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Fibromyalgia drug nearing approval after a 16-year lull

BY DANIELLE GOLOVIN, SENIOR BIOPHARMA ANALYST

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After 16 years without a new approval, fibromyalgia patients may be on the cusp of getting a therapy that improves pain, sleep and fatigue — the triad of symptoms that define the chronic condition.

While the biological underpinnings of fibromyalgia, a condition that predominantly affects women, are poorly understood, the etiology is thought to involve "a change in the brain's interpretation of external stimuli" called nociplastic pain, Seth Lederman, CEO of Tonix Pharmaceuticals Holding Corp. (NASDAQ:TNXP), told BioCentury. That change is "not limited to the sensation of touch; it affects all senses and causes widespread pain."

The condition is characterized by pain in many parts of the body, poor sleep quality — especially a lack of restorative, deep sleep — and fatigue.

FDA approved three drugs for the indication in consecutive years starting in 2007, and none since.

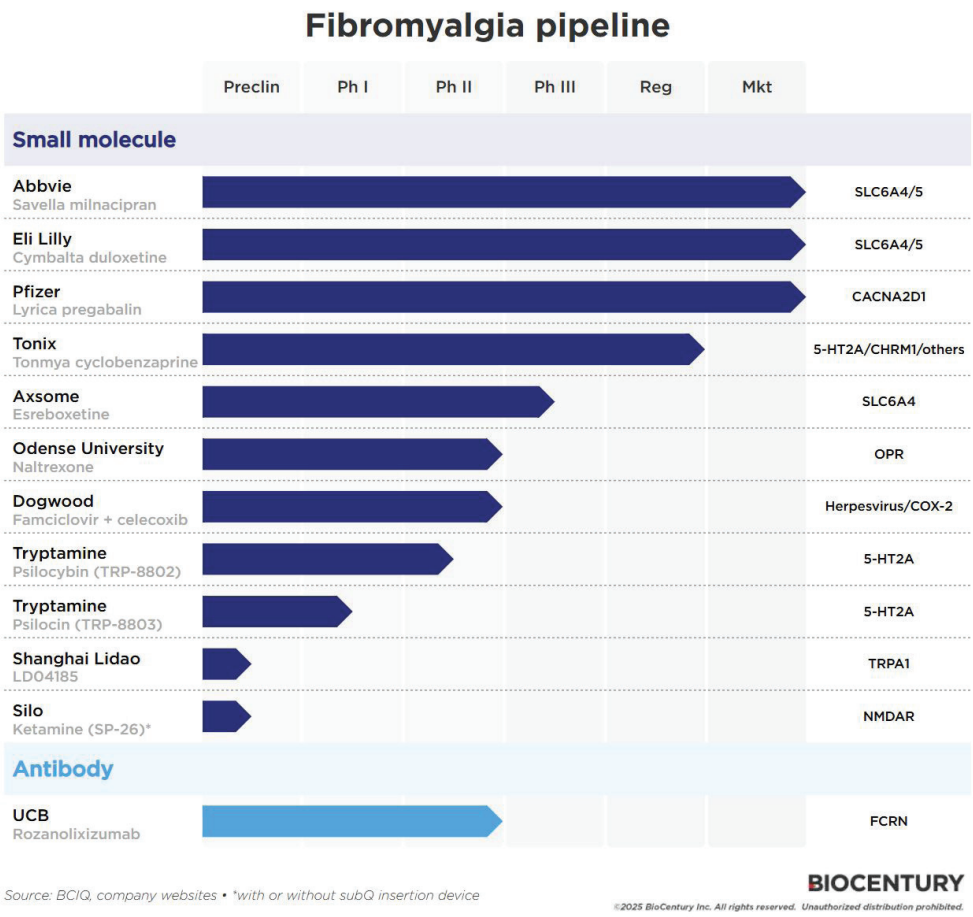
Cymbalta duloxetine from Eli Lilly and Co. (NYSE:LLY) and Savella milnacipran from Abbvie Inc. (NYSE:ABBV) are serotonin and norepinephrine reuptake inhibitors (SNRIs). These increase neurotransmitters that help reduce pain and fatigue and generally improve mood. The third is Lyrica pregabalin from Pfizer Inc. (NYSE:PFE), a structural derivative of GABA that binds to calcium channels and reduces release of neurotransmitters involved in pain signaling.

These agents primarily improve pain, with mixed results on fatigue and sleep quality.

Moreover, only about 25–35% of patients get at least 50% pain relief from these drugs, collectively. Lederman said that within 18 months of a fibromyalgia diagnosis, about half of patients are prescribed opioids to control their pain. The company has estimated the population size at 6-12 million adults in the U.S.; 80-96% of these patients are women, ranking fibromyalgia among the largest women's health indications.

Despite the need and market size, research into fibromyalgia remains limited and the pipeline small. That's partly due to the complexity of the underlying biology, the indication's reliance on subjective, symptomatic clinical trials endpoints, such as pain assessment, and its lack of clear biomarkers.

"It's way too risky for big pharma right now," said Lederman, who noted development is also expensive and the FDA's efficacy analysis requirements have gotten more stringent.



"We've spent hundreds of millions of dollars over fifteen years," he said. "Also, since Lyrica, Cymbalta and Savella were approved, FDA has moved the goalpost." The registrational endpoint hasn't changed, but the primary statistical analysis must now account for missing data differently.

