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**JOURNAL SENTINEL**

# Side Effects

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By John Fauber

# Researchers get royalties, papers omit sterility link

Doctors receiving funding differ from others on complication

By JOHN FAUBER

jfauber@journalsofmedicine.com

Since 2002, Medtronic and a group of doctors with financial ties to the medical device company were aware that a new biological agent used in back surgery was linked to sterility in men.

But that crucial information was not revealed in medical journal articles written by those doctors, including surgeons who would receive millions of dollars in various royalties from Medtronic.

Prompted in part by Journal Sentinel stories, independent researchers at Stanford University looking at their own patients have found strong evidence connecting the lucrative product to retrograde ejaculation, a condition that causes sterility in men.

Though original data linking the product to the complication was included in information sent by the company to the Food and Drug Administration as part of the approval process in 2002, those doctors were still claiming there was “no relationship” between the product and the complication as recently as last year.

Medtronic and the doctors contend that the sterility complication was caused by surgical technique, not the product. But professional guidelines and independent doctors contacted by the newspaper say serious complications should be listed in published papers, regardless of what they assume to be the cause.

A new Journal Sentinel analysis found that last year alone Medtronic paid more than \$6 million in royalties to a handful of doctors who over the last nine years co-authored papers about the product, known as Infuse, without cautioning that it was linked to male sterility. None of the royalty payments was for Infuse.

One of the authors, Thomas A. Zdeblick, is a University of Wisconsin School of Medicine and Public Health orthopedic surgeon. Zdeblick and Taz Consulting have received more than \$23 million in various royalty payments from Medtronic since 2002. Zdeblick also is the editor of the journal where two of the Infuse papers that failed to mention the link were published.

Last year, a Journal Sentinel investigation found that doctors who had financial relationships with Medtronic produced substantially better results with Infuse in the clin-

ical trial leading to its FDA approval than doctors who did not have financial ties to the company.

The newspaper articles documented growing concerns about Infuse side effects and how associated surgeons authored research that has been criticized as little more than marketing.

Meanwhile, Medtronic is under investigation by the U.S. Department of Justice on allegations of off-label marketing of Infuse, a case that could be settled in the near future with civil and criminal penalties, according to a Wells Fargo analyst’s report issued last month. Companies are not allowed to promote their products for unapproved, or so-called “off-label,” uses.

The Stanford study linking Infuse to increased risk of sterility, which is being published online Wednesday in the Spine Journal, a publication of the North American Spine Society, was done by independent surgeons.

“To have such strong evidence that a life-changing complication of sterility exists and then cover it up in my opinion is obscene,” said Charles Rosen, an orthopedic surgeon and president of the Association for Medical Ethics who has read the Stanford study.

As a result, thousands of men may have become sterile without knowing that the product even posed such a risk, said Rosen, a clinical professor of orthopedic surgery at the University of California, Irvine.

In an email, Ken Burkus, a Columbus, Ga., surgeon who co-authored four of the papers, said the link between Infuse and the complication was not mentioned in the papers because it was not deemed to be “statistically significant.”

But that claim was undercut by original data provided to the FDA that stated the sterility complication rates were at least five times greater in the Infuse patients. Stanford researchers found a similar outcome in their own Infuse patients.

Asked about his obligation to share such information with other surgeons and their patients, Burkus said in an email statement:

“These concerned physicians, surgeons and colleagues have several avenues to address these concerns. They can contact the FDA. They can contact the office of medical

affairs at Medtronic. They can contact their local or national medical societies. They can write a ‘letter to the editor’ at the journal in which the manuscript was published.”

Burkus, whose RBCK Research & Consulting was paid \$782,000 in various royalties by Medtronic last year, declined to say whether financial relationships played a role in the failure of the papers to report the complication rate among the Infuse patients.

Under growing pressure from Congress, the Justice Department and the public, drug and medical device companies have recently begun listing payments to doctors.

“My co-authors and I made the appropriate and required disclosures for the journals in which the manuscripts were published,” he said in an email. “I do not make the rules for these journals — I just try to follow the rules as best I can.”

#### **Latest issue**

The sterility issue is the latest question raised about Medtronic’s Infuse, known in the spinal field as bone morphogenetic protein-2, or BMP-2, a genetically engineered substance used in spinal fusion surgery. The product has generated annual sales of several hundred million dollars because it eliminates the need to obtain a small amount of a patient’s own hip bone to create a fusion between vertebrae.

However, since its approval for use in some spinal fusion surgeries, a series of complications, including some that are life-threatening, have emerged.

A 2002 paper co-authored by UW’s Zdeblick, Burkus and two others said there were no “unanticipated” adverse events related to Infuse in the clinical trial of the product. The paper was published in the *Journal of Spinal Disorders & Techniques*. Zdeblick has served as editor-in-chief of that journal since 2002.

Despite that conclusion, data from the Infuse clinical trial submitted to the FDA showed a link between the product’s use and retrograde ejaculation.

That connection was never mentioned in at least four published papers by a group of doctors with strong financial ties to Medtronic, the *Journal Sentinel* found. In two of the papers the complication was attributed to surgical technique, not Infuse. In two other papers, the complication was not mentioned at all.

In an email responding to the Stanford paper, Zdeblick said different researchers can reach different conclusions.

“As a practicing surgeon, I would certainly want to know if Infuse leads to higher complications,” he said. “Personally, I have not seen this. In my experience there is no direct link between Infuse and RE (retrograde ejaculation).”

In their findings, the Stanford School of Medicine researchers concluded that multi-

ple lines of evidence strongly suggest that Infuse increases the risk of retrograde ejaculation.

The Stanford researchers went back and looked at 243 of their own patients who underwent spinal fusion surgery between 2002 and 2004, after Infuse was approved. They compared rates for the complication with or without the product. They also compared their findings with the original FDA data.

The review found that retrograde ejaculation occurred in more than 7% of Stanford’s male patients treated with Infuse, compared with less than 1% of those who received a standard graft. The Stanford group’s complication rate with Infuse was similar to the rate found in the unpublished clinical trial data submitted to the FDA.

Five of Stanford’s 69 male patients treated with Infuse developed the complication, compared with one in 174 men who got a standard graft. After one year, the complication resolved in two of the five Infuse patients.

Eugene Carragee, who headed the Stanford study and performed all the surgeries in the Stanford review, said he could not speculate on why the complication was not reported in the published articles.

“It is certainly strange,” said Carragee, chief of spinal surgery at Stanford and editor-in-chief of the *Spine Journal*. “The data was there. You don’t have to be 99% certain before you say there can be a problem.”

#### **Reporting standards**

The Consolidated Standards for Reporting Trials endorsed by many medical journals in 2004 say failing to list serious harms found in clinical trials, regardless of statistical significance, constitutes poor reporting of clinical trial results.

“With the serious possibility that RE (retrograde ejaculation) is associated with (Infuse) use in the lower lumbar spine, it is important that men be counseled about this risk and advised that avoiding (Infuse) in favor of alternative grafting methods may minimize the risk,” Carragee and his co-authors wrote.

Marybeth Thorsgaard, a Medtronic spokeswoman, said the company disclosed to the FDA that retrograde ejaculation is a potential complication related to anterior surgical procedures.

She said the company also includes information about the complication in package inserts with Infuse. The insert shows higher rates of the complication with Infuse than with the control group.

“Medtronic has been transparent about this issue on its labeling and in its PMA (pre-market approval) submission (to the FDA),” she said.

Thorsgaard also pointed to a 2010 letter published in the *Journal of Bone & Joint Surgery*. The letter was co-authored by Bur-

kus, Zdeblick and two other doctors who have received Medtronic royalties.

The letter was a response to a letter written by three doctors in Croatia who had raised concerns about Infuse causing sterility. The two letters were published together.

In their letter, the American doctors flatly denied any relationship between the complication and Infuse. They also noted that the complication eventually had resolved in five of 11 patients.

Retrograde ejaculation occurs when sperm and semen enter the bladder instead of the urethra.

It is believed that Infuse, a potent biological protein that stimulates bone growth, may have an inflammatory effect on nerves and soft tissue surrounding the spine, including on the nerves that control whether semen enters the bladder or the urethra.

While scientists know a lot about how Infuse affects bone, not much is known about its effects on other tissues, especially with the doses used for bone fusion, said James Kang, an orthopedic surgeon at the University of Pittsburgh School of Medicine, in a commentary that accompanies the Stanford paper.

#### **Concerns in Croatia**

In early 2010, the Croatian doctors began raising questions about the failure of medical journal articles to tie Infuse to retrograde ejaculation.

Tomislav Smoljanovic, an orthopedic surgeon at the Zagreb University School of Medicine, and his colleagues sent a flurry of letters to various medical journals raising concerns about retrograde ejaculation and other complications associated with Infuse.

One of the letters, which Smoljanovic shared with the Journal Sentinel, was sent to Zdeblick in February 2010. Less than a month later, Zdeblick, as editor of the Journal of Spinal Disorders & Techniques, rejected it for publication.

Smoljanovic's concerns and questions raised by Journal Sentinel stories prompted the review by researchers at Stanford.

In the main arm of the clinical trial that led to approval of Infuse, five out of 78 men who got Infuse developed the complication compared with one of 68 men who received the standard hip bone graft, according FDA records. In another arm of the clinical trial, an additional six of 57 men (10.5%) who got Infuse also developed retrograde ejaculation.

The associated doctors' denials of a connection between Infuse and the complication is at odds with other data filed with the FDA by Medtronic prior to the 2002 approval of Infuse.

In that 16-page document obtained by the Journal Sentinel from FDA files, the company states that retrograde ejaculation is a potential adverse event that may occur with Infuse.

#### **'Dramatic difference'**

Several independent doctors contacted by the Journal Sentinel say that while the surgical technique may be a factor in the development of the complication, the Medtronic authors should have stated Infuse also was linked to the condition.

"I'm concerned that the published reports don't match up with the FDA data," said Sohail Mirza, a professor of orthopedics at Dartmouth Medical School. "Our standard in medicine is to use the published literature to counsel patients."

Dan Spengler, a professor of orthopedics and rehabilitation at Vanderbilt University Medical Center, noted that the rate of retrograde ejaculation in the Infuse clinical trial was about five times higher among patients who got the product.

"It was a pretty dramatic difference," Spengler said.

"I have no idea why they didn't do it. You have to seriously question whether it was a willful thing and whether it was linked in any way to the finances."

Richard Deyo, a professor of evidenced-based family medicine at Oregon Health and Science University, said Infuse is an example of medical industry-funded studies showing a product in the most favorable light.

"I have to be worried that conflicts of interest are playing a role here and that the reports have been written in such a way that minimize undesirable effects and maximize the benefits," said Deyo, who has done research on spinal surgery. "No one wants to bite the hand that feeds them."

For public health reasons, he said, the data about retrograde ejaculation and Infuse needed to be put in those published reports.

Kang, of the University of Pittsburgh, questioned how two groups of researchers — the Medtronic-funded surgeons and the Stanford surgeons — could find similar rates of retrograde ejaculation in their Infuse patients yet come to completely different conclusions.

