L: You’d think that disulfiram would be a sulfa drug because of the name. Evidently it’s not a sulfa drug, it does have, I think four sulfur atoms in it, but it’s not a sulfa drug as far as I know. I have had patients who have had sulfa drug allergies who have not had any problems with disulfiram. Obviously that is a question that should be addressed by the patient to their physician, running it by pharmacologists and or pharmacists.

H: Are there any tell-tale symptoms that are side effects that are definitely caused by disulfiram and likely not attributed to the Herxheimer?

Dr L: You’d have to be vigilant for any things that one might see as a major drug reaction. Unusual rash, breathing difficulties, hives, precipitous dropping of blood pressure. That would be distinguishable from herxheimer type effect.

H: One person asks what to do if optic neuritis develops? If that’s very common?

Dr L: There's something called the toxic optic neuropathy from disulfiram. It's alarming that there could be a toxic optic neuropathy. I did try to look into that more in depth, to get the original articles on it. I couldn't find them. Obviously you would discontinue the drug right quick and seek ophthalmological consultation right away.

H: Have you seen people having mood changes from this drug?

Dr L: Yes. I've seen a couple of patients have had mood disturbance. One patient was a little bit paranoid, nothing dangerous. But that was a reason we discontinued the drug. Another patient developed a hypomanic status which was not her usual baseline. It was not exactly maladaptive but it was not normal for her so we discontinued.

I've had a number of patients develop a not very well characterized state of emotional distress that seemed to be related to the drug itself. It wasn't psychosis, a sort of an anxious state, a mild agitation that they perceived was not normal. It was alarming to them. I definitely think it was related to the disulfiram and that was a reason to suspend treatment in their cases.

I told you that case 1 had required psychiatric hospitalization but we aren't sure if it was related to the drug. I never heard him use the word, that he was psychotic or anything like that. We have not seen anyone that I know of that developed psychotic state in the 50 or so patients we've used it in. Again, we were very mindful of that possibility.

H: One person who has mast cell activation syndrome was asking whether or not disulfiram might make things worse for them. And whether you have patients with mast cell activation syndrome?

Dr L: That's an excellent question. There's not that much data on it. I know that there are some that feel mast cell syndrome is quite common, or overlaps, or presents coincidentally in patients with Lyme. And that's a concern too, because the disulfiram has such a long activity, it's not like a drug where you take the drug and the drug is out of your system in a day or so. Disulfiram, even if you take a small dose, it's in your system for two weeks. What would be the consequences if it did trigger a mast cell activation syndrome response? This is another area where there is not much data, I don't have too many patients that I know that have mast cell activation syndrome for sure or who are actively working with a mast cell activation specialist.

As you probably know getting in with someone who has expertise with mast cell activation syndrome is harder than getting in to see someone who is a so-called a Lyme

literate physician. There's not that many people in the country who do that. I'm fortunate I have someone who is fairly close to my office who has a world-class reputation with mast cell. Thus far we've not had a situation where a patient has actively worked with that practitioner and with me, but it's certainly crossed my mind. It's a reason to proceed with care, special care, somebody who has that, you don't know what the impact is going to be on mast cells.

H: I actually have mast cell activation syndrome myself. I'm seeing Dr Lawrence Afrin. Is that who you are talking about by any chance?

Dr L: It is.

H: Interesting. I took disulfiram and I personally didn't have any issues with my allergy symptoms from it, but I had a lot of symptoms that I have from treating Lyme from it.

Another question: is there any known effect that you know of on the gut microbiome from taking disulfiram vs an antibiotic? I'm assuming it's not as harsh on the gut.

Dr L: Well disulfiram has a lot of antibacterial activity, aside from Lyme. I have not made it a habit, nor has it seemed necessary, to insist patients on disulfiram take probiotics as they would when they take antibiotics. I don't even recommend probiotics per se, although I'm not against it if people want to use it, but it hasn't seemed necessary. I haven't had any patients develop either yeast infections with it, or have anything that seemed remotely suggestive of c. diff. That's another advantage of it, it seems that people don't need to go out and buy probiotics, which can get expensive.

