SOUND MEDICINE

Illustrations by Sydney Smith

Everyone from rock stars to nonagenarians experiences hearing loss, but no drugs have ever been approved specifically to prevent or treat this problem. Recently, a handful of drug companies have started to make some noise, with a number of experimental compounds now in human trials. **Elie Dolgin** sounds off on what could be a multibillion dollar market.

Sonja Wittermann woke up in her Munich apartment with a dull pressure in her left ear. She got out of bed, but "I was not sure if I was standing right," Wittermann recalls. It was 1 April 2009, but this was no April Fools' joke. "I recognized that there was something very wrong."

Wittermann rushed to seek medical attention at the nearby Ludwig Maximilians University Grosshadern Clinic, where she was diagnosed with idiopathic sudden sensorineural hearing loss, a mysterious one-sided deafness condition with no known cause that affects approximately one in 10,000 people per year. Wittermann, 30 years old at the time, had lost 30% of the hearing in her affected ear.

The standard of care for treating idiopathic hearing loss, if caught early enough, is a gradually diminishing course of corticosteroids. According to a large US clinical trial published last year, more than 75% of people who experience sudden deafness respond to steroids if treated within two weeks, and around 20% totally recover their hearing[1]. Physicians, however, don't really know why the steroids work.

"For us, [steroid therapy] feels a lot like chicken soup—it won't hurt, it might help," says Steven Rauch, an otologist at the Massachusetts Eye and Ear Infirmary (MEEI) in Boston who led the work. "That's a simplification. It can hurt. But we're so comfortable with the spectrum of side effects that we feel pretty safe offering steroids as a treatment."

Because steroids are far from perfect, researchers and drugmakers have been on the hunt for more targeted drug therapies. One of these experimental agents was offered to Wittermann on that April day three years ago. Instead of receiving steroids, Wittermann, who helps run a large restaurant with a beer garden in Munich, signed up to participate in a phase 2 trial testing a compound known as AM-111. This peptide drug inhibits an enzyme called c-Jun N-terminal kinase, which is involved in so-called 'cell suicide', or apoptosis, in the inner ear, a major contributor to permanent hearing loss. She received an injection through her eardrum—an experience that sounded "like thunder," Wittermann says—and a week later half of the lost hearing returned. It has stayed that way ever since.

Wittermann still doesn't know if she received a placebo injection or one with the active drug, and the results of the trial, which launched in late 2008 and involved more than 200 people at some 20 sites across Germany, Poland and the Czech Republic, won't be known until later this year. But Markus Suckfüll, an audiologist at the Martha-Maria Hospital in Munich who is leading the trial, is cautiously optimistic. "Having an apoptosis inhibitor that you can use locally—I think that's a clever idea," he says. "The risks are very low, but the possible benefits are high."

AM-111, which is being developed by

the Swiss company Auris Medical, is one of only a few so-called 'otoprotective' drugs—compounds that stop damage in the ear before it starts or becomes permanent—in human testing. To date, "no large pharma company has a hearing-loss prevention branch," notes Kathleen Campbell, an audiologist at the Southern Illinois University School of Medicine in Springfield. "None."

That may soon change. Recently, the big players in the drug industry have started investing in the hearing space, mostly through partnerships and licensing agreements that remain in the preclinical stage. In 2010, for example, the Swiss drug giant Novartis inked a $214 million deal to co-develop gene therapy treatments for hearing loss together with Maryland-based GenVec. And, last year, France's Sanofi signed a two-year agreement with the Dutch biotech firm Audion Therapeutics to advance small-molecule drugs capable of regenerating sensory hair cells in the inner ear.

Listening to the market

These actions speak to the growing recognition of a huge untapped market, with one in five Americans over the age of 12 now reporting some degree of hearing loss, according to a recent report[2]. Age-related hearing loss is the most common problem, notes Ralph Holme, head of biomedical research at Action on Hearing Loss, a London-based nonprofit. But "trying to design a clinical trial to test something against age-related hearing loss could be quite a headache," he says. The disease has many driving factors, and it typically progresses quite slowly. As such, "things like noise-induced hearing loss and ototoxicity will be more attractive."