He said the only rational explanation is that the Stanford researchers had no commercial conflicts of interest and the Infuse studies were corporate sponsored.

In an era of public scrutiny of surgeons' conflicts of interest, "We must come to the hard realization that data analysis and interpretation in such studies can be biased in favor of funding sources," Kang wrote. "After all, it is against our nature to publish a negative result or an adverse event that condemns a product that is being studied if we are being funded by the sponsors of the product."

thors whose studies had been questioned by Smoljanovic received more than \$6 million in various royalty payments from Medtronic, according to a Journal Sentinel investigation.

“I could easily accept that my work was not always good enough to be published in selected leading journals (I did not win all races during my rowing career as well) if the rejecting decisions were supported by clear facts why our work was rejected,” he said in an email.

He said he was once told by a medical journal reviewer that as a Croatian he did not have the standing to make comments about Infuse.

Once that happened, he said, he and his colleagues began writing more letters pointing out potential problems with Infuse. He called it the “Croatian guerrilla science approach.”

#### **Downplaying risks**

Independent doctors who are familiar with the issue say Smoljanovic’s concerns about Infuse highlight a problem in medical research: Published research about industry-funded clinical trials tends to downplay risks and portray new therapies in a more positive light than non-industry funded research.

“That’s the pattern,” said Charles Rosen, an orthopedic surgeon and president of the Association for Medical Ethics who has seen the Stanford study. “A guy in Croatia comes up with something that is bad for business and they try to stop him from saying anything.”

“He comes across as an honest guy who is frustrated that nobody is paying attention,” said Dan Spengler, a professor of orthopedics and rehabilitation at Vanderbilt University Medical Center. “Now a lot of people are paying attention to him.”

Spengler preceded Zdeblick as editor of the Journal of Spinal Disorders & Techniques.

Smoljanovic said he protested Zdeblick’s rejection of his letter to the publisher of the journal. To handle his protest, two reviewers and a special editor who did not have conflicts of interest were appointed.

They too rejected Smoljanovic’s letter.

“This process was conducted under the guidance and full knowledge of our publisher,” Jonathan Kemmerer-Scovner, the journal’s editorial coordinator, assured Smoljanovic. “Dr. Zdeblick was not involved in the process in any way.”

Eventually, a letter from Smoljanovic and his colleagues about Infuse and retrograde ejaculation was published in another American journal, the Journal of Bone and

Joint Surgery. A response from Zdeblick and his co-authors was published along with the letter.

The American doctors said flatly there was “no relationship” between Infuse and retrograde ejaculation.

Retrograde ejaculation occurs when sperm and semen enter the bladder instead of the urethra.

It is believed that Infuse, a potent biological protein that stimulates bone growth, may have an inflammatory effect on nerves and soft tissue surrounding the spine, including on the nerves that control whether semen enters the bladder or the urethra.

On Wednesday independent researchers at Stanford University, spurred by Smoljanovic’s concerns as well as stories about Infuse in the Journal Sentinel, published their own findings in the Spine Journal.

The Stanford researchers went back and looked at 243 of their own patients who underwent spinal fusion surgery between 2002 and 2004, after Infuse was approved. They compared rates for the complication with or without the product. They also compared their findings with the original data submitted to the FDA by Medtronic.

The Stanford review found that retrograde ejaculation occurred in more than 7% of its male patients who got Infuse, compared with less than 1% of those who received a standard graft. The Stanford group’s complication rate with Infuse was similar to the rate found in the clinical trial data submitted to the FDA before 2002, data that was not included in the papers published by the American doctors.

The Stanford researchers said men need to know of the possibility that Infuse may cause retrograde ejaculation.

Published along with the Stanford paper in the Spine Journal was a commentary by Smoljanovic and another Croatian orthopedic surgeon.

The two doctors laid out their case for why Infuse may increase the risk of retrograde ejaculation as well as their long-standing concerns about it.

They said the categorical denial of a link between Infuse and the complication by the American doctors “was not credible.”

More than a year ago, Smoljanovic and his colleagues asked a simple question in their original letter to Zdeblick: “Should we counsel patients about the increased incidence of retrograde ejaculation . . . ?”

Now they have an answer.

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This article is part of an ongoing series about how money and conflicts of interest affect medicine and patient care. John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [medpagetoday.com](http://medpagetoday.com).

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# Infuse cited in patients' painful bone overgrowth

## More surgery needed after use, surgeon says

By **JOHN FAUBER**  
jfauber@journalsentinel.com

Enthusiasm seemed to bubble over in 1999 as a group of surgeons from around the country began to implant a new spinal fusion product in patients that initially appeared to safely grow bone and help fuse vertebrae.

Then something bad happened.

Only a few months into one of the first clinical trials of the Medtronic product known as Infuse, CT scans showed unwanted bone had formed in the spinal canal of 70% of the patients. The clinical trial, intended to include hundreds of people with degenerative disc disease, was halted after only 34 patients received Infuse implants.

In 2004, a paper written about the trial by doctors with financial ties to Medtronic maintained that patients weren't harmed by Infuse. The paper downplayed the bone growth, known as ectopic bone, saying that while it showed up on CT scans, patients did not suffer ill effects.

But David Malone, a Tulsa surgeon involved in the clinical trial, told the Journal Sentinel that two of his patients had to undergo additional surgery because the bone overgrowth was painfully impinging on nerve roots. One of the patients, a man who was in his 50s at the time, needed three operations — one for the implant, a second to remove the unwanted bone formation, and then a third when the additional bone grew back yet again, Malone said.

"It was a pretty amazing biological response," Malone said in an interview. "It grew back even larger than the first time. It got to the point that secretaries in our clinic could look at X-rays and tell who got the BMP (Infuse) and who did not. You could see that much bone growth."

Medtronic now is facing criticism on multiple fronts.

Earlier this month, a U.S. Senate committee launched an investigation into reports that doctors with financial ties to Medtronic were aware of serious complications with Infuse yet failed to reveal those problems in medical journal articles.

That follows a report last month by researchers at Stanford University that found strong evidence Infuse was linked to a complication that causes sterility in men. That

crucial information was not revealed in medical journal articles written by doctors with financial ties to Medtronic.

The doctors who wrote the 2004 paper would go on to receive millions of dollars in royalties and other payments from Medtronic.

"This is very troubling," said Richard Deyo, a physician and professor with the Oregon Health and Science University who has done research on spinal fusion. "If we can't trust the scientific medical literature to be accurate, we can't provide the best patient care."

Malone said his patient who needed two follow-up operations made a confidential financial settlement through the intercession of Ron Pickard, a top executive of the spinal division of the company at the time. Pickard, who since has left Medtronic, could not be reached for comment.

In 2002, Malone sent a letter to the U.S. Food and Drug Administration relaying much of that information. The letter was read into the record of a 2002 FDA advisory panel hearing involving Infuse. Later that year, the FDA approved Infuse for spinal fusion for a different use. The letter was not acknowledged in the 2004 paper.

### A familiar script

Infuse, also known as bone morphogenetic protein-2, is a genetically engineered product that stimulates bone growth in a confined space between vertebrae. It eliminates the need to harvest a small amount of a patient's own bone for use in spinal fusion surgery.

Infuse was allowed on the market in 2002 following a trial that involved a surgical approach to the spine from the front of the patient. The 2004 paper involved a separate clinical trial — the one that was stopped in 1999 — using a posterior surgical approach.

The approval of Infuse followed what drug industry critics say is a familiar playbook:

First, a buzz is created about a potential new therapy. Then, research — often by doctors with financial ties to the product — is presented to the FDA for a specific use in a narrow group of people. Once the product is on the market, other uses for it are promoted in articles and presentations, often by doctors with financial ties to the company.

As much as 85% of Infuse use now is in those so-called off-label applications, according to the research.

Infuse sales amount to several hundred million dollars a year.

Researchers writing in the Spine Journal this week will mention Malone's experience in the 1999 clinical trial. The Spine Journal paper is part of an unprecedented critical review of Infuse complications that were not reported in the medical literature. That review found a systematic failure to report Infuse complications over the course of nearly a decade in 13 published papers involving Medtronic-funded research.

The 2004 paper has drawn a growing amount of criticism as an example of industry-funded research on drugs and devices by doctors with financial conflicts who go on to write papers that promote those products. Doctors interviewed by the Journal Sentinel last year said the medical paper was more marketing than science.

Last year alone, the newspaper found, three of the four authors of the 2004 paper received nearly \$4 million in royalties from Medtronic through the first nine months of the year. None of the royalties involved Infuse.

#### **Other cases**

The newspaper also reported that in 2008 a different group of doctors in Denver reported on ectopic bone forming in the spinal canals of five patients who had undergone similar fusion surgery with Infuse.

In those cases, neurological impairment occurred, challenging the finding of the surgeons with Medtronic financial ties. The authors of that article did not have a financial relationship with Medtronic.

The authors of the 2004 paper acknowledged there were six follow-up operations each among the Infuse patients in the study and the patients in a control group — those who received their own hip bone graft. The authors did not attribute any of the follow-up operations in the Infuse patients to ectopic bone formation.

"Although not desirable, bone formation in the spinal canal does not appear to have a discernible effect on patient outcomes," they wrote. "Even though bone formed, no negative outcomes were found."

In an email response, Medtronic spokeswoman Marybeth Thorsgaard would not address questions specifically about the follow-up operations in Malone's patients and why they were not mentioned in the paper. She also would not comment on whether Medtronic reached a confidential financial settlement with one of the patients.

She said that before the clinical trial started, patients were told that ectopic bone was a possible complication.

"It was listed as an anticipated adverse event in the trial design, and patients were made aware in their signed consent forms," she said in an email. "The article makes the point that there were no adverse events in the trial that we did NOT recognize as a potential risk."

She said there was an early report about the ectopic bone that was presented at a spine-related medical meeting in October 2001.

She also said that when Infuse came on the market in 2002, it included a warning of potential ectopic bone, especially if it was used in a manner similar to the halted clinical trial.

She said financial ties between the authors of the paper and Medtronic were acknowledged in the paper.

#### **Medtronic royalties**

Regis Haid, lead author of the 2004 paper and an Atlanta neurosurgeon, did not respond to attempts to reach him for comment. Through September last year, Haid and Spinal Engineering LLC received about \$2 million in royalties from Medtronic.

Co-author Ken Burkus, a Columbus, Ga., surgeon, also did not respond to emails. His RBCK Research & Consulting received \$573,000 in royalties from Medtronic through nine months of last year.

Charles Branch Jr., one of the co-authors of the 2004 paper and chairman of neurosurgery at Wake Forest University, took issue with Malone's assessment that the follow-up operations were caused by bone growth related to Infuse. Branch and Wake Forest received a total of \$1.2 million in royalties through the first nine months of last year.

While Branch did not agree to be interviewed, he directed questions to Bonnie Davis, media relations manager at Wake Forest Baptist Medical Center.

Referring to Branch's relationship with Medtronic, Davis said: "It is very unfair to automatically impugn someone or their motives because they have a relationship. Dr. Branch's particular financial relationship was unrelated" to Infuse.

