TONIX PHARMACEUTICALS

Easing the Pain and Suffering of Fibromyalgia

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Dr. Seth Lederman believes the drug being developed by his company, TONIX Pharmaceuticals Holding Corp. (TONIX), could change fibromyalgia treatment.

Dr. Seth Lederman is a physician, scientist and experienced inventor and developer of prescription pharmaceuticals. He's also a founder and builder of pharmaceutical companies. He's co-founded such companies as Vela, Validus, Fontus and Targent Pharmaceuticals. Targent's drug for colorectal cancer is now selling at a rate of $300 million per year for Spectrum Pharmaceuticals as Fusilev®, and if the rate of growth continues, it could become a blockbuster.

Lederman's latest company is TONIX, which he founded in 2007. TONIX is focusing on developing new treatments for central nervous system disorders like fibromyalgia, post-traumatic stress disorder and traumatic brain injury.

Q: What is fibromyalgia? How bad is it?

Dr. Lederman: In typical patients, fibromyalgia pretty much takes over their lives. They have pain all over their bodies. They suffer from fatigue and don't have the energy to get around and do things. They also suffer from poor sleep.

There used to be a lot of people who were skeptical that fibromyalgia was a real condition. No more. Just about anyone who cares for these patients has learned that the condition is real and serious. More and more primary care doctors are becoming comfortable making the diagnosis. Fibromyalgia used to be diagnosed and treated almost exclusively by rheumatologists. So our specialty organization, the American College of Rheumatology, established the diagnostic criteria. Rheumatologists used to tell a grim joke about diagnosing fibromyalgia. The joke was that they could diagnose a fibromyalgia case when the patient was still in the waiting room. They could make the diagnosis, because the patient's husband was banging his fist on the receptionist's desk, saying: "We're not leaving until you do something for my wife." That joke is dated now, but the sad truth behind it is like a memory capsule. That joke gives people today a glimpse of a recent past when fibromyalgia patients were frustrated by being told: "There's nothing wrong with you." For whatever reason, skepticism about fibromyalgia in the medical community pushed these patients away and kept them outside. It was like a 'Cold War' and the fibromyalgia patient was left out in the cold.

According to the National Institutes of Health, there are five million Americans with fibromyalgia. One study showed that the economic impact of the disease, in terms of disability claims, lost workdays and other consequences, was as severe as rheumatoid arthritis.

Q: Can fibromyalgia be treated?

Dr. Lederman: There are now three drugs approved for the management of fibromyalgia. The first one, Lyrica®, was approved by the US Food & Drug Administration (FDA) in 2007. Lyrica's approval was a watershed in the history of fibromyalgia. Lyrica had already been approved for treating neuropathic pain, which occurs after a nerve is damaged or gets infected with herpes viruses. The approval by FDA for treating fibromyalgia turned the heads of many skeptics because it was a validation of all the science and clinical experience that fibromyalgia is a real problem—and a distinct syndrome.

The second drug, Cymbalta®, had first been FDA-approved for treating depression. The third drug, Savella® has been approved in Europe for treating depression. Cymbalta and Savella are from the same class of anti-depressants called SNRIs, which means scientifically that they both block the reuptake of the brain neurotransmitters serotonin and norepinephrine. Clinically, it means they are pretty similar and physicians will use one or the other based on other factors like cost.

The major impact of these three drugs has been ending the "Cold War" against fibromyalgia patients, validating fibromyalgia as a diagnosis, winning over skeptical doctors, and providing some relief. However, these drugs don't have the impact we had hoped for. In the clinical trials, less than half of the patients responded. Even for those who benefit, the benefit can wear off. So, despite three FDA approved drugs, fibromyalgia patients are not satisfied with the available treatment options. I subscribe to the motto, '99% of solving a problem is identifying the problem.' The FDA approval of Lyrica identified fibromyalgia as a problem for drug developers to solve. Fortunately, I'd been working on developing treatments for fibromyalgia for many years before 2007, so that's why at TONIX, we have a big lead relative to drug developers who just learned about fibromyalgia in 2007. Sometimes it helps to be a pioneer. I had a lot of confidence because of my training and clinical experience with actual fibromyalgia patients. For us, the FDA approval for Lyrica was important beyond validating our mission. After the FDA validated fibromyalgia as a syndrome, we were able to attract investors to finance our mission.

Q: How can drug developers solve the problem and meet the medical need?

Dr. Lederman: Our work at TONIX shows that the key to easing the pain and suffering from fibromyalgia is enabling patients to get a good night's sleep, or more specifically, restorative sleep.

Q: How do you know that sleep is a central problem?

Dr. Lederman: If you ask fibromyalgia patients about sleep, more than 90% say they have a problem. More telling, if you ask a fibromyalgia patient: "Do you ever feel better?" it is very common for them to say: "I feel better whenever I can get a good night's sleep."

