

Drug Compliance:

A Wearable Device Improves Drug Efficacy with Patient-Specific Timing and Support

CHRONO THERAPEUTICS



Hayward, CA

Sector: Improved Outcomes for Pharmaceuticals with Wearable-Enabled Support

Founded: 2003 initially, but expanded its vision in 2013

Contact: Alan Levy,
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Founder: Guy DiPierro, who licensed the patents for biologically-timed drug delivery from the University of Basel in Switzerland.

Funding to date: \$34 million from a Series A round. Investors include Canaan Ventures, 5Am Ventures, Fountain Healthcare Partners, Mayo Clinic, GE

Ventures and Rock Health. The company has also received two grants from the National Institutes of Health.

How the company gets paid: Under the Affordable Care Act, FDA-approved smoking cessation products are reimbursed and many companies reimburse their employees for smoking cessation products and programs.

The proven efficacy of drugs is based on rigorously controlled clinical trials but in the real-world, the patient is a wild card capable of single-handedly throwing off the results. With all drugs, compliance is a major issue. Patients are compliant about taking pills as directed less than 50% of the time; for transdermal patches, compliance is believed to be even lower. Obviously, drugs can't help if patients don't take them.

Chrono Therapeutics Inc. has developed a wearable device and smart phone-enabled support platform that offers several strategies (compliance among them) to mount a multi-pronged attack that will help patients succeed on their drug therapies.

The company was initially founded in 2003 by Guy DiPierro, an attorney specializing in corporate M&A and technology licensing, who licensed some pat-

ents concerning biologically timed drug delivery from the University of Basel in Switzerland. In 2013, Alan Levy, PhD, a seasoned veteran of both the pharmaceutical and medical device industries, joined as chairman and CEO. Previously, Levy served as the founding CEO of the pharmaceutical firm Incline Therapeutics, which was acquired by The Medicines Company; the president and CEO of Northstar Neurosciences, which was developing an innovative neurostimulation therapy for stroke survivors; and also as the CEO of Heartstream Inc. and the president of Heart Technology Inc.

With Levy at the helm, Chrono Therapeutics began crafting a broader strategy, including compliance monitoring and behavioral support. "Our focus is on improving patient outcomes by putting together four distinct technologies: biologically timed drug delivery, compliance monitoring, behavioral support, and data analytics," says Levy.

A Large Market and a Clear Business Model

For its initial commercial product, the company is developing a smoking cessation device, which provides a good entry point for its platform for a couple of reasons. First, smoking is a major public health problem. According to the US Centers for Disease Control and Prevention (CDC), cigarette smoking kills more than 480,000 people in the US each year, 41,000 of them from exposure to secondhand smoke. In addition, smoking-related illness in the US costs more than \$300 billion a year, including nearly \$170 billion in direct medical care for adults and \$156 billion in lost productivity. The CDC estimates that in 2014, 40 million adults were cigarette smokers.

Second, nicotine, the established smoking cessation drug, has been safely used for 20 years, which lowers

the regulatory hurdles for the company. It will be eligible to pursue the 505(b)(2) regulatory process, which allows companies to rely on the safety and toxicity data of previously approved products.

Finally, in this application, the business model is established. Under the Affordable Care Act, FDA-approved smoking cessation products are reimbursed. A large number of Fortune 100 companies also provide smokers with cessation support programs, including fully covered smoking cessation medications (e.g., nicotine patch/gum or prescription drugs like varenicline), since studies have shown that each employee who quits smoking saves companies \$6,000 per year, approximately half in healthcare costs, the other half in lost productivity. Going in, the company has a clear idea of how it will get paid for its product. (Levy also notes that GE Ventures is an investor in Chrono Therapeutics. It has a personal interest in the space, partly because it is developing sensors, and partly because it is a large self-insured corporation. Says Levy, “They insure close to one million lives for healthcare, and they estimate that about 20% are smokers, so if we could get all of them off smoking, they could save about \$1 billion!”)

Therapy on the Patient’s Own Time

Levy explains how each of Chrono Therapeutics’ four technologies helps patients in the smoking cessation application, starting with biologically timed drug delivery.

“In the case of smoking cessation, biological timing means preventing cravings from occurring, and studies have shown that if you can do that, you can significantly improve the quit rate.”

Smokers crave cigarettes at well-known and predictable times. The strongest craving occurs in the morning, when the individual first wakes up after having been deprived of nicotine for seven or eight hours. “That’s why one out of four smokers lights up the first cigarette within five minutes of waking up.” The other three quarters, he notes, smoke within 30 minutes of waking. Smokers also crave nicotine at mealtimes because metabolism increases when one eats food, including the metabolism of nicotine, which increases by about 50%, Levy says. Finally, the evening is another difficult time when smokers are tempted to smoke because of social cues or ingrained

behavioral habits; because they’re around other smokers, for example, or because they’re having a glass of wine.

The Chrono Therapeutics’ solution starts with a transdermal drug delivery wearable pod (which can be adhered to any part of the body) that dispenses nicotine in such a way as to avoid cravings at these specific times. The smoker will enter the wake-up time (just as if he or she were setting an alarm on a clock) and the wearable pod will deliver nicotine an hour and a half before wake-up to prevent the first strong craving of the day. The patient will continue to get nicotine throughout the day, but will receive peak levels in anticipation of meal times (see Figure 3). The device stops drug delivery at night because nicotine can interfere with sleep and cause insomnia. While transdermal nicotine patches result in a quit rate of only 5-10%, studies have shown that biologically timed nicotine results in quit rates of 30-50%, according to Levy.