Davis continued: "To the best of Dr. Branch's recollection from 10 years ago, no one could be certain that the reoperations on Dr. Malone's patients were Infuse related or surgeon related or vagaries. . . . Dr. Malone made the decision to re-explore those patients after they had persistent symptoms and had exuberant bone growth."

"Frankly, to state that these were device-related complications might have been erroneous," Davis added. "These were reoperations based on the surgeon's clinical

judgment that the patient might be helped with a re-exploration.”

**Has no doubt**

However, Malone said he has no doubt the ectopic bone formation and need for reoperations were caused by Infuse.

“I was sure I was right (then),” he said. “I am sure I am right today.”

He said he stopped enrolling patients in the trial after the complications in his two patients.

“After the first patient had trouble with the overgrowth of bone, I lost my enthusiasm to enroll anyone else in the study,” he said. “It was a very upsetting thing to be a part of.”

Malone said he later invented a device that could be used with Infuse that is designed to keep bone growth out of the spinal canal. He said he was granted a patent on it last year, and he has sold the rights to DePuy, a spinal products company that is part of Johnson & Johnson.

Doctors who were not involved in the 2004 paper said that even if there was a dispute about whether the follow-up operations were caused by Infuse, that information should have been presented in the paper — especially since the disagreement pitted the authors’ opinion against a surgeon who had firsthand knowledge of the patients.

“The ‘first do not harm’ principle of medical ethics would say the first priority should be that the authors must be very cautious against saying the drug is safe

when it is not,” said Eugene Carragee, a Stanford University spine surgeon. “Is the corporate interest the priority or the patient safety the priority?”

Carragee is the lead author of the main review article about unreported Infuse complications as well as a critical editorial that will be published Wednesday in the *Spine Journal*. He also is editor-in-chief of the journal.

**Cause ‘ignored’**

In an interview last week, Charles Rosen, an orthopedic surgeon and president of the Association for Medical Ethics, said the 2004 paper “conveniently ignored” the cause of the follow-up operations.

“Ethically, intellectually and for the sake of objectivity in research, I believe there is an obligation to report this,” said Rosen, a clinical professor of orthopedic surgery at the University of California, Irvine.

The 2004 paper was published in the *Spine Journal*, where Branch served as deputy editor. He became editor-in-chief a couple months later after the paper was published.

He said he did not use his influence as an editor to get the paper published.

“Absolutely not!” spokeswoman Davis said. “The manuscript review process excluded Dr. Branch from any consideration of this manuscript.”

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JUNE 29, 2011

# Experts repudiate Medtronic's research

Medical journal devotes entire issue to exposé

By JOHN FAUBER  
jfauber@journalssentinel.com

Doctors who received millions of dollars from device maker Medtronic repeatedly failed to reveal serious complications linked to the company's lucrative back surgery product in 13 papers they co-authored for medical journals over the course of nearly a decade, according to a scathing new review.

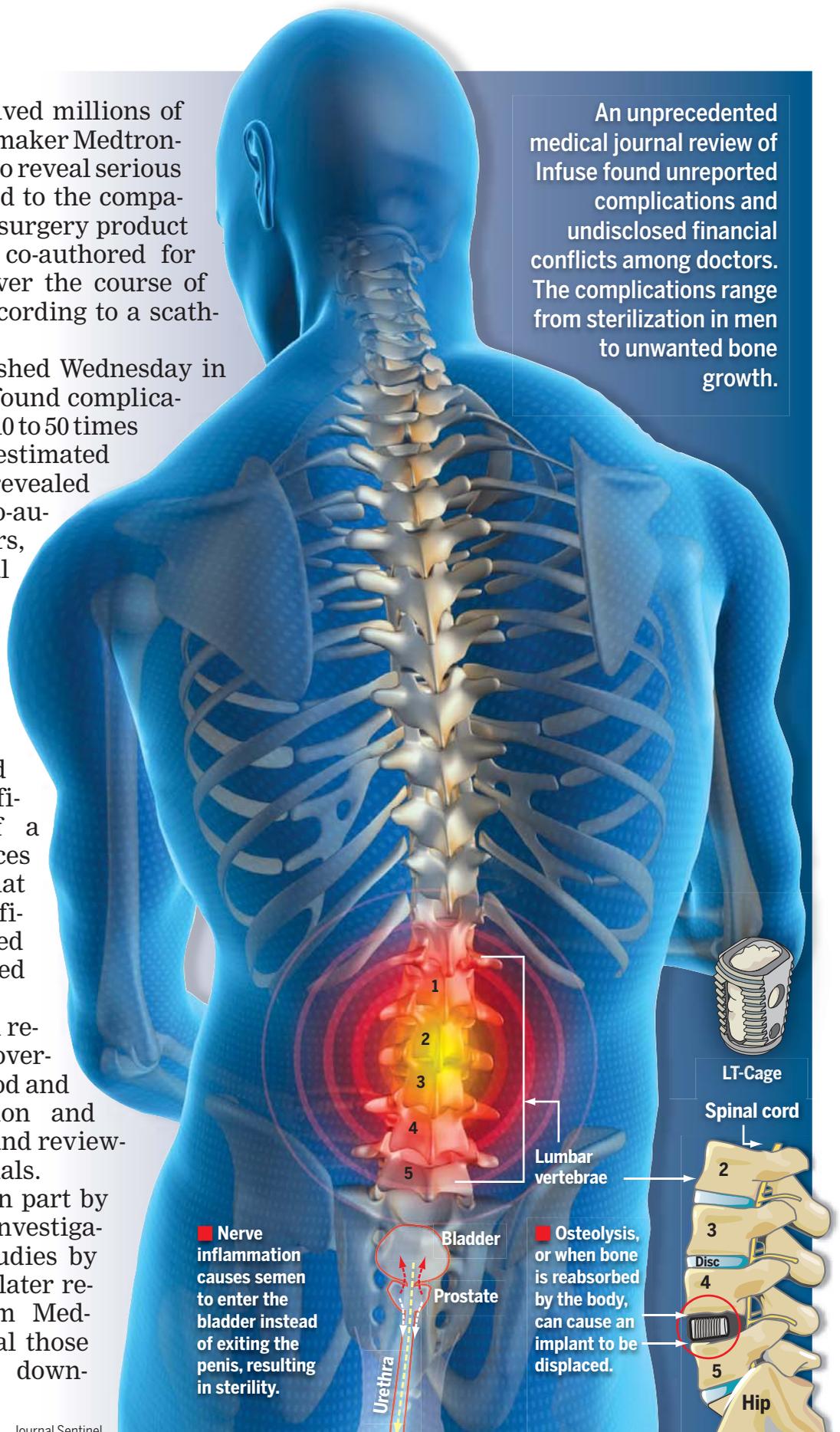
The review, published Wednesday in the *Spine Journal*, found complication rates that were 10 to 50 times greater than the estimated complication rates revealed in the papers co-authored by the doctors, who had financial ties to the company.

The analysis is part of an unprecedented event in medicine: The entire issue of a medical journal devoted to a scientific and financial exposé of a product, the practices of the company that markets it and the financially conflicted doctors who tested and promoted it.

The *Spine Journal* review also cites lax oversight by the U.S. Food and Drug Administration and failures by editors and reviewers of medical journals.

It was prompted in part by Journal Sentinel investigations that found studies by doctors who would later receive millions from Medtronic did not reveal those financial ties and down-

An unprecedented medical journal review of Infuse found unreported complications and undisclosed financial conflicts among doctors. The complications range from sterilization in men to unwanted bone growth.



played serious side effects with the product, known as Infuse.

Last week, also citing the newspaper's work, a U.S. Senate committee launched an investigation into reports that doctors with financial ties to Medtronic were aware of serious complications with the product yet failed to reveal those problems in medical journal articles.

In the main analysis published Wednesday, editors of the *Spine Journal* found a systematic failure of the 13 studies to report serious complications with Infuse, a powerful biological agent used in spinal fusion surgery.

The review examined payment data from Medtronic to doctors who co-authored papers about clinical trials of Infuse. When the payments were totaled and compared with the number of studies, the median amount to the doctors was at least \$12 million to \$16 million per study, the journal said.

None of the royalty payments were for Infuse.

In each study, those conflicts of interest were either not reported or were unclear, the *Spine Journal* notes.

It also found the studies co-authored by the Medtronic-associated doctors indicated there were no complications related to Infuse when they knew the product was linked to several serious side effects.

Among those problems: Uncontrolled bone formation and the need for additional surgery; life-threatening inflammation; infections; implant movement; cancer risk; and effects on nerves leading to radiating leg pain, bladder retention and a complication that causes sterility in men.

"We find ourselves at a precarious intersection of professionalism, morality, and public safety," a *Spine Journal* editorial accompanying the study said. "We work under a burden of suspicion that new technology research and publication is simply a 'broken system' as currently practiced."

In a statement, Medtronic chairman and CEO Omar Ishrak, said he strongly believes in the safety of Infuse as it is described in data submitted to the FDA and is summarized on the product's label.

"Integrity and patient safety are my highest priorities," said Ishrak, who became chairman and CEO this month. "While the *Spine Journal* articles raise questions about researchers' conclusions in their peer-reviewed literature, the articles do not raise questions about the data Medtronic submitted to the FDA in the approval process or the information available to the physicians today through the instructions-for-

use brochure attached to each product sold."

But critics say the problem has long been a lack of transparency and reporting of serious complications in medical articles written by doctors — not FDA or product labeling data. They say surgeons and patients learn about the safety and effectiveness largely from the published literature, not a package brochure.

A separate statement from the Medtronic said the company agreed that the issues about published studies raised by the *Spine Journal* "deserve further review and analysis." The company said it would work with journal editors and other academics to determine what actions it should take.

### **Infuse a financial success**

Infuse is a genetically engineered substance, also known as bone morphogenetic protein-2, that stimulates the growth of bone and eliminates the need to harvest a small amount of a patient's own bone, typically the hip, for use in fusing two vertebrae.

As a result, it has been a huge financial success. Its sales are about \$700 million dollars a year. Since 2002, the product has been implanted in more than 500,000 patients.

How has it gone from magic molecule to a cause for concern?

Much of it can be found in the *Spine Journal*'s analysis of the 13 Infuse studies involving nearly 800 patients.

Consider just one issue: Infections that occurred in patients who received Infuse implants.

A high rate of infections in Infuse patients (39 infections in 35 out of 288 patients who got Infuse) was reported in data originally submitted to the FDA by Medtronic, the *Spine Journal* paper said.

However, according to the *Spine Journal* review, that finding was not reported in five subsequent published papers — including three co-authored by Thomas Zdeblick, an orthopedic surgeon at the University of Wisconsin School of Medicine and Public Health, as well as other surgeons who receive millions of dollars in royalties from Medtronic.

The *Spine Journal* paper noted the rate of infection was three to five times greater in Infuse patients than in control group patients.

