

HEALTH

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THE HEALTHY SKEPTIC

Can a pill protect us from the sun?

Heliocare may help head off UV damage, but it's no substitute for sunscreen.

CHRIS WOOLSTON

Have you ever slathered on sunscreen but somehow managed to miss your nose? Or the back of your hand? Or the tops of your feet? You're not the only one. According to the American Academy of Dermatology, most people apply less than half of the optimal amount of sunscreen, a habit that adds up to a lot of burned patches and uncomfortable rides home from the beach.

If you don't completely trust your sunscreen skills, you might be interested in Heliocare, a supplement that promises sun protection in a pill. Each Heliocare capsule contains 240 milligrams of an extract of *Polypodium leucotomos*, a tropical fern rich in antioxidant compounds such as caffeic acid and ferulic acid.

Users are instructed to take one capsule every day with water or juice. Two capsules are recommended before heavy exposure to the sun.

Heliocare is sold at major drug stores including CVS, Walgreens and Wal-Mart. A bottle of 60 capsules costs about \$50.

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MARK RALSTON AP/Getty Images

FEAR: Travelers at LAX wear masks as a precaution.

A CLOSER LOOK:
H1N1 swine flu virus

Some viruses have history of foreshocks

JILL U. ADAMS

H1N1 swine flu may be fading from the news some, but the number of confirmed cases nationwide has been higher than is usual for seasonal flu in the month of May. What does that mean? Is this flu's ability to linger into the spring suggestive of how different a beast it is? And what does it portend for how the virus might infect Americans over the summer and come fall?

The Centers for Disease Control and Prevention publishes confirmed cases of the novel H1N1 swine flu virus each week. The official count of probable cases in the U.S. as of Friday was 8,975 in 49 states with 15 deaths. However, the total number of people infected in the country is estimated to be as high as 100,000, says CDC spokesman Joe Quimby, taking into account those who were sick but

[See Closer, Page E6]

FUN WAYS TO GET A MOVE ON

E6



TOUCHING THE BRAIN

Getty Images / 3D4Medical.com

Electrical therapy, used for years to treat movement disorders, may soon tackle depression and more.

ANDREAS VON BUBNOFF >>> Under the skin, a battery is surgically implanted — generally within the upper chest. From the battery, wires snake up to the head, to tickle different targets deep inside the brain.

Such is the hardware for deep brain stimulation — the equivalent of a cardiac pacemaker for the mind.

Until recently, deep brain stimulation was approved in the U.S. only to treat certain movement disorders, primarily those of Parkinson's disease, for which it diminishes tremors and rigidity and improves mobility. To date, more than 60,000 patients worldwide have had the devices implanted.

But now use of the technique seems set to mushroom.

This year, the Food and Drug Administration granted a so-called humanitarian device exemption for the treatment to be used in severe cases of obsessive-compulsive disorder — the first approval of deep brain stimulation therapy for any psychiatric condition.

Large clinical trials are also in the works for use of deep brain stimulation for epilepsy and depression, and experimental studies in the U.S. and elsewhere — still in their early stages — are exploring the treatment for obesity, traumatic brain injury, severe chronic pain, Alzheimer's disease, anorexia, tinnitus and addiction.

There are discussions too on the possible use of deep brain stimulation to treat hypertension.

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DAVID M. GROSSMAN Associated Press
BRAIN SURGERY: The device is implanted in a patient.

WORDS OF CAUTION

Better studies of deep brain stimulation are needed and there are dangers in rushing, some experts say. Much is still unknown about how it works. **E5**

OBESITY AND BEYOND

Deep brain stimulation is being tried for Alzheimer's, traumatic brain injury, even anorexia. Can it truly help? latimes.com/health

Go carefully, experts warn

ANDREAS VON BUBNOFF

With the flurry of tests being done on deep brain stimulation for a variety of conditions, some warn that the field is moving too fast.