I can't emphasize enough the importance of that observation. Our technology was invented by Dr. Iredell Iglehart, who is a rheumatologist in Baltimore. He's different from many other physicians because he always asks patients about their sleep. Most doctors don't take the time. Iglehart was the first person to hear fibromyalgia patients when they described the power of good sleep, or at least the first person to recognize its importance. Iglehart recognized that if fibromyalgia symptoms improve if patients get a good night's sleep, then drug discovery for fibromyalgia should focus on improving sleep.

I think of that observation as his 'Jenner' moment. Edward Jenner was the doctor who listened to milkmaids when they said that cowpox prevented them from getting smallpox. Jenner used that observation to invent the vaccine for smallpox, which eradicated a disease that used to kill a third of the people it infected. Like Jenner, Iglehart started by listening to patients. Iglehart used that observation to devise a medical treatment for fibromyalgia. Iglehart wasn't satisfied that good sleep benefitted some patients and only benefitted them sporadically. Iglehart wanted to make the benefit of good sleep available to more patients and wanted to make it predictable. Like Jenner, it took Iglehart a lot of experimentation to hit on the right technology. In Iglehart's case, the invention was using low-dose cyclobenzaprine to improve sleep quality.

While Iglehart invented bedtime cyclobenzaprine, he was influenced by by the work of Dr. Harvey Moldofsky. Moldofsky is truly the pioneer of poor sleep in fibromyalgia and is the recognized, world-renowned thought leader. So it was very important for us that Moldofsky recognized the potential of Iglehart's contribution and Moldofsky agreed to be principal investigator on our Phase 2a trial to test our treatment.

Recognizing the therapeutic potential for good sleep has also demystified some other aspects of fibromyalgia. For example, we think it explains why we find fibromyalgia patients chasing different prescription sleep drugs. The problem is that while there are drugs that can help put people to sleep, it is not the right kind of sleep that gives relief.

Q: What is the right kind of sleep?

Dr. Lederman: The science of sleep is in the midst of a revolution. Sleep scientists still believe it's useful to divide sleep into rapid-eye movement (REM) and non-REM sleep. But beyond that, computer techniques for analyzing brain waves during sleep have opened up new frontiers. The poor quality sleep of fibromyalgia was linked to two non-REM brain wave patterns called cyclic alternative pattern (CAP) A2 and A3.

Q: So the trick is decreasing the amount of CAP-A2 and CAP-A3 sleep?

Dr. Lederman: Yes. We think CAP-A2 and CAP-A3 are the best surrogate markers for non-restorative sleep.

Q: How? Can it be done with drugs?

Dr. Lederman: There are two drugs that have been shown to increase the amount of restorative sleep and reduce the pain suffered by fibromyalgia patients. One drug is the Rekinla® formulation of sodium oxybate and the other is our drug, TNX-102 SL.

Sodium oxybate, which is also known as gamma hydroxybutyrate or GHB, is a very potent sleep drug. It induces a state of sleep that is basically a stupor. In that state of deep sleep, patients do enjoy restorative sleep. However, sodium oxybate is challenging for several reasons. First, it is very short acting so patients have to wake up in the middle of the night to take a second dose. Second, it has been used as a weapon in 'date rape', so law enforcement agencies are concerned about it becoming widely available. Third, it has a potential for addiction.

Q: Since that drug has so many shortcomings and the potential to be misused, is there is better alternative?

Dr. Lederman: Unfortunately, there is no drug on the market for improving sleep quality in fibromyalgia patients. In the future, if we get FDA approval, we believe our TNX-102 SL medicine will be a better solution. It's a novel, sublingual (or under the tongue) formulation of cyclobenzaprine. Cyclobenzaprine has already been on the market for 35 years. The drug was first approved by the FDA in 1977 under the brand name Flexeril® for the treatment of acute muscle spasms.

Once Dr. Iglehart realized that cyclobenzaprine had an effect on sleep, he experimented using cyclobenzaprine at bedtime to help fibromyalgia patients. But he soon found that the originally approved dose was far too high for treating fibromyalgia. So he tried giving his patients lower doses before bedtime. He also experimented with giving the dose a few hours before bedtime because it takes two or three hours for patients to feel the effect of the medicine.

With low dose cyclobenzaprine given a few hours before bedtime, Dr. Iglehart was able to improve the sleep and relieve the pain of many of his fibromyalgia patients. Compared to sodium oxybate, the drug is like a feather instead of a sledgehammer. Patients get a little sleepy after they take a low dose of cyclobenzaprine, but it doesn't induce anything resembling a

stupor. Cyclobenzaprine is not recognized to have any addiction potential. Patients don't get amnesia.

Q: So it really does work?

