



Research on ‘regenerative’ treatments don’t support clinics’ claims

By Laura Beil

Joanna had just turned 62 when she noticed that she couldn’t stand very long before her right leg would hurt. She thought it was from an old injury, when her dog had slammed into her thigh. When the ache moved to her wrist, she went to a doctor who said she might be getting arthritis.

The pain quickly intensified. “It just happened so rapidly, and I couldn’t figure out why,” says Joanna, who lives in a Houston suburb. Her doctors chalked it up to wear and tear. “You’re getting older,” she remembers them telling her. This was in early 2018.

Then she got an e-mail with a link to a video about stem cells and the conditions they could cure, including arthritis. “I started watching it and then I just turned it off for a while because I thought, ‘I’m afraid I’m going to get my hopes up too high,’” says Joanna, who asked that her last name not be used to protect her medical privacy.

She started seeing full-page ads for stem cell seminars in the newspaper. She attended one at a local hotel, and the presenter

announced that thousands of patients had benefited from stem cell injections. It was natural, the woman said. No one had ever been harmed. The idea that the treatment wasn’t a drug reassured Joanna.

She made an appointment for the next day. “It sounded too good to be true, but I was desperate,” she says. She received injections into her back, neck and shoulder of stem cells from donated umbilical cord blood followed by an IV of the product the next day. The cost was \$30,000, siphoned from her husband’s pension. She knew she was taking a risk, but she felt hopeful.

Two days later, her face began to burn and itch. Then her feet. She had pain in places that had never hurt before, like the joints of her fingers. Her hair started falling out, and she descended into a deep depression. “I’m totally miserable,” she says, months later. “I’m just agonizing in pain.... Now I don’t see any hope.”

Stem cells sold at clinics are driving what’s thought to be a \$2 billion global industry. Facebook pages announce seminars.

1,000

Estimated number of U.S. clinics offering stem cell treatments

Local newspapers are wrapped in ads vowing “relief without surgery.” Stem cells are billed as treatments for everything from autism to multiple sclerosis to baldness. Most commonly, the ads focus on orthopedic issues, especially aching knees.

An important point gets left out of the cheery ads: There’s not enough science to justify using stem cells for any of the advertised conditions, including joint pain. None of the treatments advertised have been approved by the U.S. Food and Drug Administration. (The only approved stem cell treatments are for certain cancers and blood disorders.) Very few of the orthopedic studies in humans have been scientifically rigorous, and none have shown stem cells regrowing cartilage.

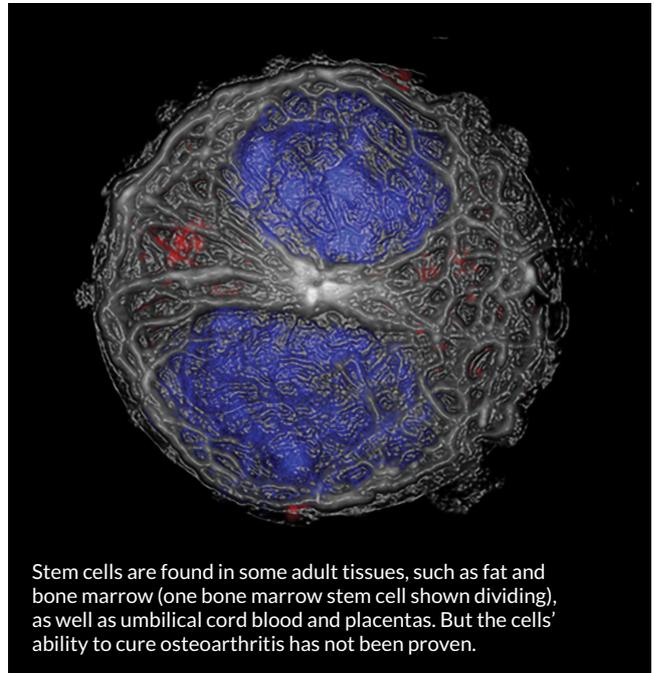
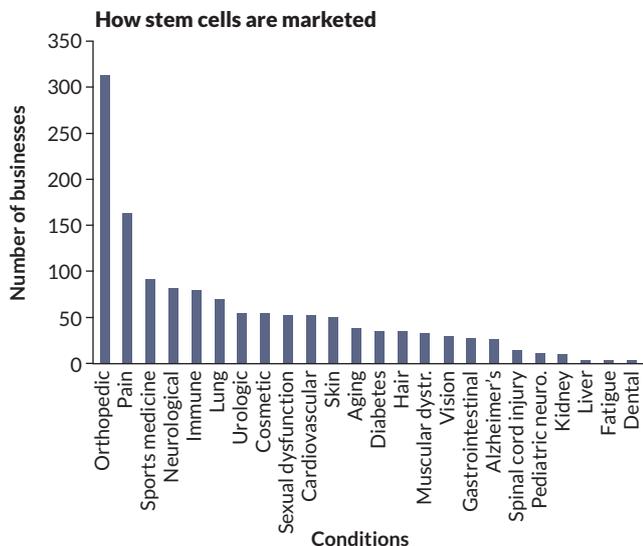
It’s not even clear whether treatments being touted as “stem cells” contain viable stem cells or whether the contents should be defined as stem cells at all. As the stem cell industry grows rapidly, many researchers who are studying stem cells for their potential to regenerate tissues worry that the booming marketplace, which conflates hype with reality, might ultimately damage research progress.