Leveraging Support Services through Technology

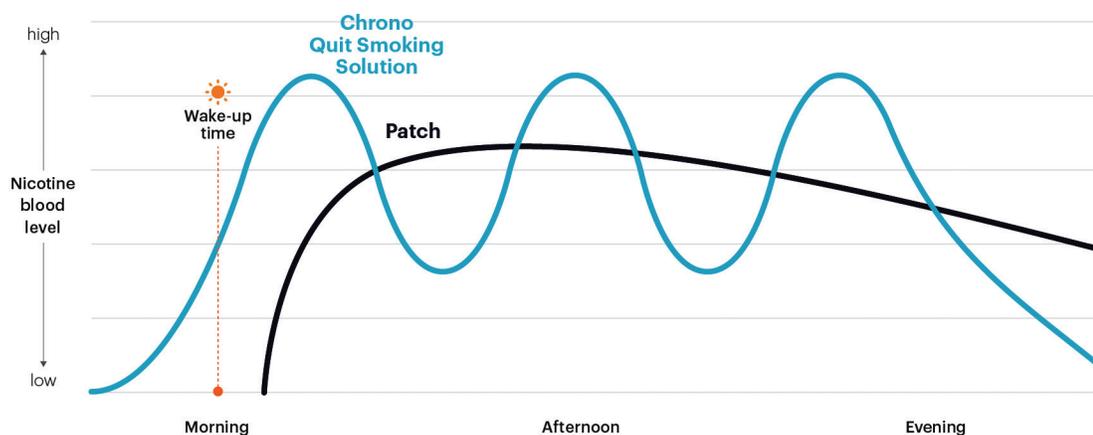
That’s only part of the solution, however. The second pillar of the company’s strategy deals with compliance.

The drug delivery pod contains sensors and is Bluetooth-enabled, so it can communicate with a smart phone (see Figure 4).

Every evening, the compliant user will put in a new nicotine cartridge, an event that sends a signal to the user’s smart phone and also to a monitoring system overseen by Chrono Therapeutics. In addition, the sensor signals when nicotine is being delivered. “We know

Figure 3

Chrono Quit Smoking Wearable Delivers Nicotine When Patients Need it Most



Source: Chrono Therapeutics Inc.

that you are using it and that you are getting the drug at the appropriate time." This feature, which provides the sense that the patient is being watched over, has proven to be important for patient engagement with wearables generally speaking, but it's particularly helpful in the smoking cessation application. Levy notes that smokers have a chemical dependency, which the nicotine replacement therapy addresses, but smoking is also a habit, which is why it's so difficult to quit. "The more support and reinforcement you can give smokers, the better they do." Levy points to studies that show that just having nurses or other professionals call smokers every two weeks helps improve quit rates. "But that is not a very scalable approach. We want to be able to reach 20 million people who are trying to quit each year in the US."

Thus, if the patient doesn't comply with changing the cartridge, he or she will get a reminder message via the program's mobile app. Through the app, patients will also get periodic encouragement, and they can become part of networks that are similar to the communities that Fitbit users set up, to compare themselves, anonymously, to others who share the same goals.

To deal with social cues that tempt the smoker, there is a "crave" button on the wearable pod. "They can press the button to record the craving and trigger an immediate response from the app: 'Take a deep breath. Walk around for a few minutes' and the craving will pass." With the patient's permission, family members can also receive alerts so they can provide encouragement and support. "All of the things that have been demonstrated to work when clinicians and other care givers call patients, we are able to do via smart phone and just in time, as opposed to every two weeks," says Levy.

The smoking cessation product doesn't yet have FDA clearance; the company will be meeting with the FDA to discuss the next studies,

which will likely revolve around demonstrating that the quantity of nicotine delivered over a 24-hour period is comparable to previously approved products.

In the near term, the company is scaling up a pilot production line of its smoking cessation product to support pivotal trials, with the goal of filing in the US and Europe at the end of 2017 or early 2018.

A Platform for Many Diseases

Chrono Therapeutics has future products in its pipeline: indications where patients will benefit from biologically timed drug delivery, compliance monitoring, and behavioral support. Parkinson's disease (PD) is one such application. Many PD patients suffer from levodopa-induced dyskinesia, or LID, and experience motor fluctuations as a result of chronic treatment with the drug. "When they wake up, they are often very stiff and have difficulty getting out of bed until they take their medication. We can deliver that drug about an hour before they get up so they can get right up and function."

While the smoking cessation product will be sold over-the-counter (OTC) at a price comparable to other smoking cessation products, the Parkinson's product would contain drug and be prescribed by a physician. The company hasn't arrived at a pricing model for this product, but it will take value into consideration. Value will be assessed in part by the degree to which, in reducing symptoms of the disease, the Chrono Therapeutics product is able to cut

Figure 4

Chrono Wearable Drug-Delivery Pod and App



Source: Chrono Therapeutics Inc.

down on office visits or take other costs out of the equation.

Levy says he's not aware of any other drug-delivery company that's wrapped its arms as broadly around the patient, but **Proteus Digital Health** comes closest. Proteus has developed a tiny ingestible sensor that can be manufactured into pills to record patient drug dosage compliance and other information. The pill communicates with a patient-worn patch that can send information to a smart phone. Proteus and **Otsuka Pharmaceutical Co. Ltd.** worked together to turn *Abilify* (aripiprazole, a treatment for schizophrenia and other severe mental illnesses) into the first "digital drug" to file an NDA with the FDA.

Levy notes that Proteus is exploring applications that provide great value, for example, for patients with neuropsychiatric problems who aren't compliant, or to improve compliance for very expensive medications. He points to *Sovaldi* (sofosbuvir, from **Gilead Sciences Inc.**) as another such an example. "It can cure Hepatitis C, but you have to stay on it for two to three months and if you stop taking it, you have to start all over again." *Sovaldi* costs \$80,000 for a course of treatment. "If you can improve compliance, there are enormous savings to the healthcare system." 📱