"Biased research placed patients at risk for harm . . ." wrote Sohail Mirza, an orthopedic surgeon at Dartmouth Medical School, in another *Spine Journal* commentary. "Large payments or the prospect of future payments may have influenced inves-

OCTOBER 23, 2011

# Doctors failed to note risk of cancer

## Spine-product paper omitted key data

By JOHN FAUBER

jfauber@journalsentinel.com

Doctors paid millions of dollars by Medtronic failed to identify a significant cancer risk with the company's spine surgery product in a 2009 paper about results of a large clinical trial.

The surgeons left out important data and claimed there was no significant link between the product and cancer.

The company and doctors had become aware of information on an additional cancer case, which pushed the concern to a critical level, at least two months before the paper was published, a Journal Sentinel/MedPage Today investigation found. Independent researchers say they had an ethical duty to report the cancer risk.

The breach is the latest conflict-of-interest controversy facing Medtronic, which is under investigation by a U.S. Senate committee and the U.S. Justice Department for its marketing of the spine surgery product known as bone morphogenetic protein-2, or BMP-2.

The product is the bone growth stimulating biological agent used in the company's Infuse, which has been approved by the U.S. Food and Drug Administration, and Amplify, the unapproved product that was the subject of the 2009 paper.

In June, independent researchers found a systematic failure to report serious complications with BMP-2 in 13 papers published over nearly a decade. The papers were written by doctors who received millions of dollars from Medtronic. The unprecedented rebuke, which was published in the Spine Journal, was prompted in part by stories in the Journal Sentinel.

Medtronic and the lead author of the Amplify paper say there was no "statistically significant" cancer connection to the product at the time the paper was accepted for publication in the Journal of Bone & Joint Surgery. Medtronic also said results from the Amplify clinical trial can't be applied to BMP-2 in general.

The researchers had information showing that at two and three years after being implanted with the genetically engineered protein, significantly higher numbers of Amplify patients were being diagnosed with cancer, but they did not report it on their paper.

The authors mentioned the cancer link only in a table accompanying the paper. The text itself never addressed the concern of whether BMP-2 might fuel cancer.

"As a physician, you go by what your colleagues publish," said Charles Rosen, an orthopedic surgeon and president of the Association for Medical Ethics. "It's an abuse of trust."

The Journal Sentinel found a full airing of the cancer question in more than 1,000 pages of U.S.



MEDTRONIC FILING WITH FDA

Amplify, a product used in spinal surgery, includes hardware and the (white) absorbent matrices that act as carriers for bone morphogenetic protein-2 as well as a scaffold for new bone formation.

*"The primary statistical concern is an apparent association with malignancy."*

FDA staffer, at a 2010 Amplify hearing

*"Aside from the lack of statistical significance, the diversity of cancers did not suggest any indication of a relationship between Amplify and cancer."*

Marybeth Thorsgaard, a Medtronic spokeswoman

Food and Drug Administration records. That information included FDA reports and information filed with the agency by Medtronic as part of its application to win approval for Amplify.

At a 2010 Amplify hearing, for example, an FDA staffer said "the primary statistical concern is an apparent association with malignancy."

Several independent spine surgery experts were asked by the Journal Sentinel to look at the FDA data and compare it with what was written in the June 2009 paper that was published in the journal. The experts found several problems with the way the numbers were used.

First, the paper said there were eight patients who were diagnosed with cancer 24 months after being treated with Amplify, compared with two patients who got the standard treatment—a graft of their own hip bone. That resulted in the probability of a real cancer risk that fell a little short of what is considered statistically significant.

However, the actual cancer numbers were nine for those receiving Amplify and two for

those who received bone grafts, according to the FDA records. At nine patients the cancer risk becomes significant, based on the way it is measured.

The ninth case involved a woman in the trial who underwent surgery with Amplify in 2003 and was diagnosed with stomach cancer in 2005. The patient did not report the cancer to researchers until her five-year follow-up in 2009.

In addition, cancer cases occurring three years after Amplify was implanted showed a clear statistical significance, said Brook Martin, a researcher with Dartmouth Medical School who analyzed the data for the *Journal Sentinel*. That data indicates that 12 patients had been diagnosed with cancer in the Amplify group, compared with three who got their own hip bone.

Martin said the authors had an ethical obligation to report all the cancer information.

“It absolutely should be presented, in my view,” he said.

A three-year analysis was not done because that time point was not pre-specified, Marybeth Thorsgaard, a Medtronic spokeswoman, said in an email.

Thorsgaard and the paper’s lead author said the ninth cancer patient wasn’t discovered until after the paper had been accepted for publication in the journal, but they refused to provide the date. Thorsgaard said that when the company became aware of the case, it reported to the FDA in an April 2009 update.

That was at least two months before the paper actually was published. Neither Medtronic nor the authors could point to any evidence they moved to update the paper to reflect the accurate and more alarming cancer report.

Michelle Hache, spokeswoman for the *Journal of Bone & Joint Surgery*, declined to comment, but noted that authors have an obligation to report the complete facts of any research.

### **A popular product**

Since coming on the market in 2002, BMP-2 has become popular in spinal surgery. By stimulating bone growth, it can eliminate the need to harvest a small amount of a patient’s own bone for use in a spinal fusion surgery.

The product was approved for a narrow use after an earlier clinical trial showed it worked about as well as a standard hip bone graft in a specific kind of spinal fusion surgery. But doctors quickly began using it in other, unapproved ways, known as “off-label” use. That helped fuel annual sales of \$700 million.

With the Amplify trial, Medtronic was

seeking additional FDA approval for a different BMP-2 spinal fusion product. The FDA has refused to grant approval, a decision Medtronic is appealing.

The clinical trial that was the subject of the paper involved 463 spinal fusion surgery patients, including 239 who got the higher-dose BMP-2 preparation used in Amplify.

The 2009 paper on the trial was written by six physician authors. The first three authors of the paper — or entities they are associated with — received about \$10 million from Medtronic, mostly in royalties, in 2010 alone. The royalties were for other products, not for BMP-2.

Two of the other authors received no compensation from Medtronic in 2010. Another author received between \$5,000 and \$9,999 for advisory services to the company.

In its own documents, the FDA’s reviewers expressed serious concerns about the cancer risk.

At the 2010 advisory panel hearing, an FDA doctor noted that cancer deaths among those in the Amplify clinical trial who got BMP-2 were caused by malignancies that tended to be “highly morbid” and occurred in patients who died relatively soon after being implanted with the product.

“This suggests the possibility of a synergistic effect of the device that could potentially accelerate pre-existing cancer growth,” an FDA medical officer said, according to a transcript of the hearing.

A separate FDA document concluded that the cancer incidence was an important concern because of elevated cancer rates in the Amplify clinical trial and trends toward higher cancer rates found in a separate analysis combining the results of Medtronic’s other clinical trials of BMP-2.

In a statement last week, the FDA said it could not disclose whether it is investigating whether BMP-2 causes cancer. The agency noted it is examining available information about whether BMP-2 promotes the growth of existing cancers rather than initiating cancer.

### **Different pictures**

In the 2009 paper, authors concluded there was no significant difference in serious complications between those patients who got BMP-2 and those who did not.

How can two such starkly different pictures of a medical product be presented — one in the published medical literature that doctors read, the other in FDA records that many doctors never see?

Papers about company-funded research are more likely to present positive results and gloss over a potential complication, said George Lundberg, the former editor-

in-chief of JAMA, the Journal of the American Medical Association.

“The authors by virtue of how little attention they paid to it, . . . they didn’t want it to be there,” he said. “And the company especially didn’t want it to be there — out where everybody would see it. They also knew that nobody much reads the FDA reports.”

Lundberg also serves as an editor-at-large at MedPage Today and as a consulting professor of pathology and health research at Stanford University. He was not involved in the editing of this report, part of a long-running investigation by the Journal Sentinel in partnership with MedPage Today.

The three co-authors who received substantial royalty payments from Medtronic were contacted for this story, but none agreed to be interviewed.

In an email, lead author John Dimar II, an orthopedic surgeon with the Norton Leatherman Spine Center in Louisville, Ky., noted the paper only included an analysis of 24 months after the surgeries were performed, whereas the FDA data included information going out five years.

Although the clinical trial was set up to test the effectiveness of Amplify at 24 months, independent doctors say the authors were obligated to include information they possessed about serious safety issues such as cancer that occurred beyond two years if those findings contradicted their original conclusions. In addition, the clinical trial was designed to continue to evaluate patients up to five years after their surgery.

Dimar said the lack of statistical significance — based on the eight cases, not the actual nine — plus the fact that there were a variety of different cancers, indicated to the authors that Amplify did not cause the cancers.

He did not respond to questions about why the paper was not updated with the more worrisome cancer numbers before being published or changed after publication.

In 2010, Medtronic paid more than \$9 million in royalties to Concept Properties LLC, a Louisville entity associated with Dimar and co-author Steven Glassman, also an orthopedic surgeon at the Norton Leatherman Spine Center. None of the royalties were for BMP-2.

Co-author Kenneth Burkus, an orthopedic surgeon in Columbus, Ga., and his RBCK Research & Consulting received more than \$800,000 in royalty and other payments from Medtronic in 2010, none for BMP-2. He did not respond for this story.

## Diversity of cancers

Medtronic spokeswoman Thorsgaard

said the cancer cases in the Amplify clinical trial can’t be generalized to BMP-2.

She also said Amplify is a different product than BMP-2 with a different dose and a different piece of equipment. As such, it is not available to surgeons. However, doses of BMP-2 similar to what was used in the Amplify trial are commercially available.

“Aside from the lack of statistical significance, the diversity of cancers did not suggest any indication of a relationship between Amplify and cancer,” Thorsgaard said in her email.

However, the diversity of cancers raises even more concern about whether they were caused by BMP-2, said Eugene Carragee, a professor of orthopedic surgery at Stanford University. He spearheaded the rebuke of BMP-2 in June in the Spine Journal, where he is editor-in-chief.

Normally, if the cancers were occurring randomly, as they do in the general public, you would expect to see more of the most common cancers, such as breast cancer in the women and prostate cancer cases in men, Carragee said.

But the Amplify patients were diagnosed with cancers of the pancreas, ovaries, vocal cord and stomach.

The possibility that BMP-2 might promote cancer has been a concern ever since it was brought to market because it is a growth factor that causes cells to proliferate, he said.

It continues to be a risk that needs to be taken seriously, including for patients who are predisposed to cancer or who may be receiving anything but a very small dose of BMP-2, Carragee said.

“There is no question that BMP has biological effects that we don’t fully understand,” said Raj Rao, a professor of orthopedic surgery at the Medical College of Wisconsin and a member of the 2010 FDA advisory panel on Amplify.

Cancer is one of them, said Rao, who voted against granting approval for Amplify.

The Amplify clinical trial may have been too small to fully explore the cancer association, he said.

A separate analysis of all of Medtronic’s clinical trials using BMP-2 showed a trend toward high cancer rates, according to FDA records.

That analysis involved 18 clinical trials. It found that 2.4% of BMP-2 patients got cancer, compared with 1.4% who did not get BMP-2.

In four high-dose clinical trials of BMP-2, 3.6% patients developed cancer.