“The scientific and medical community is having to play defense,” says Shane Shapiro of the Mayo Clinic Jacksonville in Florida, who has conducted one of the very few published trials that compared stem cells with a placebo for people with osteoarthritis. “Misinformation and misunderstanding about how cells are used to treat disease is proliferating.”

Early infamy

The explosion of advertising reflects a dramatic turnaround from the controversy over stem cells that occupied the public in the early 2000s. At the time, scientists had learned how to generate lines of cells from embryos that were left over from in vitro fertilization and donated for research. In theory, the embryonic cells had the potential to treat disease by becoming

Seeking relief U.S. clinics advertise stem cells to treat a variety of diseases (top ones shown below), but most treatments are for orthopedic conditions and pain. SOURCE: L. TURNER AND P. KNOEPFLER/CELL STEM CELL 2016



Stem cells are found in some adult tissues, such as fat and bone marrow (one bone marrow stem cell shown dividing), as well as umbilical cord blood and placentas. But the cells' ability to cure osteoarthritis has not been proven.

a slew of different tissues, but their use became entangled with the politics of abortion. Then in 2001, President George W. Bush banned federal funding for research on embryonic stem cell lines not already in labs. Embryonic stem cell research has ridden the political tides since then: Restrictions were eased under Barack Obama’s presidency, then Donald Trump’s administration added restrictions on fetal tissue use.

Scientists tried to persuade the public to support the research by focusing on the great promise. They argued that stem cells might one day cure diseases by naturally repairing lost or damaged tissue. Actor Michael J. Fox, the most famous Parkinson’s patient of his generation, testified to Congress in 1999 that stem cells could one day cure degenerative brain diseases. Joanna remembers Fox’s passion. “That’s what kind of made us aware of what stem cells were at the time,” she says.

Broadly speaking, stem cells are cells capable of renewing themselves and taking on the identity of the tissue around them (*SN*: 3/19/16, p. 22). The early controversy about using embryonic cells has largely quieted down. The stem cells being marketed today are not embryonic; they come from bone marrow, fat tissue or birth products such as umbilical cord blood or amniotic fluid, all advertised as being able to regenerate cartilage. Clinic websites usually feature earnest testimonials with no hint of any possible negative side effects.

Free market

For the first part of the 2000s, stem cell treatments were largely sought through medical tourism. U.S. patients would travel to other countries for experimental treatments to cure diseases such as multiple sclerosis or spinal cord injury.

Bioethicist Leigh Turner of the University of Minnesota in Minneapolis noticed a shift around 2012. “One of the businesses

that ... was part of that marketplace, a company in South Korea, ended up popping up in the United States,” he says. The company, operating under the name Celltex, offered to remove stem cells from a patient’s own fat tissue, grow the cells in a lab and then reinject them.

When the FDA sent a warning letter to the company in September 2012 stating that its products must be approved before use in patients, the company moved its treatments to Mexico. Regulations there are less stringent, though the business remains headquartered in Houston.

Today, many clinics have learned how to operate just inside the margins of federal regulations, or simply ignore them. Turner and Paul Knoepfler of the University of California, Davis mapped the rise in U.S. stem cell clinics that market unapproved therapies, reporting in 2016 in *Cell Stem Cell*. The first few clinics emerged about 10 years ago, Turner says. “By 2014, 2015, companies are pouring into the marketplace at a very rapid rate.”