They could also be quite lucrative: Action on Hearing Loss has pegged the drug market for noise-induced hearing loss at around $2 billion, with other hearing-related indications adding even more value. That's only a fraction of today's $6 billion hearing implants and devices market, but the new drugs could offer some key advantages. For one thing, drugs are neither uncomfortable nor cosmetically off-putting, two common complaints of hearing aids. But, moreover, otoprotective agents should offer real therapeutic value.

"Hearing aids and cochlear implants work well, but neither of them is like true hearing," says Jonathan Kil, president and chief executive of Sound Pharmaceuticals, a Seattle-based start-up with an experimental drug for hearing loss in phase 2 testing. "The ability to hear pure tones and to discriminate

speech requires this complex effort, involving input from many structures in the cochlea, and that complexity demands some repair of critical structures and regeneration."

Still, despite ample preclinical evidence showing that many drugs work in various rodent models of noise-induced hearing loss, including mice, guinea pigs and chinchillas, translating those findings to humans has proven difficult. For one thing, notes David Weber, president and chief executive of San Diego–based Otonomy, finding participants for placebo-controlled trials is a tall order. "Both from a patient perspective and a clinical perspective, to be treating someone with a placebo when all the clinical evidence says there's a response to [existing] steroids is just hard to consider," Weber says. Last year, Otonomy reported positive phase 1 trial results showing that OTO-104, the company's novel sustained-release formulation of the steroid dexamethasone, improved the symptoms of an inner-ear disorder called Ménière's disease better than a placebo comparator. But, to complete that 44-person trial, the company had to enlist 15 hospitals across the US, and some of these sites, such as the MEEI, didn't manage to sign up a single participant.

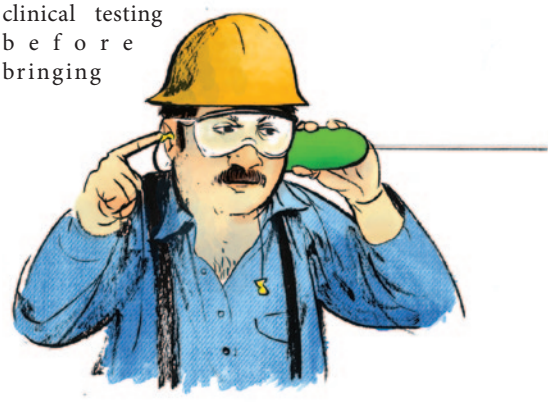
Trial recruitment is further complicated because participants need to be enrolled within the small timeframes during which the otoprotective drugs are expected to have therapeutic benefit. For example, in Auris's phase 1 study of the AM-111 compound that Wittermann later received, the company advertised on radio stations and in the subway systems of Munich and Berlin in late December 2005 in hopes of finding people who ultimately experienced firecracker-induced hearing loss during celebrations on New Year's Eve. "We probably had the world's shortest enrollment period," says company chairman and managing director Thomas Meyer. "It was just one single day: January 1st."

Yet, among all the residents of these two of Germany's most populous cities, only 28 individuals showed up on New Year's Day. Of these, the 11 who had experienced sufficient hearing loss to be eligible for the trial were treated between 11:40 a.m. and 10:20 p.m. (One person had a piece of a firecracker in his ear canal, but after the object was removed, his hearing improved and he didn't qualify for treatment anymore.) The phase 1 data looked promising, with two participants experiencing improvements of more than 28 decibels, a level that far exceeds what is normally seen in people who spontaneously recover from noise trauma[3]. But, on the basis of the recruitment experience in that small trial, Auris decided to advance the drug mostly for idiopathic, rather than noise-induced, hearing loss in its next phase of development.