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*John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at medpagetoday.com.*

# Millions paid to UW chairman

## Surgery chief reviews others' Medtronic deals

By JOHN FAUBER  
jfauber@journalsentinel.com

Paul Anderson, an orthopedic surgeon at the University of Wisconsin-Madison, gets so much money from the medical device firm Medtronic that the university put its most stringent oversight on the relationship.

One of the requirements is that Anderson, who has received \$225,000 in consulting fees from Medtronic in 2008 through 2010, has to meet annually with his department chairman to review the relationship and its potential influence on his university activities.

But the chairman, Thomas Zdeblick, got more than 25 times that amount from Medtronic himself during the three years. And a new accounting by the Journal Sentinel and MedPage Today shows he received more than \$25 million in royalties from the company since 2003.

What's more, UW Hospital spent \$27 million for Medtronic spinal products from 2004 to 2010, according to documents obtained through an open records request. And Zdeblick, a renowned spinal surgeon, has co-authored several positive research papers about the company's spine products.

Academic leaders questioned whether Zdeblick could objectively serve as a department chairman.

"I really don't know how you would manage that conflict of interest," said Jordan Cohen, a former president of the American Association of Medical Colleges. "It (his financial relationship with Medtronic) is bothersome."

Cohen, a professor of public health at George Washington University, said it would be preferable for Zdeblick not to serve as chairman to avoid the potential for conflicts of interest.

Zdeblick is not alone — other department chairmen across the country get payments from drug companies and device-makers. But the ethical grounds may be shifting under their feet. While having a financial tie to industry once was considered a status symbol, more and more critics are questioning those relationships. Zdeblick de-

clined to comment for this story.

Robert Golden, dean of the UW School of Medicine and Public Health, said Zdeblick is an outstanding chairman who has the enthusiastic support of his faculty, staff and the leadership of the medical school.

"Dr. Zdeblick is one of the most talented and innovative orthopedic surgeons in the nation," Golden said in an e-mailed statement. "We are most fortunate to have him as department chair."

University records show Zdeblick received more than \$1 million in UW compensation in 2010, tops among UW doctors.

Medtronic and UW noted Zdeblick does not receive royalty income for any Medtronic spinal implants used by UW Hospital.

### Medtronic payments, purchases

UW surgeon Thomas Zdeblick has received more than \$25 million in royalties from Medtronic since 2003. UW Hospital spent \$27 million for Medtronic spinal products from 2004 to 2010.



Source: University of Wisconsin-Madison, Medtronic, LLC, Journal Sentinel

### Products used at UW

Zdeblick long has been at the center of a swirling debate about Medtronic and its controversial back surgery product, Infuse — and the influence of money in medicine.

The fact Medtronic products invented by Zdeblick are implanted in patients at UW Hospital was revealed in 2009, in response to an inquiry by the U.S. Senate Finance Committee, which was investigating payments to doctors by medical companies.

In the letter to U.S. Senate investigators, university officials acknowledged Zdeblick had implanted four kinds of Medtronic devices that he invented or had a role in inventing a total of 179 times in the previous three years.

The most implanted device (89 times) was the LT-Cage. It is used in spinal fusion surgery and was part of clinical trial that helped gain U.S. Food and Drug Administration approval for the bone growth agent known as Infuse, or BMP-2.

Documents from the committee indicated Zdeblick's Medtronic royalties since 2003 totaled \$19 million. Since then, UW records obtained by the newspaper show his total Medtronic royalties now exceed \$25 million.

Before 2009, UW doctors only were required to indicate ranges of outside income with the top category being \$20,000 or more.

That obscured just how much any of the doctors had made.

Also unknown: the annual sales figures for Medtronic spine devices used at UW Hospital.

Through an open records request, the Journal Sentinel and MedPage Today sought spinal products purchasing agreements between Medtronic and UW Hospital. The records were provided only after the university got approval from Medtronic.

The documents were redacted heavily, with officials saying they consider the contracts to be a trade secret, but provide a more complete picture of the relationship between the company and the hospital where Zdeblick and Anderson practice.

Dozens of Medtronic spinal products were included in the records with annual purchases hovering around \$4 million.



Golden

### **Ethicist questions role**

The type of management plans under which Zdeblick and Anderson must operate are aimed at providing a range of safeguards against undue influence from their financial relationship with Medtronic.



Zdeblick

They must inform others who may be impacted by the conflict, including students, fellows and other researchers who they supervise. They can't serve as the

principal investigator for any UW human subjects research without written approval from a committee that examines conflicts. They may not be directly involved in making decisions involving the purchase of items from Medtronic using funding under their control. Their agreements with Medtronic must not limit their ability to publish research.

But independent experts say Zdeblick's relationship with Medtronic is so huge it calls into question whether he can serve objectively as chairman of the department of orthopedics and rehabilitation.

"Is that the ideal situation?" asked Arthur Caplan, a professor of medical ethics and health policy at the University of Pennsylvania. "I don't think so. It is just such a huge sum of money. It's just too big a connection."

He said there may be ways to manage the situation, such as disclosing the relationship to others and making sure that an independent conflict of interest committee approves of Zdeblick's activities. But Caplan added: "I'd really be discouraging it (serving as chairman)."

Consider the issues involved in a single 2003 study authored by Zdeblick and two

non-UW doctors who have received millions of dollars from Medtronic. Those surgeons and others with ties to the firm have been criticized for failing to connect the Medtronic spine surgery product BMP-2 with several serious complications in their published research.

The study was published in the journal at which Zdeblick is editor-in-chief. And the study involved another product, the LT-Cage, from which Zdeblick receives royalties. None of his royalties — or those of the other authors — is from BMP-2.

In unusually glowing language, the 2003 study declared the product could become "the new gold standard" in spine surgery — and then the authors went on to say the product was being used "exclusively" at their institutions.

Lisa Brunette, a spokeswoman for UW Hospital, said the comment was not an endorsement of the product by the hospital. She said when the product came on the market, it was the only one of its type that was available. Now, there are several options, and UW uses different products.

### **Safeguards touted**

Several academic experts said that Zdeblick's financial relationship with Medtronic also is something that can affect his interaction with other faculty as well as his students, residents and fellows in orthopedic surgery.

If residents learn how to implant mostly Medtronic products, it can create a "farm system" in which as doctors they may be more inclined to use the company's products, said David Rothman, president of the Institute on Medicine as a Profession, part of Columbia University College of Physicians & Surgeons.

In addition, managing other faculty who may have their own financial relationships with Medtronic or competing device companies at the least creates the wrong appearance, said Rothman, who also serves as a consultant to the North American Spine Society, which publishes the Spine Journal.

"What kind of message goes out when the chairman of the department who is going to be evaluating promotions is so deep into the pocket of Medtronic?" he said. "That message, that you can have it all, that you can take millions from Medtronic and still be chairman of the orthopedics department, that's a message that should make people uncomfortable."

In his email, Golden, dean of the UW medical school, pointed to several safeguards.

He said the selection of implant devices is done by a review committee, which uses a competitive process after input from surgeons. Zdeblick recuses himself from any role in the selection of vendors, Golden

said.

In addition, residents and fellows work with multiple surgeons in the department who may have differing views and preferences for various devices, Golden said. They are taught how to assess critically the medical literature and draw conclusions from the evidence.

He also said the students are told about the royalties Zdeblick receives.

And he noted the management plans Zdeblick and Anderson operate within amount to a shared arrangement with the primary responsibility falling to the dean's office and the graduate school.

"To my knowledge, Dr. Zdeblick has effectively carried out his responsibilities as department chair to review activities of faculty," Golden said.

A 2007 study in JAMA, the Journal of the American Medical Association, found that 60% of department chairmen at medical schools had some kind of personal relationship with the medical industry, such as being a consultant, paid speaker or member of an advisory board.

Department chairmen often are influential in their fields of medicine, said Eric Campbell, lead author of the study and an associate professor of health policy at Harvard Medical School.

And, he said, drug and device companies seek them out as opinion leaders.

"If you have a product, are you not going to want to have the chairman (of orthopedics) at the University of Wisconsin in your corner?" Campbell said. "It's Marketing 101."

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*John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [medpagetoday.com](http://medpagetoday.com).*

## **The Milwaukee Journal Sentinel and MedPage Today**

*The stories in this entry were done by Milwaukee Journal Sentinel reporter John Fauber under the direction of Journal Sentinel editors.*

*After they were completed, Fauber rewrote some of them under an agreement with MedPage Today, a website aimed at physicians.*

*The Journal Sentinel has a contractual relationship with MedPage Today that involves sharing content after it has been completed for publication.*

*The stories were not jointly reported in any way.*

MILWAUKEE • WISCONSIN

# JOURNAL SENTINEL

## SUPPLEMENTAL MATERIAL

# FDA orders review of jaw joint implants

## Action prompted by various problems, questionable trials

By **JOHN FAUBER**  
jfauber@journalsentinel.com

The Food and Drug Administration has ordered a review of the performance of artificial jaw joint implants after finding a substantial number of problems with the products in recent years.

The action comes a couple months after a Journal Sentinel investigation found that the agency had approved four such devices beginning in 1999, despite weak and incomplete research clouded by potential conflicts of interest.

In announcing the action, the agency said it found a substantial number of adverse events involving the devices between 2004 and 2010, including patients who had to have devices removed prematurely after they were implanted because of extreme pain.

Many of those patients were forced to undergo surgery to remove the devices in less than three years. That is considerably shorter than the expected five-year minimum, the agency said.

It is not known how many patients have been implanted with the devices since they were approved beginning in 1999 — the year of the FDA's first such approval — but it is believed to be in the thousands.

"It is definitely too late in coming," said Terrie Cowley, president of the TMJ Association, a Brookfield-based national patient advocacy organization. "The number one priority of the manufacturers and the FDA should be the safety of the patients receiving these implants."

The FDA's latest action involved implants used to treat a condition known as temporomandibular joint disorder, or TMJ — a group of ailments affecting the joint connecting the jaw to the head.

It affects more than 10 million Americans, including a small number who undergo radical surgery to implant an artificial jaw joint.

Among the medical device reports it has reviewed, 52% of the devices that had to be removed were taken out less than three years after they were implanted, the agency said in an e-mail to the Journal Sentinel.

Device problems included the need for re-

moval or replacement, loosening, difficulty removing, noise, fracture and breaking, the FDA said.

Patient problems included pain, surgical procedure or repeat surgical procedure, additional therapy and nonsurgical treatment or treatment with medication, infection, swelling, hospitalization and headache, it said.

"It is premature to discuss whether any devices would be taken off the market," FDA spokeswoman Erica Jefferson said in an e-mail. "We will evaluate the data that is supplied and may take further regulatory action at that time."

### **Trial data inadequate**

Beginning in 1999, the FDA approved four such devices made by three companies. At the time of approval it ordered the firms to collect the market data it now is reordering.

That data was inadequate, the agency said, noting that it did not show why or how soon the devices were being replaced. In addition, the companies had lost contact with many of the patients who had received the devices.

Without knowing that information, the agency cannot determine the true safety and effectiveness of the products or whether any of them should be removed from the market.