Knoepfler estimates that today more than 1,000 clinics across the country offer stem cells, though there are probably more because many doctors and chiropractors have simply added stem cells as a sideline to their main services. For some, stem cells are lucrative enough to support a business on its own. One in 4 stem cell providers in the Southwest offers the treatment exclusively, researchers at Arizona State University reported in August in *Stem Cell Reports*.

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SHANE SHAPIRO

The business is extremely profitable, and the treatments are rarely covered by insurance. Patients pay cash — sometimes draining their life savings, taking out loans or drawing down retirement funds like Joanna did.

“Often, when you go to business websites, there’s not this kind of sober, frank, judicious accounting of risks and benefits — or the possibility that there might be no benefit, that someone could be harmed,” Turner says. The websites “tend to frame risks and benefits in a very misleading kind of way.”

And because each year tens of thousands of U.S. patients — by Knoepfler’s estimate — are getting cells in clinics outside of clinical trials, it’s difficult to know exactly what the risks of the direct-to-consumer marketplace are. No one is keeping track.

In 2018, researchers writing in *Stem Cells Translational Medicine* resorted to searching Google and the scientific literature, where they found 35 reports of serious consequences. Some patients in Florida lost their sight after getting stem cell injections into their eyes. In December, the FDA warned of “serious illnesses” in Nebraska linked to treatments with “exosomes,” products taken from placentas that are offered by some stem cell clinics.

A recent survey of neurologists, presented in March 2019 in Dallas at a meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis, asked doctors how their patients had fared after receiving unapproved stem cell treatments. About 25 percent of the 204 neurologists who responded said patients had suffered serious consequences such as strokes and seizures. Three doctors reported that patients had died. Without study, it’s impossible to know why.

The evidence on knees

It makes sense that treatments for knee pain appear to dominate the industry — the potential customer base is large and growing. More than 600,000 people in the United States had knee replacement operations in 2014, according to data released in 2018 by the American Academy of Orthopaedic Surgeons. That number is expected to rise as baby boomers age and obesity rates climb. As the body ages, shock-absorbing cartilage in the joints wears away, which can lead to painful bone-on-bone rubbing. Stem cells are advertised as an easy way to avoid surgery.

So far, though, it’s not clear that’s true. Recently, Maarten Moen, a sports medicine physician at Bergman Clinics in Naarden, Netherlands, and his colleagues reviewed every clinical trial he could find that examined using stem cells for knee osteoarthritis. “Stem cells are prohibited for use in Holland,” says Moen, a member of the medical staff of the Dutch Olympic Committee. “That’s why we were conducting this: to see if we could convince people in our country to possibly start using this therapy. But only if we answer these two questions: Is it helpful? And also, is it safe?”



Thousands of patients are paying cash for stem cell injections into their joints to cure their arthritis. But proof of effectiveness is lacking, and there’s no evidence that the injections can regrow cartilage.

The group's results appeared in 2017 in the *British Journal of Sports Medicine*. The team found only six human studies testing stem cells for knees, and none were large trials that included a placebo comparison. While the treatment appeared safe, effectiveness couldn't be determined. Every study had methodological problems. As a result, the authors didn't recommend stem cells for knee osteoarthritis. Moen has recently updated his review, but those results have not yet been published. He offers a preview: "The evidence didn't get any stronger." He found only two clinical reports that had compared the treatment with a placebo.

Both were from Shapiro, of the Mayo Clinic. "It's been nearly three years since we first published our early results," Shapiro says. With his trial as "the first piece of the puzzle," he expected that, "like anything else in science, we would be followed by a bunch of other trials." So far, other published results have not been pouring in.

Shapiro and colleagues from the Mayo Clinic and Yale University School of Medicine had tested 25 patients with mild knee osteoarthritis in both legs. The researchers took about 50 milliliters of cells from each patient's bone marrow, concentrated the cells in the laboratory and then injected them back into one knee of each patient. The other knee got an injection of saline as a placebo. The patients did not know which knee got the experimental treatment.