H: This leads me into another question which I wanted to ask earlier. Have any of your patients with candidiasis or candida build-up in their gut had problems with this drug? And do you suggest eliminating candida before starting disulfiram?

Dr L: It hasn't really come up as an issue, but if I'm not mistaken disulfiram is purported to have anti-candida effects.

H: A couple people were worried about dental amalgam fillings and whether having mercury in their system would be a problem with taking disulfiram?

Dr L: That's an interesting question because I recently had a young woman come to me, and we were all set to do the disulfiram. She'd been to another practitioner prior to me who had documented, on a standard blood test, that she had a very high level of

mercury. I actually was not going to allow her to use disulfiram, and I repeated the blood mercury level and it was normal. So it became a non-issue. But if it's true disulfiram chelates metals, which I guess it is, you encounter somebody who has a very high blood mercury level, are you going to damage them by dragging that mercury into their nervous system along with the disulfiram? It certainly gave me pause. I probably wouldn't have prescribed disulfiram if we had confirmed she had a high blood mercury level. I would probably have suggested she consult somebody who deals with mercury toxicity and get that resolved. It would have made me very circumspect in using disulfiram in somebody who had known preexisting heavy metal toxicities.

H: Apparently the fact that it's a chelator of copper means it may also be a chelator of other metals, right?

Dr L: Yes, that's what the literature says. A lot of the metals, not just mercury, copper.

H: One of the patients was asking is there anything to mitigate the effects of copper toxicity?

Dr L: No. I don't know how you do that, or whether that's necessary. Copper is a normal element found in the body at a certain level.

H: If a patient has a very severe herx to disulfiram, how do you typically handle that?

Dr L: Suspend. And reduce the dose, and or treatment. There are some patients where we're using as little as 125mg a week, in special circumstances 62.5mg a week, to make sure they can tolerate it.

H: Out of the patients who have seen improvement, how long does it typically take for them to notice improvement into their treatment? And what dosage levels are they at when they notice things changing? Does it vary?

Dr L: It's a little bit different than antibiotic usage. Although like I told you, some of the patients on these very small dosages reported feeling better, not just feeling better, but their functioning greatly improved. But it hasn't really been the idea that you get better on the treatment and you know it's working. A lot of times patients feel better only after they go off. That's what I'm seeing with some of the patients, it's not how they feel on the treatment, it's how they feel after treatment is over and the drug is out of their system and they can assess what impact the treatment has had on the infection or infections.

It's a little different than antibiotic usage, which we've often had to do open-ended treatment. The goal there is to find the regimen or combination which the patient is feeling consistently well on. It's a little bit different strategy than with the disulfiram. You're not always aiming to get them feeling well on the disulfiram, it's getting the necessary course of disulfiram that you think or hope is sufficient to either knock out, if it's possible, or knock down the infection, so that they can enjoy a period of well-being and not be in need of further of antimicrobial or disulfiram treatment.

H: Given that you've had a few patients that have gone to the 2-3 month mark that haven't been fully cured, do you suggest considering carrying treatment out even longer than 2-3 months? Or not at the moment?

Dr L: Well I've had patients who've been on it longer, but not at the so called target dose. I'm calling it a target dose, what I think is an optimal dose for their weight, I've not extended it beyond 3 months at that dose. But I have had patients who have been on it longer, who are on it in that ramp-up phase, or for various reasons their condition has been precarious and are doing very well on the small dose. So I do have a few patients who've been on it beyond 6 months, but not on the target dose.

H: So at least for now, you don't see the need to take the full target dose for any longer than 3 months?

Dr L: I don't have the experience to know that, it's a suggested strategy. Again, I'm hoping it can be used for a finite time, and not having people on this for years at a time. Although it has been used for a year or more in patients with alcohol use disorders.