They say it must not repeat the mistakes made during the era of lobotomy surgeries between 1939 and 1951, when thousands of patients were treated with little or no proof that lobotomies worked and with little or no follow up.

"There is a very bad history in psychiatry," says Dr. Helen Mayberg, professor of psychiatry and neurology at Emory University in Atlanta. "I don't want people to jump the gun and blow it for everybody."

Adds Dr. Thomas Schlaepfer, vice chairman of the department of psychiatry of the University of Bonn, Germany, "I [have] reviewed studies for obesity, anorexia, shyness, addiction, the most crazy indications you can think about. Everyone wants to get in the game early. . . . If things go haywire it might kill the whole field."

For one thing, deep brain stimulation is brain surgery. There can be complications — such as bleeding, stroke, coma, death and infection.

Other risks may depend on where the electrodes are placed in the brain. After deep brain stimulation for Parkinson's disease, for example, patients may have problems with swallowing, obsessive compulsive disorder, gambling and dementia, and there may be an increased suicide rate.

It is unclear, Mayberg says, whether these effects are related to the stimulation or merely reflect the progression of the disorder.

Mayberg says that, over five years, no side effects have been observed in patients treated for depression with deep brain stimulation in a part of the brain called area 25. Perhaps, she speculates, the area where deep brain stimulation is done in Parkinson's disease patients has more signal traffic between nerve cells than does area 25.

But Schlaepfer suggests that side effects aren't yet observed in patients treated for depression because the number of treated patients is still too small.

Schlaepfer says the two large clinical trials being conducted on deep brain stimulation for depression may be premature.

In a trial, he says, one needs to keep the area of stimulation constant in every patient. But only about 50 depressed patients so far have been treated with deep brain stimulation, and "it's just not enough to make an informed decision on what the right target [in the brain] is," he says. "This research is mainly driven by industry and not by public funding, [and] it's going a little bit too fast for my taste."

Dr. Joseph Fins, chief of the division of medical ethics and a professor at Weill Cornell Medical College in New York, thinks the Food and Drug Administration may have acted too soon in granting a "humanitarian device exemption" to deep brain stimulation for severe obsessive-compulsive disorder.

Puzzling process

Surprisingly little is known about how deep brain stimulation works, in spite of the fact that tens of thousands of Parkinson's and other movement disorder patients have been treated with the therapy.

"Right now it's not only not known which cells are the target, but also if they turn [their activity] up or down" in response to the stimulation, says Dr. Karl Deisseroth of Stanford University. "It's that level of confusion."

In the case of Parkinson's disease, stimulation of the brain's subthalamic nucleus has the same effect as damage to the subthalamic nucleus. In other words, even though the treatment stimulates the subthalamic nucleus, it may have the same effect as inhibiting it.

In other cases — for example in treating minimally conscious patients — deep brain stimulation seems to have the opposite effect to damaging the targeted brain area.

— ANDREAS VON BUBNOFF

This will allow patients to receive the therapy outside of clinical trials, he says — and there won't be a systematic collection of data, making effectiveness that much harder to establish.

In addition, small experiments on just a few patients don't always get published, says Dr. Andres Lozano, professor of neurosurgery at the University of Toronto and president of the World Society for Stereotactic and Functional Neurosurgery. "Sometimes there are only two patients," Lozano says. "Then, unless [the findings] are published, you don't necessarily hear about them."

Some have suggested guidelines for patient selection. And in a February editorial in the journal *Biological Psychiatry*, Dr. Wayne Goodman of the National Institute of Mental Health and NIMH director Dr. Thomas Insel called for a registry of all deep brain stimulation studies to make sure that all cases get follow-up to learn what does and doesn't work.

Deep brain stimulation research also raises ethical questions, such as how to make sure patients who may have diminished capacity to consent understand the risks and benefits of participating in the trials. In 2007, researchers met to discuss such issues. Recommendations will be published in an upcoming paper.