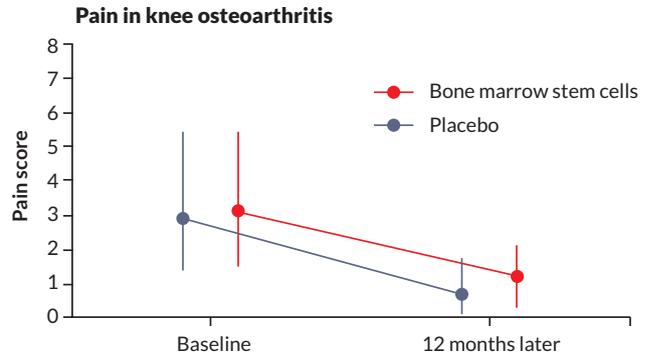
Both the stem cell knee and the placebo knee improved by about an equal degree — about 50 to 75 percent on a pain scale, the team reported in 2017 in the *American Journal of Sports Medicine*. "We weren't able to conclude that the stem cell product was any superior in pain relief to anything else," he says. "Additionally, we did not see any cartilage regrowth." A 12-month follow-up published in October in *Cartilage* found similar results.

The fact that the saline alone helped patients feel better was not surprising. A meta-analysis published in 2017 in the *American Journal of Sports Medicine* examined whether simple saline injections helped knee pain. That review, by researchers at Rush University Medical Center in Chicago and the University of Toronto, found that saltwater alone provided relief on the level of some drugs. But why the knees that got the bone marrow cells in Shapiro's study improved to an equal degree is still unclear, he says. So he's not yet ready to say the stem cells don't work.

"What I think actually happened is that we injected a therapeutic substance in one of their knees, and we injected a nonharmful substance, which is the saline, in the other knee, and the patients were able to get back to their life for a period of time that overall made them feel better," he says.

The Mayo study tested stem cells from the patients' own bone marrow. But clinics also offer cells from the body's fat tissue, extracted by liposuction. Doctors can use enzymes to strip away extraneous cells from the fat, leaving only the regenerative cells. But that therapy is also unproven. One study, conducted by researchers in Australia and published in February 2019 in *Regenerative Medicine*, involved 30 patients

No difference In one of the only placebo-controlled studies of stem cells for knee osteoarthritis, a placebo shot (blue) was as effective in reducing pain as an injection of stem cells from the patients' own bone marrow (red). SOURCE: S.A. SHAPIRO ET AL/CARTILAGE 2019



with knee osteoarthritis. Patients who received stem cells from fat reported a 69 percent improvement in their pain, compared with no change in a comparison group that did not receive the treatment. But that study offered no placebo injection for comparison.

A second study, by a South Korean team, had a placebo, but a small number of patients. Twelve patients who received stem cells from their own fat had a 55 percent improvement in pain (based on their responses to a questionnaire) compared with no substantial improvement among 12 patients who got a placebo shot, the researchers reported in March 2019 in *Stem Cells Translational Medicine*. Cartilage didn't regrow with stem cells, but it didn't shrink, which it did in the placebo group.

But the treatments in those studies differ from what is actually offered at stem cell clinics. In both of those studies, the researchers expanded or concentrated the cells in the laboratory before injecting them into patients — a practice that is allowed in the United States only in a scientific study. Under FDA rules, U.S. stem cell centers are only allowed to move a patient's own tissue from one place to another, with little manipulation of the cells, otherwise the treatment may be considered an unapproved drug.

Sports medicine physician Kenneth Mautner and colleagues at Emory University in Atlanta compared outcomes for 76 patients with arthritis who received a treatment that was closer to what doctors can do in their offices. Each patient received either cells taken from their own bone marrow or from fat tissue. In both cases, the cells were simply moved to another place within the patient's own body. After six months, both groups showed pain reductions and neither treatment was better than the other, the researchers reported in the November 2019 *Stem Cells Translational Medicine*. "There was about 70 to 75 percent improvement for those who actually did improve," Mautner says. About one-quarter of the patients did not get better. Patients with more advanced arthritis were less likely to benefit.

But his study had that common shortcoming: no placebo comparison. "When you're paying a lot of money, there's obviously a

placebo effect,” Mautner says. “It’s not just your mind convincing you that you feel better. The placebo effect can actually be chemicals and cytokines that then produce anti-inflammatory effects in your joints.”

In addition to bone marrow and fat tissue, a growing number of clinics are offering products made from donated umbilical cord blood or other birth products, Knoepfler says. Those cells are easy to administer and don’t require the expertise to extract cells from the body.

But if there is little evidence for the effectiveness of stem cells from fat and bone marrow, Shapiro says, “there is zero support” for umbilical products in human studies. “I’m not even studying them yet,” he says.

No regrowth

Hardly any evidence supports the idea that treatments marketed as “stem cells” can regenerate worn tissue, which is what many patients think they are buying. “There’s very little evidence that it will regrow your cartilage,” says orthopedic surgeon Jason Drago of the University of Colorado Denver.