H: Is there anything you think that might help potentiate the treatment? Some people believe heating up the body, hyperthermia treatment option, saunas, biofilm busters like serreptase, grapefruit extract… is there anything you think that might be a potentiator or adjuvant to the effect of disulfiram?

Dr L: I don't know the answer to that, from my point of view I'm trying to keep it simple. And see if simple works. And then there might be a role for interventions that might improve the effect of this. Because not everyone is enjoying an enduring remission with disulfiram.

H: In some cases do you think it is ok to use antibiotics simultaneously with disulfiram?

Dr L: In those first 3 patients, in order to not have the situation confused, I insisted they go off their antibiotics. Generally I'm having patients do disulfiram as a monotherapy, with some exceptions. Because I don't have any convincing data to let me know it's effective against bartonella, as you know for some of the patients bartonellosis is a big issue. One patient, where she was treated with treatment for bartonella along with the disulfiram, from her perspective she did not perceive that the disulfiram eliminated her need for further treatment for bartonella. It's not a lot of data that I'm working with, some of my colleagues using disulfiram are of the opinion it might have effect against bartonella, but we need a lot more study on that.

H: One group member brought up the fact that some Lyme doctors are insisting that patients stop antibiotics for 3 weeks prior to starting disulfiram. Do you recommend that, or do you know why they might be recommending that?

Dr L: You definitely want them to be off of the agents like tinidazole or metronidazole, because you can have adverse drug interactions between disulfiram and those agents. That's the one agent I insist that the person would stop for at least one week before starting disulfiram. I'm not sure about the other agents. We've had patients begin the disulfiram fairly shortly after discontinuing their antibiotics without a long delay.

H: Have you thought about how doxycycline might drive the bacteria into the persister state, and whether or not that might be beneficial or contraindicated for the therapy? or other antibiotics, doesn't have to be doxycycline.

Dr L: I don't know. It seems from the work that Dr Eva Sapi and others have done that traditional antibiotics commonly have that effect of driving borrelia into cystic phase, or round-body, or even biofilm. That's speculation about disulfiram, one of its metabolites is carbon disulfide, and that is known to have antibacterial properties and is a very small molecule on the order of a the size of carbon dioxide. In biofilm it has metabolism, if biofilm is a *Bona fid*e issue, which I have issue to think it is. It's possible that disulfiram may have good activity against borrelia and other organisms within the biofilm. That might be another reason why it may be more effective than many of the antimicrobials which are often quite large molecules.

H: So you think it might actually be penetrating the biofilm of that small molecular size?

Dr L: Look at the periodic table. Sulfur is directly below oxygen on the periodic table, so it's a small atom, and carbon-disulfide and carbon-dioxide are both small molecules. And therefore very diffusible.

H: Have you had any patients that combined disulfiram with ozone therapy by any chance?

Dr L: No.

I know there are a lot of patients who feel they've benefited from ozone therapy as a bio-oxidative approach.

H: I have a couple questions about babesia. You've had good results with babesia so far. One person has said that patients who were asymptomatic before disulfiram are noticing their babesia symptoms appear to be reactivating from disulfiram. Is that to be expected given that it may be hitting babesia?

Dr L: I'm not sure, that case 3, who had very significant babesiosis symptoms who anytime would stop his high-dose mepron/zithro, within a few days he'd have drenching night sweats. He reported that even at the lowest doses of disulfiram his babesia symptoms seemed to melt away within a short period of time. Which was impressive to me.

H: That leads me to a third question. You don't currently see the need to recommend other babesia treatments concurrently with disulfiram?

Dr L: Perhaps I'm naive, but I'm hoping the disulfiram might make those unnecessary. Besides they're not wonderfully effective as it is. There is a new antimalarial agent that has come about, tafenoquine, one of my colleagues pointed out it has some quite serious potential toxicity, so very high rate of corneal injury I think. Whether that's going to have a role in babesiosis treatment. I don't know, it's for malaria right now. It's new.