"It is very long overdue," said Diana Zuckerman, president of the National Research Center for Women & Families. "But it is important that they are finally doing it. This has been going on since 1999, but there is a new sheriff in town and hopefully something will get done."

Zuckerman noted the agency's acknowledgment that the device makers had lost contact with large numbers of patients who were implanted with their devices.

In reviewing the clinical trial data that was used to approve the devices, the Journal Sentinel found the same problem: Substantial numbers of patients dropped out of all the trials, and little long-term follow-up data was available — including one trial that had data on only 34 patients at the three-year mark.

Independent doctors say this casts doubt

on the findings and indicates the results may have been biased and overstated the success.

Zuckerman questioned whether, this time, the FDA would be serious about demanding long-term follow-up on patients who have received the devices.

“If they can’t keep track of their patients and the FDA approves it anyway, it is not surprising they don’t take it seriously,” she said. “There is no evidence that these products are safe and effective. We hope this is a new sign of real enforcement.”

Zuckerman credited reports in the *Journal Sentinel* and *MedPage Today*, an online national medical news website that partners with the newspaper, with prompting the FDA’s action.

U.S. Sen. Herb Kohl (D-Wis.), chairman of the Senate’s Special Committee on Aging, said he will be closely monitoring the FDA’s action and may hold a hearing on TMJ implants and other medical devices later this year. Kohl and his staff have been investigating complaints about TMJ devices.

“Having the FDA require additional study of TMJ devices is a positive step and is the only way to determine whether these devices are working as intended or failing and causing undue, agonizing pain,” Kohl said in a statement.

#### **Questionable approval**

Throughout the TMJ device approval process, the watchdog agency appeared to be looking out more for the makers of the devices than patients, the newspaper found. Despite serious concerns, FDA advisory panels unanimously voted to approve the products in three out of four cases. With the fourth device, the advisory panel voted against approval but a higher FDA authority approved it months later anyway.

The Nov. 28 report found the products were approved even though clinical trials were fraught with problems, including:

- Just two oral surgeons implanted nearly all of the devices in two of the trials.

Independent researchers say such arrangements raise red flags because clinical trials should be done at a variety of centers to get a true picture of how well a device works. When a small number of doctors implant most devices, it doesn’t reflect the real-world results of surgeons with less experience with the products.

- In addition, there were financial con-

flicts of interest in both of those trials.

In one, both doctors worked as consultants to the manufacturer, and one of them invented the device and later got royalty payments.

In the other trial, one doctor worked as a consultant to the manufacturer, helped develop the device and later received stock in the company.

Many patients were victims of TMJ implant efforts that began in the 1980s and quickly became fiascos. There was virtually no regulation of the devices because of a law that grandfathered in medical devices that were “substantially equivalent” to products on the market before 1976.

In 1998, the FDA began requiring manufacturers to prove their devices were safe and effective.

On Monday, the FDA said it may revise its recommendations or issue other recommendations after reviewing additional clinical data from the companies.

Patients who have been implanted the devices or are considering such surgery should consult with their doctor, the agency said.

The three manufacturers of the newer generation of TMJ devices — TMJ Solutions, TMJ Medical and Biomet Microfixation — make all of the currently approved TMJ devices marketed in the U.S. The companies will have 30 days to submit a study plan, which will need to be approved by the agency before any postmarket studies can begin.

The studies must address several important issues, including:

- The length of time between initial implant and its removal or replacement.

- The association between patient diagnosis and the time frame between implant and removal.

- The time between implant and subsequent removal or replacement.

- The reasons for removal or replacement.

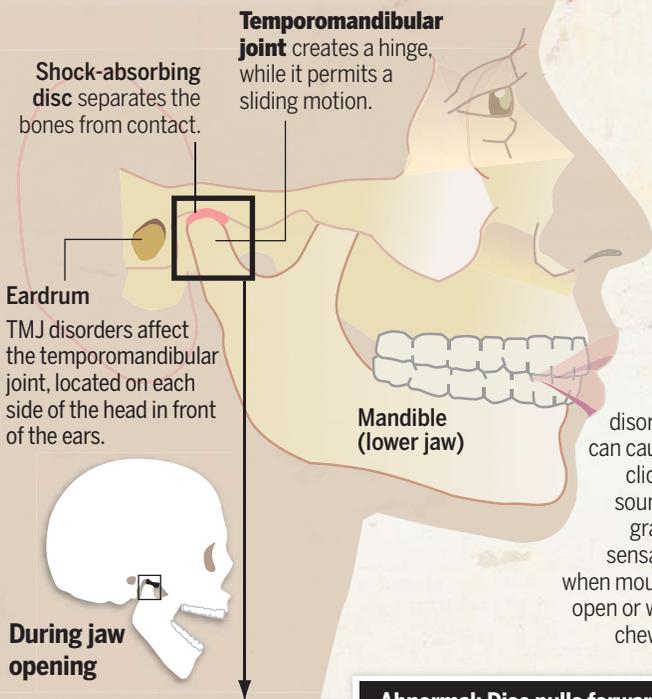
- The associations between patient demographic and clinical data and the need for removal.

- Assessment of devices that have been removed from patients.

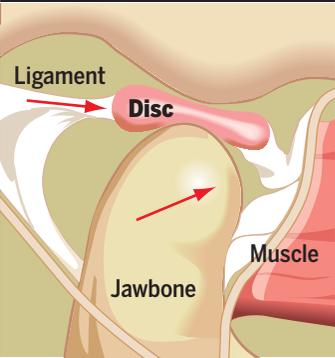
As part of its review, the FDA will consider whether labeling changes, additional preclinical and clinical testing requirements, or other regulatory actions are necessary for these devices.

# TMJ devices

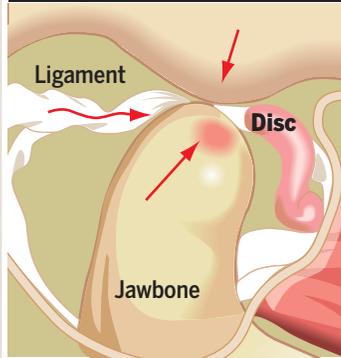
Since 1999, the FDA has approved four jaw joint replacement devices to treat temporomandibular joint disorder. Critics say clinical trial data supporting the products is weak.



**Normal: Disc prevents bones from contact**



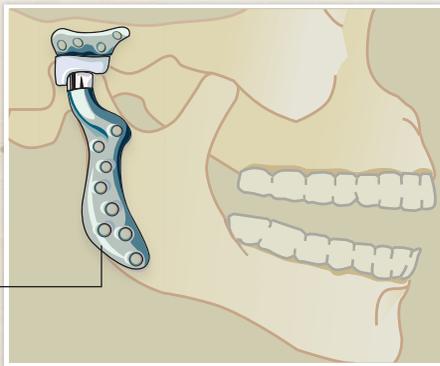
**Abnormal: Disc pulls forward, causing bone grinding and muscle displacement**



## TMJ IMPLANTS

Three companies have received FDA approval for their TMJ devices since 1999:

- TMJ Implants
- Biomet
- TMJ Concepts



## CAUSES

TMJ pain is caused by muscle spasms when chewing. Stress on the muscle groups can also be caused by grinding teeth, or a misaligned bite.

## DISORDERS CAN OCCUR IF

- Disc erodes or moves out of its proper alignment
- Arthritis damages the joint's cartilage
- The joint is damaged by impact
- The muscles that stabilize the joint become fatigued from overwork, which can happen if you habitually clench or grind your teeth

## SYMPTOMS

Signs and symptoms of TMJ disorders may include:

- Pain or tenderness of jaw
- Aching pain in and around the ear
- Difficulty in chewing or discomfort when chewing
- Aching facial pain
- Locking of the joint, making it difficult to open or close mouth
- Headache
- Uncomfortable bite
- An uneven bite, because one or more teeth are making premature contact

## SOME TREATMENTS

- Relaxation techniques
- Medication
- Mouth guards
- Surgery may be used in some cases, but only as a last resort

JULY 7, 2011

# Madison surgeon's letter bashes critic

Negative study of spinal fusion product draws note about author's Iraq service

By **JOHN FAUBER**  
jfauber@journalssentinel.com

Orthopedic surgeon Eugene Carragee spent four months in Iraq in 2005, as a doctor with the U.S. Army Reserves.

The physician returned to Iraq in late 2007, but his deployment was cut short by an attempted suicide bomb attack in January 2008. He was awarded a Purple Heart and a Bronze Star for his injuries and heroic actions.

Now Carragee's military record is being used in an attempt to discredit his research indicating that the Medtronic spine surgery product known as Infuse may increase the risk of a complication that causes sterility in men.

That research countered earlier papers by doctors with financial ties to Medtronic — including University of Wisconsin-Madison orthopedic surgeon Thomas Zdeblick — that failed to link Infuse to the male sterility complication.

Zdeblick is contending that Carragee's review of Infuse should be discounted because he took an 18-month hiatus and was not performing elective civilian spine surgeries until after he got back.

However, Carragee said he never took an 18-month hiatus or any other extended leave during the period covered in his study. And others in the field say it is improper to use Carragee's military record to criticize his research.

"I was disappointed in Tom," said Dan Spengler, a Vanderbilt University orthopedic surgeon who co-founded the Journal of Spinal Disorders & Techniques, which Zdeblick now edits. "I thought he was a classier guy than that. I can't even relate to someone who would say something like that."

The war of words is part of the surging criticism of Medtronic-funded research involving Infuse, which has annual sales of about \$700 million.

In May, Carragee's sterility paper was published.

Less than a month later, a U.S. Senate committee launched an investigation into reports that doctors with financial ties to Medtronic were aware of serious complications with Infuse yet failed to reveal those problems in medical journal articles.

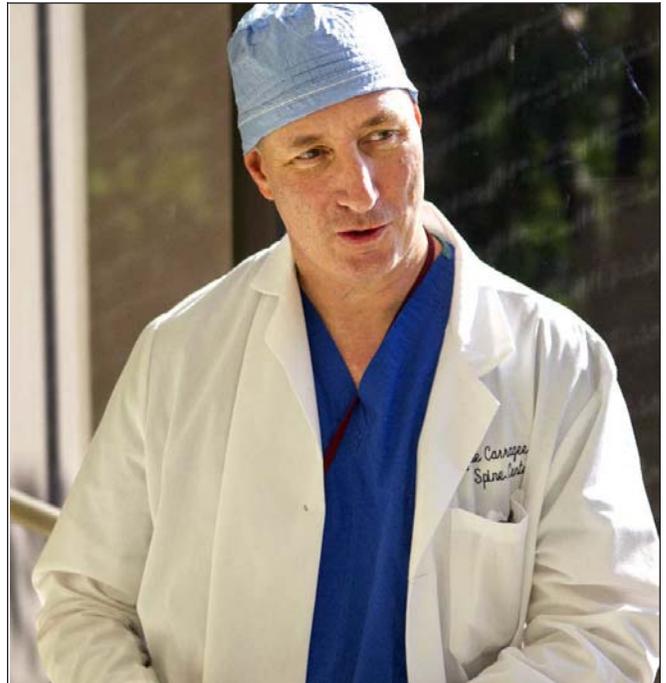


PHOTO COURTESY STANFORD SCHOOL OF MEDICINE

Eugene Carragee, a spinal surgeon, says complications from Infuse might be linked to infertility in men.