Some issues with deep brain stimulation have to do with what happens when the procedure succeeds. One of his depression patients, Schlaepfer says, lost his girlfriend because she couldn't deal with his newly found independence.

"She didn't like [that] he was not a poor guy anymore and started to be more normal," Schlaepfer says, "which was something [we] never anticipated."

health@latimes.com

Deep brain stimulation: new uses?

[Brain, from Page E1]

"The field is taking off," says Dr. Ali Rezaei, director of functional neurosurgery at the Cleveland Clinic, who has been involved in research on movement disorders, traumatic brain injury, obsessive-compulsive disorder and severe depression, among others.

Some researchers warn, however, that with all this activity — pushed in part by the industry that makes the brain-stimulation devices — the field may be moving too fast.

"There is so much progress that's been made and so much potential — you would hate to lose that potential," says Dr. Joseph Fins, chief of the division of medical ethics and a professor at Weill Cornell Medical College in New York.

Here's a look at deep brain stimulation as it moves beyond Parkinson's disease. (See the related story about reservations scientists have about the growth of the field, and go online at latimes.com/health for a look at less-explored applications such as traumatic brain injury and obesity.)

Obsessive-compulsive disorder

In studies with a total of 26 patients with severe obsessive-compulsive disorder, 60% of those whose device was turned on demonstrated "very much improved" symptoms after months of deep brain stimulation as measured by interviews and questionnaires, says Dr. Benjamin Greenberg, an associate professor at Brown University Medical School and Butler Hospital in Providence, R.I., who was one of the study researchers.

The patients had previously failed on medicines as well as behavioral cognitive therapy.

Yet the data, published last year in *Molecular Psychiatry*, can't really nail the effect of the treatment, Greenberg says, because the patients for the most part knew whether their devices were turned on or off. Thus, researchers can't rule out that some of the observed improvements were due to a placebo effect.

Patients were stimulated in an area called ventral capsule/ventral striatum, chosen, in part, because removal of nerve fibers in that area is known to cause improvement in obses-



DAVID M. GROSSMAN Phototake via AP Image

PROCEDURE: More than 60,000 Parkinson's patients have had deep brain stimulation surgery, shown above.

sive-compulsive symptoms.

Based largely on these findings, the FDA recently granted a limited humanitarian device exemption that permits the device to be used in as many as 4,000 of the country's most severe cases of obsessive compulsive disorder per year.

To get this kind of exemption, Medtronic — makers of the only deep brain stimulation device that is FDA-approved — needed only to show its safety and probable benefit.

Greenberg is now doing a randomized, double-blinded trial with 30 patients, some of whom have devices turned on right away and some who have them turned on after a delay. No one will know whose device is turned on for the first several months of the trial.

Epilepsy

Medtronic has conducted a large-scale randomized trial for deep brain stimulation on epilepsy. Data will be submitted to the FDA this year, says Paul Stypulkowski, senior director of therapy research of Medtronic.

The device was turned on, for three months, in half of the 110 volunteers, stimulating — and thereby, paradoxically, inhibiting — an area called the anterior nucleus of the thalamus. That area is believed to influence a circuit involved in seizures.

The data, presented in December at a meeting in Seattle, show that deep brain stimulation reduced the number of seizures by 38% compared with what was seen before implanting the device.

That is slightly better than improvement seen with vagus

nerve stimulation, another FDA-approved electrical stimulation treatment, which reduces seizures by about 25%.

The control group whose device was kept turned off, also improved, by 14.5%. That could be due to a placebo effect. Or it might be because people who join trials are usually at their worst — and often tend to improve somewhat on their own, says trial researcher Dr. Douglas Labar, of the Weill Cornell Medical College in New York.

If deep brain stimulation is approved, Labar says, patients will have the choice between a more efficient but also more risky treatment and the slightly less efficient but also less risky vagus nerve stimulation.