H: Couple of questions about bartonella. We answered most of these questions already. You think disulfiram has no known effect on bartonella? Some patients are reporting an increase in their bartonella symptoms while on disulfiram. Are you seeing this in your patients? Do you think this is a herx or bartonella reactivating?

Dr L: That's a good question. As far as treating bartonella concurrently with disulfiram or not, from a certain point of view it makes it easier to do one thing at a time and see what happens. Some of my patients, even those who have bartonella, have opted not to treat their bartonella while they've been on disulfiram. I have two patients who had evidence of bartonella, and the decision was made not to treat the bartonella while they were

being treated with disulfiram. They are having certain symptoms that had us scratching our heads and wondering whether those symptoms are not for Lyme, not from babesiosis, but from bartonella that's not been treated. I think those two patients are coming, soon to be reassessed, including some direct detection methods so we can see whether or not we can prove if bartonella is the reason they are having certain symptoms.

They were stopped because they were having neuropathic symptoms, but they had been on a fairly long course. So we thought it appropriate to discontinue anyways. But it's a good question, is it a mistake to not treat bartonella with other means while you treat Lyme and babesiois with disulfiram?

H: Do you currently treat bartonella infections alongside Lyme infections? Or do you treat them separately?

Dr L: I usually have a discussion with the patient, give them the option: deferring bartonella treatment while we do the disulfiram since usually the disulfiram is for a finite period of time. With the understanding you can always go after bartonella later if it seems appropriate and necessary. Some patients declined to not treat the bartonella while we're using disulfiram, and some patients have opted to defer treatment for bartonella. Some patients have gotten away with that and are doing ok with that, but it might be enabling the bartonella to be untreated for 5 or 6 months while you are treating with disulfiram. Which might not be a good idea.

H: I believe you touched on this earlier, what do you recommend to people with candida issues if they're going to get on disulfiram? Any recommendations?

Dr L: I haven't been using disulfiram with the idea that it is an anti-candida treatment, although there is some literature suggesting it might be. I would use the standard things, nystatin, or for more systemic and difficult cases you can use fluconazole along with the disulfiram.

H: The one thing I was a little concerned about, I know that candida produces acetaldehyde in the body, and that may cause the ethanol-disulfiram reaction in the body. So patients should probably try to minimize their candida load in the gut before starting treatment, I would assume this would be a prudent idea?

Dr L: I don't see why it would be a bad idea to try to get that under control before you did disulfiram. Candida ferments things, but I don't know how significant that extent of fermentation of candida would be when disulfiram would be applied.

H: What are your thoughts on the mechanism of action of disulfiram in vivo, in people, vs in vitro. Different? Similar? Not sure?

Dr L: I don't know, in my article I speculated on different things that might explain the antimicrobial action of disulfiram, but everybody realizes we don't know exactly how it works.

H: To your knowledge borrelia could build-up a resistance to disulfiram? Or too early to tell?

Dr L: It's not an antibiotic in the usual sense, a lot of those concerns about development of resistance, they are good questions to raise, but we don't even know if that is an issue being that's not an antibiotic in the usual sense.

H: You're not sure whether the metabolites are actually killing the Lyme or the disulfiram itself? We know the disulfiram itself kills Lyme, but we don't know if the metabolites are important.

Dr L: It's interesting because the work Rajadas and Pothineni did was in vitro, so depending on how the drug in vitro breaks down, how stable is it, what was it in the in vitro that was eliminating the borrelia? The parent drug? Some non-metabolically broken down products? Good question, you'd have to know in the test tube, does it remain disulfiram the parent drug, or does it somehow break down to other things even in vitro?

H: Do you know if disulfiram might cause a reactivation of latent viral infections? We did see one article that it reactivate HIV, so some patients are concerned that it could theoretically reactivate EBV or other herpes viruses.