Dr. Lederman: It worked so well that we acquired the rights to the drug and eventually formed TONIX to develop it. Dr. Moldofsky tested the treatment in a clinical trial, published in the December 2011 Journal of Rheumatology. The results were far beyond our expectations. Thirty-six patients were studied in a double blind, randomized, placebo-controlled study. The cyclobenzaprine-treated patients had a significant reduction in pain after eight weeks, which is an extremely strong result. The analysis of sleep brain waves also showed a decrease in the CAP-A2 and CAP-A3 sleep. The same journal that published our paper had an editorial by a professor from Harvard, who said that our data are so compelling that any drug for fibromyalgia would have to address sleep problems.

Q: That does sound very promising. But why does Tonix have to develop the drug at all? Cyclobenzaprine is already on the market. Can't patients just buy it and take a low dose themselves?

Dr. Lederman: What's crucial is that we have a new formulation of the drug. The form now on the market is a pill that's swallowed and absorbed in the stomach. That is far from ideal for the management of fibromyalgia. The oral drug is absorbed slowly and remains for a long time in the bloodstream. Also the liver makes metabolite that remains in the blood even longer. Over time, the bloodstream levels rise, dulling the effect.

So we've created a formation that is put under the tongue and absorbed directly into the bloodstream. That's called a sublingual formulation. It gets to the blood faster and to the brain faster, it bypasses the liver, and makes less of the metabolite, so there is less hangover and less accumulation.

In late July 2012, we released a very encouraging study showing that many advantages of this sublingual formulation. We believe that the new formulation is a dramatically better drug then the generic on the market.

Q: What do you need now to bring the drug to market?

Dr. Lederman: To get approval, the FDA requires two Phase III trials. We intend to begin enrolling patients for the first Phase III study in the first quarter of 2013.

Q: How's that going?

Dr. Lederman: I think we are making headway. A year ago, we were completely off people's radar screens; now I think we're getting the attention of the leading people in the field.

Q: Well is does sound so good that many people would be skeptical. Why should investors believe you?

Dr. Lederman: I think the best answer is that I know what I'm doing because I've been here before. In 2000, I founded a company called Targent. We had a new drug for colorectal cancer. All the clinical studies were done, and we just needed $4 million to get FDA approval and bring the drug to market.

But we couldn't raise the $4 million because people thought the story was just too good to be true. We had to sell the rights to another company. That drug became Fusilev, which sold approximately $50 million just in the second quarter of 2012 for Spectrum Pharmaceuticals. Fusilev was just approved in 2011 for colorectal cancer, so its sales are still growing rapidly. It's very gratifying for me that Fusilev is providing benefit to so many colorectal cancer patients.

Q: How is your experience with Fusilev different than developing TNX-102 for fibromyalgia?

Dr. Lederman: In all of the work I've done in drug development, I always start by asking whether the project will benefit patients. That motivated me to advance levo-leucovorin, which is now known as Fusilev. The growing sales of Fusilev indicate that it takes time for doctors to appreciate the value of new drugs even after FDA approval. I believe that TNX-102 will provide significant benefit to fibromyalgia patients. Whereas Fusilev could be described as an incremental advance, TNX-102 has the potential to be a game-changer.

Fibromyalgia, unlike colorectal cancer, is not fatal if untreated. Some people make a distinction between life-saving and lifestyle drugs. That may be a useful distinction in other conditions, but we feel that what we are doing at TONIX is as important as developing life-saving drugs. I have seen the suffering and disability of fibromyalgia patients. Fibromyalgia has stolen their lives from them. I believe that what we're doing at TONIX, in trying to give fibromyalgia patients back their lives, is arguably just as important as saving a life.
I can't think of a better goal for a physician than to help patients who are suffering to become happier and more productive.

Q: How can you get that message across?

Dr. Lederman: We have decided to become a public company in order to increase awareness of our mission. Being a public company requires us to communicate frequently with the general

public about our activities and progress. It also provides us with different possible ways to finance our drug development activities. Developing prescription drugs requires a large amount of capital and involves a significant amount of risk. Being public, we make it possible for a number of different types of investors to participate in funding our programs. We hope to gain the interest of investors who take pride in participating in the development of new medications. We believe that our product TNX-102 SL for fibromyalgia will be covered by strong patents for a period of time that will reward the risk our investors have taken. Most importantly, we think that we are going to make a big impact in the care of fibromyalgia patients.

We think it is unique for a company of our size and market cap to have a lead product in clinical development that addresses a potential market of 5 million patients in the U.S. Other companies of our size typically focus on orphan diseases or smaller indications, so we think it is distinctive that we have such big ambitions, but also we have the team and the technology that make our goals realistic and attainable.

In closing, I should say that I've gained invaluable experience working on different drug development opportunities in emerging companies. I've also developed some perspective on the industry. I'm pleased to apply that experience and perspective to the challenging realm of brain science. This is the best opportunity I've ever worked on.