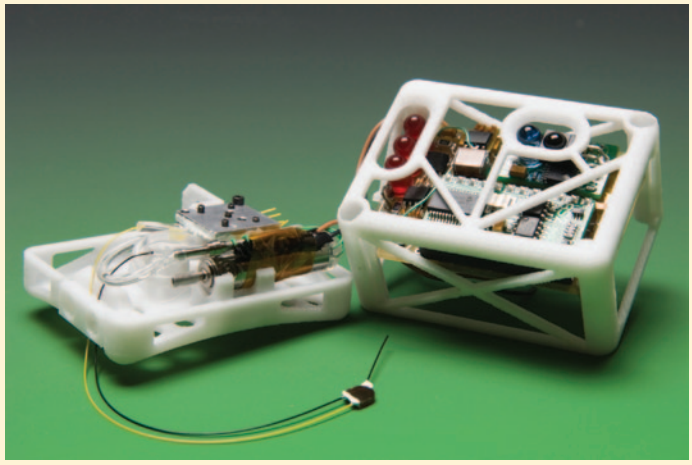
Take two and hear me in the morning

Because AM-111 is injected into the middle ear, it must be administered by a trained health professional. From a practical standpoint, however, a pill that can protect hearing is preferable, especially for the many types of people who are exposed to continuous loud noises at the workplace, such as military personnel and factory workers. "Local administration to the cochlea is not a viable option for these people," says Eric Bielefeld, a hearing researcher at Ohio State University in Columbus. "Most noise-prevention drugs would need to be something you can take on a daily or semidaily basis." (Some researchers are even testing implants to deliver drugs directly to the cochlea of the inner ear, although those devices remain many years away from human testing; see 'Innermost desires'.)

One of the first modern oral drugs advertised specifically for hearing loss hit the market in 2003. 'The Hearing Pill' was sold online by San Diego's American BioHealth Group (ABG) as a 'nutraceutical', a type of dietary supplement that doesn't require clinical testing before bringing



Innermost desires


Draper Laboratory

The inner ear is called the 'bony labyrinth'—and for good reason. This essential part of our hearing organ consists of a maze of skeletal cavities, including the snail-shell–shaped cochlea, the target of most agents designed to combat hearing loss. Unfortunately, getting drugs into the cochlea has proven a complex puzzle.

Many compounds in pills don't cross the blood-cochlear barrier and come with off-target effects, whereas drugs injected into the space behind the ear drum don't always permeate from the middle ear into the organ's inner recesses. Thus, for deeper drug penetration, some researchers have been working on implantable devices that can directly deliver compounds into the inner cochlear fluid.

The most advanced such model is being developed by Jeffrey Borenstein and his colleagues at the Charles Stark Draper Laboratory in Cambridge, Massachusetts. By combining a microfluidic pump, a drug reservoir, an electronic control system and tiny tubing, Borenstein's team has devised an apparatus that could one day be implanted in the temporal bone just behind the human ear to provide long-term drug delivery in a controlled and timed manner.

"Bringing it to clinical fruition is really what we're aiming to do," says Borenstein, whose group is working to miniaturize the device, with plans to build a prototype suitable for human clinical trials in 2015. "You can take out quite a bit of that [bone] and not do anything structurally that would cause any problems. That's what the surgeons tell me."

In collaboration with auditory scientists at the nearby Massachusetts Eye and Ear Infirmary in Boston, Borenstein's team is first testing a prototype on guinea pigs: a contraption about the size of a ring box, with all the components connected to a thin tube surgically implanted in the cochlea. The researchers had tried strapping the device (pictured) to the rodents' backs, but that didn't work. "We started referring to them as 'Little Houdinis' because they literally managed to get out of every jacket or backpack we designed for them," says Erin Pararas, a Draper scientist. The group eventually found a workaround by fastening the pods surgically to the top of the guinea pigs' heads.

Currently, the researchers are using the device to infuse a chemical called 6,7-dinitroquinoxaline-2,3-dione (DNQX), which temporarily blocks signals between sensory hair cells and nerve fibers leading to the brainstem by blocking glutamate receptors. Thanks to the fact that hair cells close to the entrance of the cochlea pick up higher-frequency sounds than cells further down the length of the coiled tube do, the researchers can track where the drug has traveled using a series of hearing tests. In the future, they plan to switch over to agents that protect or even help regenerate, rather than hinder, the ear's most delicate structure.