Dr L: I don't know the answer to that, there is a vast literature on disulfiram, and the drug is being repurposed. For a lot of other indications, including use in treating different kinds of cancers which is quite interesting, also in view of the work of Alan MacDonald (pathologist) in which he states there may be a link between borrelia and glioblastome multiforme. It's interesting that disulfiram has activity against gliostobame multiforme.

H: This has been something that a lot of people have been arguing about. Some people are saying you need to avoid any foods with acetaldehyde, others saying no it's not an issue. I've spoken with Dr. Rajadas at Stanford about this, and his perspective is foods with disulfiram seem to be fine for most people, except he would avoid vinegar. But things like coffee and melon have higher levels of acetaldehyde but he doesn't believe those should be a problem. Is that your experience with patients?

Dr L: Patients generally haven't had too many problems other than avoiding alcohol, and the few exceptions I've mentioned. But we're always interested in hearing patients' experiences, sometimes we've learned things that we wouldn't have suspected otherwise.

H: In conclusion can you summarize disulfiram and its potential for treating Lyme disease, coinfections. Are your views evolving as you see more patients treated with it, noticing any patterns?

Dr L: It's an option we didn't have before. It seems to have a lot of advantages as compared to customary antimicrobial therapy. It's role is being evaluated, my experience with it is still quite limited. No more than 50 patients over the past 2 and a half plus years. I remain very impressed by its utility, quite dramatic, I don't necessarily think it will be the solution for every patient. There will be patients who either can't take it, or they use it and it doesn't seem to resolve their problems. So the question is are they dealing with Lyme, or is there another issue? or are there some patients where it just doesn't work for them. It is relatively safe, it's quite inexpensive when you compare to a lot of the other agents, it doesn't require parenteral approach, it seems to be at least as potent or possibly more potent than some of the agents have been thought to be the best agents that we have like Rocephin (ceftriaxone). Which are expensive, have complications of their own, and you need parenteral approaches. It can eliminate the need for IV antibiotics in many cases. It's practical. But everybody needs to learn about it, practitioners need to inform themselves about, the patients need to inform themselves about it. Like any therapeutic it needs to be used with care. Anything you use as a therapeutic has potential adverse effects, people need to inform themselves about that. Personally, I'm refining my approaches and figuring out what the best way is to use this agent. It's a learning curve.

I think it's great there are some formal trials with this agent that are going forward, Dr Brian Fallon has his study at Columbia. And I just heard there was another study of disulfiram in patients, I gather that's going to be at Stanford? And then more and more practitioners, based on my recorded experience, and also personal communications

with them, are beginning to use it. The feedback I've gotten is they are also quite impressed by its potency.

As I told you, I'm dealing with 40 or 50 patients, and I learned about your chat group and other chat groups on facebook. I decided to join to learn from other patients' experiences beyond my own practice. We're all learning together.

H: The Columbia study by Dr Brian Fallon hasn't started yet?

Dr L: I think they're recruiting patients, I don't know if they've actually begun the study yet.

H: From my understanding Dr Richard Horowitz actually has over 100 patients that are under some sort of trial. Do you know anything about how that might be going?

Dr L: No I haven't, but I see that he has a 3 armed study, with a couple different groups: disulfiram alone, disulfiram with other regimens. He's been pretty prolific in reporting on his patients which is great. It will be interesting to see what his experiences are.

H: I hope we'll be able to follow up with you in a few months, and hopefully we'll have a lot more knowledge and perspective at that time. I really wanted to thank you for all the time you spent, it's been 2 and a half hours. And I know the community is going to tremendously appreciate your insight. Can't thank you enough.