When handling missing data, regulatory agencies may request 'imputation to baseline' as a conservative sensitivity analysis, which means if a patient misses visits or drops out of a trial, their missing outcome results are replaced with their pretreatment, or baseline, value. This is used to avoid overestimating a drug's benefit, especially if side effects are causing patients to leave the study.

It's unclear, he said, if the fibromyalgia therapies on the market today would have been approved if that policy had been in place when they were being developed.

Against this backdrop, FDA's acceptance of the NDA from Tonix Pharmaceuticals Holding Corp. (NASDAQ:TNXP), which has an Aug. 15 PDUFA date, is a welcome step forward, even as the refuse-to-file letter that Axsome Therapeutics Inc. (NASDAQ:AXSM) received for its candidate represents a step back.

Improve sleep, reduce pain?

That divergence reflects how thin the fibromyalgia pipeline remains, with few candidates that promise to address the condition's full symptom triad. Tonix stands out not for reinventing the therapeutic wheel, but for refining an existing mechanism to more effectively target the disorder's core symptoms.

Its candidate, Tonmya (TNX-102 SL), is a sublingual formulation of cyclobenzaprine, a muscle relaxant often used off-label to treat fibromyalgia. The advantage of the delivery route is that it avoids first-pass metabolism, leading to greater enrichment in the brain of intact cyclobenzaprine, rather than a mixture of cyclobenzaprine and its active metabolite, norcyclobenzaprine, which is thought to decrease the effectiveness of cyclobenzaprine on pain relief.

Another advantage is that it enables review under the 505(b)(2) pathway.

Once in the brain, Tonmya acts an antagonist of four neurotransmitter receptors: 5-HT2A, CHRM1, HRH1 and ADRA1. The company's hypothesis is that the combined mechanism primarily works by improving sleep quality, specifically correcting the deficit in "restorative" phases of the sleep cycle, known as non-REM sleep or deep sleep.

Antagonism of 5-HT2A and HRH1, in particular, are thought to improve sleep architecture, while alpha-1 adrenergic antagonism may have the added benefit of reducing central sensitization of sensory signals.

"In 1975, Harvey Moldofsky asserted that fibromyalgia at its core was a sleep disorder," said Lederman. Moldofsky is credited with foundational discoveries linking non-restorative sleep to the development of fibromyalgia symptoms, and was elected to Tonix's scientific advisory board in 2011. The company's approach is based on the idea that poor sleep is a central feature and possible root cause of fibromyalgia symptoms. The poor sleep and worsening pain become a vicious cycle.

Tonix saw a reduction in pain in fibromyalgia patients in two pivotal studies, with durability out to at least 14 weeks. The patients also reported improved sleep and reduced fatigue. None of the currently approved products address all three symptoms.

In the RESILIENT study, 45.9% of patients on TNX-102 SL achieved at least a 30% reduction in pain, versus 27.1% on placebo ($p<0.001$).

TNX-102 SL led to significant improvement in fatigue, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue instrument (LS mean difference from placebo: -3.0 units; $p<0.001$) and the Fibromyalgia Impact Questionnaire (FIQ-R) (symptom domain: -7.7; $p<0.001$; and function domain: -5.4; $p=0.001$).

Patients also reported improved sleep quality (-0.6 units; $p<0.001$) and a reduction in sleep disturbance (-4.2 units; $p<0.001$).

The difference of ~19% on the pain endpoint compares favorably to currently approved fibromyalgia drugs, which, in some trials, achieved 30–35% response rates with smaller deltas vs. placebo. Additionally, physicians may view the therapy's consistent pattern of significant effects across symptom domains as differentiating.

TNX-102 also has a more benign side effect profile than some of the approved therapies, with no serious adverse events occurring in >5% study subjects. Its most common side effects were localized to the delivery site, such as oral numbness or altered taste; whereas Lyrica's most common AEs were dizziness, drowsiness, weight gain and edema, and Cymbalta's nausea, dry mouth, constipation and insomnia. Both had a higher AE-related discontinuation rate than TNX-102.

On the horizon

The fibromyalgia pipeline holds at least eight additional programs, of which esreboxetine (AXS-14), a norepinephrine reuptake inhibitor from Axsome Therapeutics Inc. (NASDAQ:AXSM), is the next-most advanced.

For patients who are intolerant to SNRIs, which mostly results from side effects related to increased serotonin, AXS-14 could give them a non-serotonin-modulating option.

Fibromyalgia patients on AXS-14 experienced reduced pain and fatigue in Phase II and III trials. The studies did not include sleep improvement as a primary or major secondary endpoint, and insomnia was reported as an adverse event.

However, Axsome received a refusal-to-file letter this month for its NDA seeking approval of AXS-14. Although the company had completed two placebo-controlled trials that met their primary endpoints, FDA said the second of the two studies was inadequate because its primary endpoint was measured at eight weeks, and it allowed a flexible-dose paradigm. The first of the two placebo-controlled trials in the submission, which employed a 12-week endpoint and a fixed-dose paradigm, was deemed adequate by the agency.

Axsome said it will conduct an additional controlled trial, and anticipates initiating it in the fourth quarter.

The other seven disclosed fibromyalgia programs span preclinical to Phase II development. All but one are small molecules. The exception is an antibody from UCB S.A. (Euronext:UCB). Rozanolixizumab completed a Phase II trial last year, according to ClinicalTrials.gov, but the company has yet to announce results.

If approved, Tonmya could mark a long-awaited advance in fibromyalgia care — and a signal that addressing sleep may be key to breaking the therapeutic impasse.

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NEWSROOM
news@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589