*"Of course, I would never denigrate his (Carragee's) military service."*

Thomas Zdeblick,  
in an email

*"Zdeblick's assertions are so nonsensical that the whole letter strikes me more like the ravings of a guilty man who's been cornered."*

Charles Rosen,  
president of the Association for Medical Ethics, on orthopedic surgeon Thomas Zdeblick



Zdeblick

Then last week, the Spine Journal devoted an entire issue to Infuse complications that were not reported and linked to the product in 13 papers written by those doctors — including some co-authored by Zdeblick — and published over the course of nearly a decade.

Among those complications: uncontrolled bone formation and the need for additional surgery; life-threatening inflammation; infections; implant movement; cancer risk; and effects on nerves leading to radiating leg pain, bladder retention and a complication that causes sterility in men.

The sterility paper, Senate investigation and Spine Journal review all were prompted in part by Journal Sentinel investigations about Infuse and the financially connected doctors, reports that were published over the past year and a half.

#### **Military 'hiatus' cited**

Zdeblick's criticism came in a letter to the Spine Journal, where Carragee is editor-in-chief and where his paper was published.

"Although we all like to think of ourselves as infallible, an 18-month hiatus can certainly alter surgical technique, style, equipment, and so on; all of which can alter the incidence

of (retrograde ejaculation, which causes sterility in men),” according to an excerpt of the letter.

Zdeblick repeated the military hiatus claim again in a June 29 statement released by the UW-Madison public affairs office, though the length of the military leave increased to “nearly two years.” The statement claimed that break was “between study groups and that likely affected the outcome.”

For his paper, Carragee looked back at 243 of his own patients who underwent spinal fusion surgery between 2002 and 2004, after Infuse was approved.

Infuse, also known as bone morphogenetic protein-2, is a genetically engineered substance that stimulates bone growth. It eliminates the need to use a patient’s own bone to create a spinal fusion.

Carragee and his co-authors compared rates with and without the product of the complication known as retrograde ejaculation. They also compared their findings with the original FDA data on Infuse.

Their review found that retrograde ejaculation occurred in more than 7% of the Stanford patients treated with Infuse, compared with less than 1% of those who received a standard bone graft. Their complication rate with Infuse was similar to the rate found in the unpublished clinical trial data submitted to the FDA.

Carragee was a lieutenant colonel in the Army Reserve at the time of his service in Iraq.

He also is a professor of orthopedic surgery at Stanford University. The period covered in the study involved patients he operated on in 2002, ’03, and ’04.

In 2005, after the surgeries were performed, Carragee took a four-month leave for service in Iraq. Carragee started another tour in late 2007, but returned home in January 2008 after being injured in an attempted suicide bomber attack.

### **Millions in royalties**

Zdeblick has received more than \$23 million in royalties and other payments from Medtronic since 2002. None of the royalties is for Infuse. Zdeblick has received royalties for the LT-Cage, the device that was tested with Infuse in the clinical trial leading to the 2002 approval of Infuse by the U.S. Food and Drug Administration.

Asked for the source of the 18-month hiatus information, Zdeblick initially sent an email that said: “Carragee himself said in his article that it was his break from civilian surgery that was a natural point to start using InFuse. Read the article . . . ”

When told the paper made no reference to an 18-month military-related hiatus, Zdeblick said it was a “simple misunderstanding” of how he read the article.

“Of course, I would never denigrate his

(Carragee’s) military service,” Zdeblick wrote in an email.

### **Letter, response published**

Zdeblick’s letter will be published July 12 in the Spine Journal. Zdeblick’s letter and a response from Carragee and his co-editors at the Spine Journal were made available last week on the website of the North American Spine Society, which publishes the Spine Journal.

Zdeblick’s letter also criticized Carragee’s study for being retrospective in nature.

In addition, it noted Carragee used Infuse in an off-label manner with a device that was not tested for compatibility with Infuse or the dose of Infuse used in his study.

“Finally, to suggest that the FDA trial data were somehow obscured by a conflict of interest is misleading and inappropriate,” Zdeblick wrote in his letter. “No attempt was made to hide data.”

He added: “A single publication in the medical literature does not constitute a ‘truth.’ ”

In an email to the Journal Sentinel, Charles Rosen, president of the Association for Medical Ethics, was sharply critical of Zdeblick’s letter.

“Zdeblick’s assertions are so nonsensical that the whole letter strikes me more like the ravings of a guilty man who’s been cornered,” said Rosen, a clinical professor of orthopedic surgery at the University of California, Irvine.

In the official response to Zdeblick’s letter, Carragee and other editors of the Spine Journal wrote:

“We are astonished that Dr. Zdeblick would falsely manipulate an Army officer’s wartime service record in this manner. Although this may have been a great sound bite for Dr. Zdeblick, it has no basis in reality.”

In an interview, Carragee said the 2007 incident in Iraq — for which he was awarded the Purple Heart and Bronze Star — occurred while he and about a dozen Special Operations personnel were on the second floor of a building.

A suicide bomber driving a truck loaded with diesel fuel crashed into the lower level of the building. The detonator went off, but the containers of diesel fuel did not explode.

Carragee said he and the other soldiers fell through the floor to the lower level.

Carragee landed on the truck and suffered burns, a collapsed lung and a dislocated shoulder.

The driver of the truck survived the crash and had flown onto the hood.

“He sat up and I sat up,” Carragee said. “As he started to move I clubbed him with my rifle.”

# Senate panel probes Medtronic

## U.S. Finance Committee seeks reports on spine surgery product

By **JOHN FAUBER**  
jfauber@journalsentinel.com

A U.S. Senate committee has launched an investigation into reports that doctors with financial ties to the medical device company Medtronic were aware of serious complications with a lucrative spine surgery product yet failed to reveal those problems in medical journal articles.

Citing reports in the Journal Sentinel, two leaders of the Senate Finance Committee sent a letter to Medtronic on Tuesday demanding an extensive trail of documents, including financial records and communications between the company and doctors who have received millions in royalties and other payments. Medtronic was warned not to destroy any of the documents, data or other information in the letter signed by committee chairman Max Baucus (D-Mont.) and senior member Chuck Grassley (R-Iowa).

The growing controversy involves Medtronic's spine surgery product Infuse, which was approved by the Food and Drug Administration in 2002. Over the last year, Journal Sentinel reports have revealed large payments made to prominent surgeons around the country, including a University of Wisconsin-Madison orthopedic surgeon, who were involved in the clinical testing of Infuse or who wrote positive medical journal articles that failed to link the product to serious complications.

"We are extremely troubled by press reports suggesting that doctors conducting clinical trials examining the safety and effectiveness of Infuse on behalf of Medtronic were aware that Infuse, a treatment commonly used in spinal surgery, may cause medical complications, but failed to report this in the medical literature," Baucus and Grassley wrote. "This issue is compounded by the fact that some clinical investigators have substantial financial ties to Medtronic."

The letter was addressed to Omar Ishrak, who this month took over as chairman and chief executive of Minneapolis-based Medtronic.

Infuse, the brand name for bone morphogenetic protein-2, is a powerful biological agent used in spinal fusion surgery. The product stimulates bone growth and eliminates the need to harvest a small amount of a patient's own hip bone to create a fusion between two vertebrae.

Medtronic says Infuse has been implanted in more than 500,000 patients by more than 2,300 surgeons. Its sales amount to several hundred million dollars a year.

Medtronic also is under investigation by the U.S. Department of Justice on allegations of off-label marketing of Infuse. Though doctors can use products in ways not approved by the FDA, companies are not allowed to promote them for such unapproved ways, which often have not undergone rigorous testing for safety and effective-

ness. Research indicates that about 85% of Infuse use is off-label.

Sohail Mirza, a professor of orthopedics at Dartmouth Medical School, said he was pleased that the Finance Committee was investigating the matter.

"This is a sad failure of our profession," he said. "It's the Finance Committee doing public health work. Surgeons themselves or the FDA could have done the committee's work earlier. Our patients would have been better served if surgeons, our professional associations, and our scientific publications had established a culture or policies that prevented this circumstance."

In an emailed statement, Medtronic spokesperson Marybeth Thorsgaard said the company will respond to the senators' request.

She noted that three of the complications mentioned in their letter are listed as warnings on the FDA labeling for the product. Those complications involve retrograde ejaculation, which causes sterility in men; ectopic bone formation; and cervical complications such as swelling in the neck or throat.

She also said Medtronic acknowledged complications with the product to the FDA before its approval of Infuse "irrespective of any financial relationship between the company and the clinical investigator or study author."

Responding to concerns raised by the senators about a link between Infuse and cancer, she said that in 44 clinical trials, cancer rates were not statistically different between patients who received Infuse and those who did not.

In a statement, Baucus said: "These reports that doctors conducting medical trials while on Medtronic's payroll may have hidden serious side effects for patients are deeply troubling. We need to do everything we can to ensure companies aren't concealing serious medical complications from patients just to increase profits."

Patients must rely on their doctor's knowledge of the risks and benefits of a medical device, Grassley added.

"If the medical literature has been written by those with financial ties to the device maker, the doctor and his patient should know that," he said. "A lack of transparency leaves doctors and patients in the dark on something any of us would want to know before surgery."

Prompted in part by Journal Sentinel reports, independent researchers at Stanford University last month found strong evidence that Infuse was linked to a complication that causes sterility in men, a connection that was not revealed in the medical literature. Their paper was published in the Spine Journal.

Eugene Carragee, lead author of that study and editor-in-chief of the Spine Journal, said his publication has received many complaints for more than a year, suggesting serious concerns about published Infuse studies. Carragee is chief of spine surgery at Stanford.

“There has been a corrosive suspicion surrounding researchers’ financial ties to Medtronic, possible company influence on data presentation and the basic safety reporting by some industry-sponsored surgeons,” he said in an email to the Journal Sentinel. “For the sake of our patients, I hope the Senate’s investigation will lay the matter to rest so doctors, patients, and their families can find out whether they can have confidence in those Medtronic studies, as reported, or not.”

Next week, independent researchers are expected to publish more papers revealing additional serious complications with Infuse that were not reported in numerous articles published over the last decade and co-authored by doctors with financial ties to Medtronic. The independent researchers said their research also was prompted in part by Journal Sentinel reports.

The Baucus/Grassley letter noted that last year the Journal Sentinel reported on a Medtronic-funded study published in 2004 that found that 75% of patients who got Infuse developed ectopic bone, a type of unwanted bone growth outside the targeted fusion area. The authors, several of whom had financial ties to Medtronic, concluded that “although not desirable” the bone formation in the spinal canal did not appear to have an ill effect on patients.

The paper was published in the Spine Journal before Carragee became editor, in 2008. In a Journal Sentinel report last year, independent doctors described the paper as more marketing than science.

Last year alone, three of that paper’s four authors received about \$4 million in various royalty payments from Medtronic, the newspaper reported. None of the royalties was for Infuse.