Dr L: You're welcome Harrison. It was very enterprising of you to set up the disulfiram group, and the patients and other patient advocates who set up their own groups. I made a joke about this. I'm a trumpet/cornet player, and one of my teachers, William Spalding, who was a proponent of bebop, he used to tell me about the days when he used to participate in what was caused the "University of the Streets," where jazz musicians get together and play on the street. And they'd learn from one another, and that's how people got better. I jokingly call the Facebook group "University of the Streets," where patients are sharing their experiences and are all learning from one another. There's actually a real group called "University of the Streets," out of the Bronx, and one of the things they do is music education, jazz. This is our kind of disulfiram "University of the Streets."

H: I feel the same way, everyone's learning as we go. It doesn't feel like that with other drugs, Lyme is such a challenging disease, as are the coinfections, it's great that the internet has enabled the ability for this information to pass freely all over the world.

Hopefully it will lead to an accelerated cure.

Dr L: One other thing, Jenna-Luche Thayer, she's the one who promoted this Ad Hoc Committee to get the ICD codes changed. She was instrumental in that, and she has a big background in human rights. She and one of her friends that is a pharmacist have been doing a lot of work, putting together a lot of research, pharmacology on disulfiram. When that comes out, I think people will find that very valuable. That's something to look forward to.

H: Before we wrap up, is there anything you want to add?

Dr L: I would say for everybody using this agent, be careful. Be cautious. Desirably be under the care of a healthcare practitioner. Also be careful in being overzealous in the use of this agent, respect it. Try to maximize benefit. Know when to stop.

Fiona Stanislawski: What would class as unacceptable liver enzymes? How high would they have to be before you'd say no more disulfiram?

Dr L: We've been impressed by how remarkably boring the surveillance labs have been overall. If I see liver function tests, I don't really have a clear cut, but if they're progressively rising that's a warning sign. Because you don't know where they are going to end up. I usually don't get too upset if liver functions are 1-2x the upper limit of normal. But if I see them progressively get higher while the patient is on disulfiram, and there is no other reason for it, prudence dictates discontinuing the drug but continuing to follow the liver function tests to make sure they return to normal.

The two patients where we did discontinue it, and one of them had a positive Murphy sign. It must've been ALT which was elevated. I usually check AST, ALT, and actually the GGT is one of the specific enzymes for liver. Also bilirubin as well.

Dr L: One last thing, it's amazing what you can accomplish when you get over the denial and acknowledge the problem. I truly believe that disulfiram is useful, but I don't think it's the only agent, and I'm very hopeful with the great work being done by Dr Rajadas and his group, Dr Sapi and her group, Dr Lewis and his group, Dr Zhang and his group, that we will have even more options that patients can avail themselves of. Disulfiram kind of fell into my lap, I wasn't looking for it. We had amazing results with those first three patients, it's a tremendous amount of work to get anything published these days. But I felt it was worth it to get it published.

H: You were the trailblazer for the Lyme LLMDs.

Dr L: It was the patient who was the trailblazer. That case 1, I invited him to come to the conferences, he's a very self-effacing guy, and he's not looking for any glory. In this case it was the patient who was really the pioneer. But I listened to him, and I didn't think it was unreasonable so I cooperated with him, and seemingly hit a home run out of the park, unexpectedly.

H: We should also give credit to all the charities that helped fund the research. Bay Area Lyme, Global Lyme Alliance, LivLyme, Steven and Alexandra Cohen Foundation donated a lot of the money that those foundations used to fund this research. And obviously Dr Rajadas for his discovery of disulfiram's efficacy…

Dr L: That initial research, if I'm not mistaken, was funded by the Bay Area Lyme people. I would like to make a pitch for Dr Rajadas and his group. They did the foundational work on this, and they continue to do excellent work. They do need support, I would encourage anybody who can to support them. I personally made a donation to their research early on, usually it has to be a check to Stanford University, but I specified it is to be allocated to the Lyme lab of Dr Rajadas.

H: I'm hoping to interview Dr Rajadas about this as well. If there is any way people can donate I'm hoping we can give details on that in the coming interview.

I also want to thank everyone in the group who submitted questions. We got 200, I'm sorry if we didn't get to everyone's question.

Thank you Dr Liegner.