Depression

Medtronic and a second company, St. Paul, Minn.-based St. Jude Medical, have two large-scale randomized trials underway for severe, treatment-resistant depression. (St. Jude Medical recently received approval to sell its device for the treatment of Parkinson's disease in Europe and is now completing studies aimed at securing FDA approval for treating Parkinson's and another movement disorder in the U.S.)

Medtronic's depression trial will follow about 200 patients stimulated in an area called the anterior limb of the internal capsule for at least one year.

This brain target for depression was identified by accident: When obsessive-compulsive disorder patients who also had depression were stimulated in this area, their depression also improved.

In one case, a patient pro-

duced a one-sided smile when stimulated on one side of the brain and also expressed feelings of happiness, says study researcher Dr. Wayne Goodman of the National Institute of Mental Health.

In a recently published unblinded study, about half of 15 patients showed at least a 50% improvement in severe depression symptoms a year or more after surgery when the anterior limb of the internal capsule was stimulated, says Rezaei, who was involved in the study.

St. Jude Medical chose a different brain target, area 25, for its depression trial, which will enroll more than 100 patients. Brain imaging studies have shown that area 25 is more active in depressed people.

In a study of 20 patients, 55% still responded to treatment as late as one year after surgery, says study author Dr. Helen Mayberg, professor of psychiatry and neurology at Emory University. That is an "unheard-of response rate" given that these patients had tried and failed every other treatment, including several medications and electroconvulsive therapy, Mayberg says.

By comparison, Mayberg says, stimulation of the vagus nerve in the neck, approved by the FDA for depression, has only a 15% response rate at 10 weeks in similarly severely depressed patients.

Dr. Thomas Schlaepfer, vice chairman of the department of psychiatry of the University of Bonn in Germany, has been treating severely depressed patients by stimulating yet a third brain target, the nucleus accumbens.

The nucleus accumbens doesn't show normal activity in depressed patients, which could explain why they are less able to experience pleasure.

Last year, Schlaepfer showed that deep brain stimulation in this area led to acute improvements in three severely depressed patients. He says he has extended the work to 10 patients, half of whom showed an improvement when examined a year later.

With deep brain stimulation now being tried in at least three brain areas for depression, the question is, which target is the best? All agree that it's too early to tell.

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Deep brain stimulation being tested with brain injury, Alzheimer's, obesity and more

But tests for DBS' use with traumatic brain injury, Alzheimer's, obesity, anorexia and addiction are being conducted on small numbers of patients and not in formal clinical trials.

By Andreas von Bubnoff

June 1, 2009

Other conditions

Deep brain stimulation for depression and epilepsy is already being tested in large clinical trials, but it has only been tested in a few patients for other conditions such as traumatic brain injury, Alzheimer's disease, obesity, anorexia and addiction.

Reports, when published, are of only a few people and are not part of formal clinical trials with placebos or blinded participants and scientists. Thus, though the data are intriguing, they must be viewed very guardedly, researchers say.

Brain injury: Dr. Nicholas D. Schiff at Weill Cornell Medical College in New York was part of a team that used deep brain stimulation to help a man who was in a minimally conscious state after a traumatic brain injury.

The man had been hit on the side of the head, which caused bleeding and swelling of the brain. He was initially in a coma, then in a vegetative state for about 12 weeks and then in a minimally conscious state for six years.



His eyes were closed much of the time, he could not swallow, and he had to be fed by a tube in his stomach, Schiff says. On rare occasions, he could move his thumb to trigger a communication device. He did utter words on rare occasions but could not give verbal responses in formal testing.

The man received deep brain stimulation in the central thalamus, an area in the middle of the skull that controls arousal, sleep and wakefulness. After treatment, he could chew and swallow, communicate in short sentences and use his hands or limbs to demonstrate the functional use of objects.