"Implantable-type devices are all in the fairly early stages," says David Borkholder, a biomedical engineer at the Rochester Institute of Technology in upstate New York who is working on an intracochlear drug delivery system in mice. "But I view them as an essential tool that will enable advanced deafness therapy research and development beyond what people do today." *—ED*

to market. Based on intellectual property developed by Richard Kopke, a former ear surgeon at the Naval Medical Center in San Diego, the drug contained an antioxidant called *N*-acetylcysteine (NAC), which is used as a prescription drug to counteract acetaminophen overdose and as a nutraceutical for its liver- and lung-protective functions.

In extensive preclinical testing, Kopke and many others showed that NAC protected against various forms of hearing loss, including loud noise, by scavenging the free radicals that form during and after the metabolic stress and contribute to acquired deafness. But the results from human testing were more lackluster. A 2003 Navy trial, the largest conducted to date, enlisted 566 Marine recruits undergoing two weeks of weapons training with M-16 rifles. Subjects in the still-unpublished study were randomized to receive 900 milligrams of NAC or placebo three times a day with each meal for the duration of the boot camp.

According to Kopke, who helped run the trial, less than a third of the recruits, all of whom wore ear plugs for protection, experienced any hearing loss, and, for those people who did, the NAC treatment only reduced the occurrence of significant hearing loss by about 25%. However, a similar follow-up study in another population of recruits-in-training that tested a higher dose of NAC and controlled for smoking and painkiller use found no such effect.

"There may be some suggestion of benefit, but there are some statistical measures that don't support this," says Michael Hoffer, a Naval Medical Center neurotologist who was not involved in the two trials but who has worked with the study authors testing NAC in other settings, including in soldiers fighting in Iraq.

Beta testing

"The Hearing Pill was really a beta test for the concept, and the concept was, 'Will people buy an orally dosed nutraceutical to address

and treat sensorineural hearing loss?'" says David Karlman, chief executive of American BioHealth Group. The answer was a resounding 'yes'. "We sold several thousand bottles."

Nonetheless, ABG stopped promoting the product to focus on a new combination approach that, according to Karlman, "will allow us to take the best of NAC and make it better." In 2009, Karlman, together with Kopke and Robert Floyd, head of experimental therapeutics at the Oklahoma Medical Research Foundation in Oklahoma City, launched Otologic Pharmaceutics to advance a dual-compound pill containing NAC and another antioxidant, α-phenyl-tert-butyl nitrone (HPN-07). In the 1990s, Floyd showed that HPN-07 helped protect against oxidative damage in the central nervous system, which then led the British drug giant AstraZeneca to develop the drug for the treatment of stroke. (It ultimately failed in phase 3 testing.)

Earlier this year, Kopke, Floyd and their colleagues reported that the two-drug combo, called NHPN-1010, significantly reduced the amount of damage to the ear's outer hair cells as well the synapses of the auditory nerve and the brainstem in rats exposed to blast-induced hearing loss[4]. "Our preliminary data looks like it's synergistic in its action. We find that HPN-07 seems to be more protective of the outer hair cells, and NAC might preserve neurons better," says Kopke, now retired from the Navy and working as chief executive of the Hough Ear Institute in Oklahoma City. "This is going to be quite a bit more effective than either drug by itself." In March, Otologic received $2.4 million from the US Department of Defense to launch a phase 1 trial of the combination in healthy individuals.

Even if NAC—with or without another drug—never fully pans out, many researchers are still hoping that other antioxidants will prove their therapeutic worth. For example, Kathleen Campbell is leading a 600-person, Department of Defense–funded trial testing oral liquid suspensions of an antioxidant amino acid called D-methionine given to drill sergeant instructors during and after their 11-day weapons training. Campbell, together with Colleen Le Prell of the University of Florida in Gainesville, is also planning to test a combination of antioxidant vitamins and minerals at either a military airbase or at a metal stamping factory in Spain.