His research team is conducting a study to see whether there are treatments that might increase cartilage thickness. One study pairs the cellular treatment with surgery. The existing tissue may be more receptive to regrowth, he says, “if you clear away the debris and all the other things, get it as ‘cleaned up’ as possible, then give the cells.” He’s also conducting a study comparing the ability of cells from fat to repair tiny tears in cartilage that is otherwise mostly healthy, a process he compares with filling potholes.

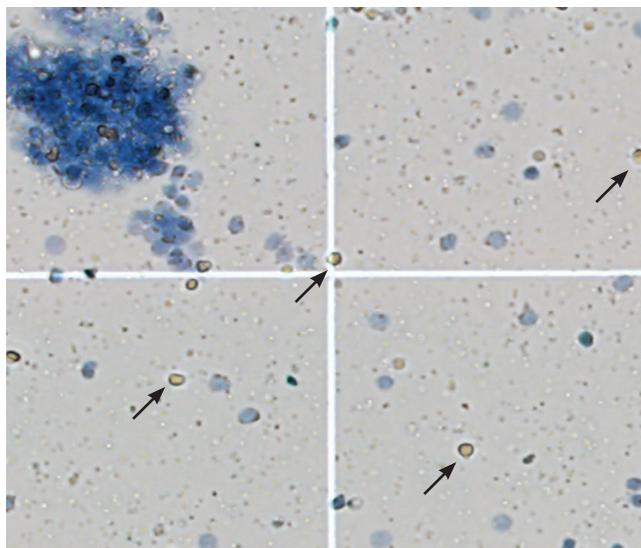
But even if cartilage won’t regrow, he and others say, the procedure may still reduce inflammation, which could quiet a painful knee. There’s also early evidence from animal studies that cells from bone marrow or fat might send chemical signals that jump-start a person’s own healing.

Biomaterials scientist Sowmya Viswanathan of the University of Toronto and colleagues reported a study of 12 patients receiving bone marrow cells in August in *Stem Cells Translational Medicine*. The study had no control group. “We saw improvement in symptoms, in pain, in quality of life and in joint stiffness for all the patients. These are the things that the patients care about. The fact that it doesn’t regenerate cartilage doesn’t disprove its ability to still be a functional, useful cell therapy,” she says. It might work, but maybe not in the way that patients expect.

All in a name

Viswanathan worries that the current stem cell market is exploiting the work of scientists, piggybacking off of the legitimate — but early — studies for immediate commercial gain, she says.

“Everything gets called stem cells. Nomenclature is still very important because if you can’t name it properly, then you don’t even know that you’re talking about two different or three or four different things,” she adds.



Some experts question the viability of stem cells taken from umbilical cord blood or placentas. In this analysis of one product, 70 percent of the cells were dead, as shown by the blue stain. The arrows point to live cells.

Many clinics call the cells in their products “mesenchymal stem cells,” a term taken from a 1991 paper by biologist Arnold Caplan of Case Western Reserve University in Cleveland. Yet in 2017 in *Stem Cells Translational Medicine*, Caplan advocated for a name change: “Stem cell misconceptions have led some practitioners in the United States and worldwide to advertise the availability of stem cell treatments (i.e., MSCs can cure the blind, make the lame walk and make old tissue young again).”

Viswanathan and other members of the International Society for Cellular Therapy published a position statement in October in *Cytotherapy* that cells commonly identified as “mesenchymal stem cells” should more precisely be called “mesenchymal stromal cells” in the scientific literature to reflect the lack of evidence that, when used as a medical treatment, those cells can renew themselves and form different tissues. (Stromal cells form the body’s connective tissue.) As long as everything is called “stem cells,” she says, clinics focused on profits will be able to exploit legitimate research for marketing purposes.

And there are so many questions left to answer. She worries about what happens when people have bad reactions, like Joanna did. “We don’t fully understand repeat injections. We don’t know the dosing. If there is an adverse event, then what?” she says. “Then it sets back the kind of legitimate work that’s being done because the difference isn’t apparent to the funders and to the lay public because everyone’s calling it exactly the same thing.” ■

Explore more

- International Society for Stem Cell Research. “Nine things to know about stem cell treatments.” bit.ly/9thingsonstemcells

Laura Beil is a contributing writer based in Texas. Her most recent podcast, “Bad Batch,” is about the stem cell industry.

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