This is the first case, Schiff says, where deep brain stimulation has clearly been shown to improve people with traumatic brain injury. To prove that deep brain stimulation was the reason for the man's improvement, the six-month study had one-month-long phases where the device was turned on or off and his condition was observed to get better or worse.

He also was at the "higher end" of a minimally conscious state, in that he could follow commands. Schiff says that in other cases, such as Terri Schiavo, the 41-year-old brain-damaged woman who became the centerpiece of a national right-to-die battle, deep brain stimulation didn't work because the brain damage was just too great.

Schiff says the team has Food and Drug Administration approval to treat 12 patients.

Obesity: Dr. Andres Lozano, professor of neurosurgery at the University of Toronto and president of the World Society for Stereotactic and Functional Neurosurgery, used deep brain stimulation to treat obesity in a 420-pound man.

The patient lost about 25 pounds but later regained the weight. One possible reason? He turned off the device at night to snack.

That's why patients in the first deep brain stimulation-obesity experiments in the U.S. don't have the option to turn off their devices, says Dr. Donald M. Whiting of the Allegheny General Hospital in Pittsburgh, who is conducting the U.S. obesity trials with colleague Dr. Michael Oh.

So far, only two patients have been treated, chosen because they failed numerous diets as well as gastric bypass surgery.

Carol Poe from Morgantown, W. Va., joined the trial in February and says that nine weeks after the device was turned on she had lost 11.5 pounds.

But it's too soon to say if the therapy worked, Whiting says, because the initial effects could be due

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Deep brain stimulation being teste...

to a placebo effect from the surgery -- the patient knew you did something and thus expects a change that may not last.

Whiting has FDA approval to treat just three patients for now. He says he stimulates -- and thereby theoretically down-regulates -- the lateral hypothalamus, a brain area that acts as the feeding center of the brain. Animals with damage in this area simply stop eating.

The theory, Whiting says, is that the area has a certain density of receptors for hunger hormones that determine a person's metabolism level and energy set point, and the stimulation changes that.

Indeed, Whiting says, he does get the appropriate responses from the patients during the surgery. When he hits the right spot with the electrode, they report feeling nauseated, and even belch.

Alzheimer's: Lozano of the University of Toronto is also using deep brain stimulation to try to improve memory in patients with mild or early Alzheimer's disease.

Lozano discovered the area he stimulates by accident. While stimulating the hypothalamus to treat obesity in his 420-pound patient, the man -- who was under only local anesthesia -- remembered things from his life that happened 20 years earlier.

"He got a flashback," Lozano says. "He was in a park with his girlfriend. He could tell us what kind of day it was, what kind of clothes he was wearing, what they were saying, et cetera. As we turned off the stimulation, this memory would go away [and when] we turned it back on, it would reappear immediately." The case was published last year in the *Annals of Neurology*.

Lozano also found that whenever the electrode was on, the man remembered pairs of related words in a test better than when it was off. And brain imaging showed that the stimulation turned on the memory circuit in his brain.

Lozano has now started a pilot study to treat patients who have mild or early Alzheimer's disease. "We have operated on six patients so far," Lozano says. "So far, it appears safe and promising."

Addiction and anorexia: Dr. Bomin Sun, associate professor of neurosurgery at the Shanghai Jiatong University Rui Jin Hospital in China, has been testing deep brain stimulation for treating people with heroin addiction and anorexia. He targets the nucleus accumbens, inhibiting that brain region. Brain imaging shows that this area becomes overly active in people with these conditions, Sun says.

Sun has so far used deep brain stimulation to treat three anorexic girls who refused to eat and had body mass indexes of less than 14 when they were treated. He says they are now all back to

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Deep brain stimulation being teste...

normal weight.

He also treated two heroin addicts. One, he says, is cured, and the other only needs to take methadone once a day instead of heroin injections, he says. Neither of the findings are published in journal articles, although the heroin addiction cases are to be published in an upcoming book, "Neuromodulation."

health@latimes.com

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