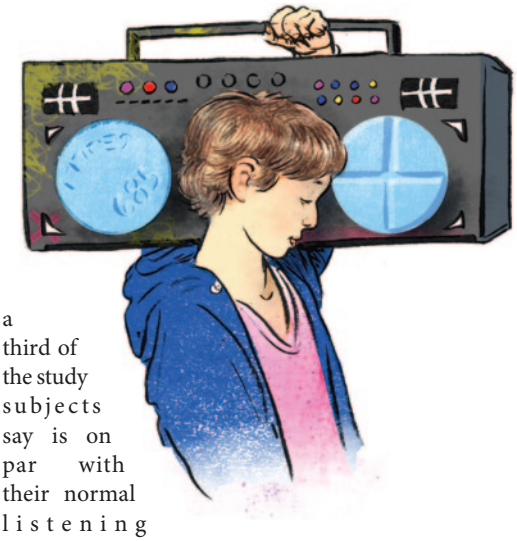
But Le Prell is not putting all of her eggs in one basket. "We're going to need more than one solution," she says. "We don't have one birth control pill, one cholesterol drug, one blood pressure medication. If we can develop many [hearing] drug options, everyone wins, especially the people who need it the most."

Last year, Le Prell teamed up with Seattle's Sound Pharmaceuticals to test SPI-1005, an oral preparation of a small molecule called ebselen that mimics and prompts production of the enzyme glutathione peroxidase 1. In animal models, ebselen has been shown to help stop oxidative injury and stress in a range of ailments, including diabetes, ischemic stroke, acoustic trauma and hearing loss caused by chemotherapies, such as cisplatin, which are well known to damage people's hearing ability. The drug was rejected by Japanese authorities after completion of clinical trials of the drug there for the treatment of stroke, owing to poor efficacy data. But Sound Pharmaceuticals' Kil remains confident that ebselen will help repair the hair cells of the outer ear and protect other cochlear structures in the inner ear, thereby reducing the levels of both temporary and permanent hearing loss.

A 32-person study completed in 2007 showed that SPI-1005 was safe and bioavailable in healthy people[5]. To follow up, Sound Pharmaceuticals had planned to conduct a phase 2 trial in military recruits undergoing weapons training at the US Naval Medical Center in San Diego (as Kopke had done with NAC). But, after failing to get that trial off the ground, the company turned to a new study population exposed to loud sounds: college students listening to music on their iPods. Earlier this year, Sound Pharmaceuticals launched an 80-person interventional trial led by Le Prell.

Hear me baby one more time

The students in the iPod study are being given SPI-1005 or a placebo twice daily for four days and are then asked to listen to four hours of music through headphones. Study subjects can choose whether to listen to a selection of Top 40 pop songs, including hits by Britney Spears, Kelly Clarkson and Rihanna, or a rock music playlist with tunes by Aerosmith, Billy Idol and Bon Jovi, among others. Both options maintain a steady 100 decibels throughout—about the same loudness as a motorcycle—which around



a third of the study subjects say is on par with their normal listening volume. They are then tested for any changes in their hearing thresholds. At the same time, the company is running an equally sized trial testing SPI-1005 for the treatment of chemotherapy-induced hearing loss at the US Department of Veteran Affairs Puget Sound Health Care System in Seattle.

Recently, even big pharma has started to enter the clinic. In December of last year, New York–based Pfizer started recruiting people with age-related hearing loss for a phase 1 trial involving a compound that is also in development for the treatment of schizophrenia.

Hearing experts say they are encouraged by the growing number of experimental treatments entering human testing, but, given the lack of phase 2 efficacy data, most are reserving judgment. "Until the final word is in, I think it's better to be hopeful than not, especially when dealing with medical treatments that can prevent hearing loss or recover hearing loss before it becomes permanent," says Gordon Hughes, program director for extramural clinical research at the US National Institute on Deafness and Other Communication Disorders in Bethesda, Maryland. "But we need more rigorous scientific evidence."

Given the heightened commercial activity in the hearing field, that plea does not seem to be falling on deaf ears.

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