A separate 2008 study by doctors without financial ties to Medtronic found neurological impairment from ectopic bone in five patients treated with Infuse.

### Millions in royalties

The Baucus/Grassley letter also noted the male sterility complication.

Last month, the Journal Sentinel reported that since 2002, Medtronic and a group of doctors with financial ties to the company were aware that Infuse was linked to sterility in men.

But that crucial information was not revealed in medical journal articles written by those doctors, including surgeons who would receive millions of dollars in various royalties from Medtronic.

A Journal Sentinel analysis found that last year alone, Medtronic paid more than \$6 million in royalties to a handful of doctors who, over the last nine years, co-authored several Infuse papers without cautioning that it was linked to male sterility. None of the royalty payments was for Infuse.

One of the authors, Thomas A. Zdeblick, is a University of Wisconsin School of Medicine and

## Spine fusion device

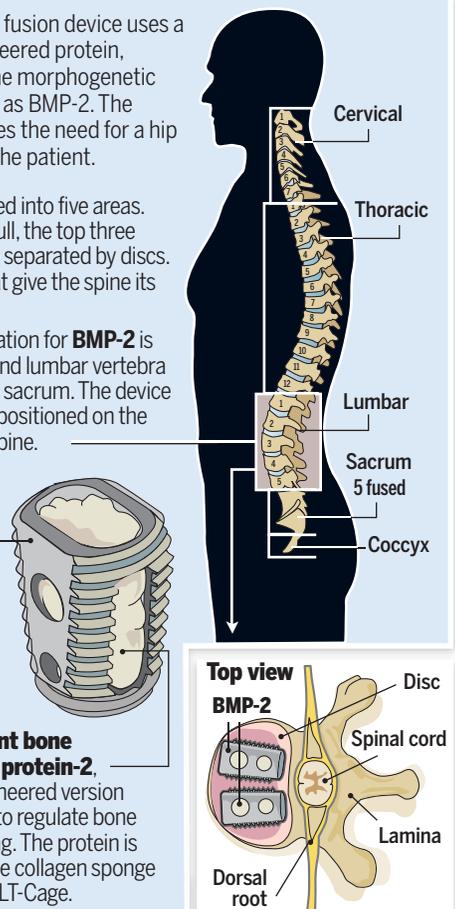
The Infuse spinal fusion device uses a genetically engineered protein, recombinant bone morphogenetic protein-2, known as BMP-2. The product eliminates the need for a hip bone graft from the patient.

The spine is divided into five areas. Starting at the skull, the top three contain vertebrae separated by discs. The discs are what give the spine its flexibility.

The approved location for **BMP-2** is between the second lumbar vertebra and the top of the sacrum. The device is designed to be positioned on the front side of the spine.

The Infuse system consists of the **LT-Cage**, which is positioned between the two vertebrae to be fused, and the grafting substance made from **recombinant bone morphogenetic protein-2**.

a genetically engineered version of a protein used to regulate bone growth and healing. The protein is infused into bovine collagen sponge and placed in the LT-Cage.



Source: Medtronic Inc.

Journal Sentinel

Public Health orthopedic surgeon. Zdeblick and Taz Consulting have received more than \$23 million in royalty and other payments from Medtronic since 2002. Zdeblick also is the editor of the Journal of Spinal Disorders & Techniques, the medical journal where two of the Infuse papers were published.

Zdeblick did not respond to a request for comment.

“We are also concerned that other severe side effects of Infuse and similar bone-growth products developed by Medtronic may have been unreported or underreported in clinical literature,” Baucus and Grassley wrote. “Reports have linked Infuse to potentially fatal swelling in the neck and throat and radiating leg pain.”

Last year, the Journal Sentinel also found that doctors with financial ties to Medtronic produced substantially better results with Infuse in the clinical trial leading to the FDA’s approval of the product than doctors who did not have financial ties to the company.

The Baucus/Grassley letter requested a variety of records, including a detailed account of payments made by Medtronic to all of the Infuse clinical investigators.

The names of the Infuse investigators and their financial disclosures have remained redacted in FDA files since before 2002 when Infuse was approved by the agency. In May 2010, the Journal Sentinel filed a Freedom of Information Act request for the information. While the agency acknowledged that information should be public, it has failed to release it.

tion by the U.S. Department of Justice over allegations of off-label marketing of BMP-2.

The BMP-2 controversy surfaced again in Friday's letter in the Spine Journal written by the authors of the 2009 paper. In that letter, they said they wrote to "clarify" points raised in the June Spine Journal analysis.

The first three authors of the paper and Friday's letter — or entities they are associated with — received about \$10 million from Medtronic, mostly in royalties, in 2010 alone, the Journal Sentinel found. The royalties were for other products, not for BMP-2.

In 2010, Medtronic paid more than \$9 million in royalties to Concept Properties LLC, a Louisville entity associated with co-authors John Dimar and Steven Glassman, both orthopedic surgeons at the Norton Leatherman Spine Center in Louisville. None of the royalties were for BMP-2.

Co-author Kenneth Burkus, an orthopedic surgeon in Columbus, Ga., and his RBCK Research & Consulting received more than \$800,000 in royalty and other payments from Medtronic in 2010, none for BMP-2.

In their letter to the Spine Journal, signed by all five authors of the 2009 paper, the surgeons said an independent Data Safety Monitoring Board reviewed all reports of adverse events.

However, neither the authors nor Medtronic would say who was on that board when the information was requested Thursday by the newspaper.

The doctors also brought up the cancer issue, saying that the increased number of cases among the Amplify patients was not "statistically significant" and that the paper only included data that was available at the time. They also said the diversity of cancers did not suggest BMP-2 was the cause.

That prompted a response from three editors of the Spine Journal, who said

that long before the 2009 paper was published, there was evidence of increased malignancies among the patients who got Amplify. They said the authors used "poor reporting practices" under established guidelines in their handling of the cancer data.

### **Medical editor rebuts**

"Unfortunately, to date, (the authors) continue to deny the significance of these observations of a clear association of cancer risk with BMP-2," wrote Eugene Carragee, editor-in-chief of the Spine Journal, and two deputy editors. "Nor in their numerous publications have they communicated the concern of independent investigators and analysts regarding the risk of cancer with the BMP-2 products (the authors) promote."

Carragee, an orthopedic surgeon at Stanford University, and his deputy editors, also noted that a related 2007 paper written by some of the same doctors erroneously stated that they had not received "any benefits in any form" from a commercial entity.

"That is also incorrect," the Spine Journal editors wrote. "The authors received substantial funds for consulting, royalties and other support from Medtronic and had extensive financial ties with this manufacturer for many years before and after publication."

They said various public documents show that Medtronic paid Dimar and Glassman "well more than \$20 million" and that a news report indicated that Burkus received \$1.5 million in undisclosed consulting fees from Medtronic in the years leading up to the papers.

An email seeking a response to the allegations by the Spine Journal editors was sent to Dimar, Glassman and Burkus.

None of them replied.

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John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [medpagetoday.com](http://medpagetoday.com).

# Medtronic hires Yale group to review

After exposé, spinal product Infuse will get second opinion

By JOHN FAUBER  
jfauber@journalsentinel.com

Medtronic, which already is under investigation by a U.S. Senate committee, will spend \$2.5 million to hire Yale University researchers to do an independent review of the safety and effectiveness of its controversial spine surgery product known as Infuse.

The move comes after months of news reports, including several in the Journal Sentinel, and research studies by independent doctors raising concerns about serious complications with the product. Those complications were not revealed in medical journal articles published over nearly a decade — articles that were written by doctors who have received tens of millions of dollars in royalties and other payments from the company.

In June, the entire issue of the Spine Journal was devoted to an exposé of research papers and commentaries about unreported complications with Infuse. Earlier that month, Omar Ishrak took over as the new chairman and CEO of the Minneapolis-based medical device company.

Medtronic will provide the Yale reviewers with patient data from all Infuse clinical trials as well as all adverse events reported to the U.S. Food and Drug Administration since Infuse came on the market in 2002.

Infuse, also known as bone morphogenetic protein-2, is a powerful stimulator of new bone growth. The product became a \$700 million-a-year seller because it eliminated the need to harvest a small amount of a patient's bone for use in spinal fusion surgery.

Harlan Krumholz, a professor of internal medicine at Yale, said he will appoint two independent academic groups to perform the Infuse review. Medtronic will have no control over the process and will have to turn over all data, he said.

As part of his agreement with the compa-

ny, all of the data eventually will be made available to other researchers, Krumholz said.

## 'Big breakthrough'

Spine Journal editor Eugene Carragee, the Stanford University orthopedic surgeon who spearheaded the journal's initiative, said he was delighted by Medtronic's decision to allow the Yale review.

It appears Medtronic has agreed to do all the things he and his co-researchers asked for, Carragee said.

"It's a big breakthrough," he said. "We'll see. I don't want to buy into the whole thing right away."

Carragee said he was concerned that the Yale reviewers may never be able to get to the bottom of some important concerns. "Unfortunately, the Yale University researchers will not be able to fix the study design flaws and assessment biases that were used in some of the original studies," he said. "There is no way of getting the toothpaste back in the tube."

More important, there may be problems collecting reports to the FDA of serious complications with Infuse after it got on the market, he said. Because many of the published papers written by doctors with financial ties to the company never linked the product to various complications, practicing surgeons who were implanting it into patients likely were not aware that the product might cause those kinds of problems, he said. That may have made them less likely to report those complications to the FDA, he said.

The complications include serious infections, cancer, radiating pain and a condition known as retrograde ejaculation, which causes sterility in men.

In addition, the Yale review probably won't be able to assess the safety and effectiveness of Infuse in one of the ways it became most commonly used.

Infuse was approved for use in lumbar fu-

sions in which the surgical approach is from the front.

However, soon after it reached the market, surgeons began using it in posterior-approach fusions. In 1999, Medtronic halted an Infuse clinical trial of posterior fusion because unwanted bone was forming in the spinal canals of more than 70% of patients.

The clinical trial, which had intended to include hundreds of patients with degenerative disc disease, was halted after only 34 patients received Infuse implants.

It was not until five years later that results of that trial, written by doctors who would receive millions of dollars in royalties from Medtronic, finally were published. The paper downplayed the bone formation, saying that no patients were harmed.

### **Enough data?**

Posterior spinal fusion with Infuse would become one of its most common uses, Carragee said.

But because the posterior fusion trial was stopped early, the Yale reviewers will not get enough data to determine the safety and effectiveness of Infuse in that kind of surgery, he said.

“Today, we know that (Infuse) may be a useful addition to spinal fusion techniques in a small group of patients, particularly those who have serious problems in healing bone, but we do not have an accurate assessment of safety in 85%-90% of the people receiving the product,” Carragee said.

“Obviously, this remains a big problem.”

In a statement, Medtronic’s Ishrak said integrity and patient safety are the company’s highest priorities.

“So it is important that a respected academic institution provide a publicly trusted source of information by way of these systematic reviews and the novel data access program for researchers,” he said.

Charles Rosen, an orthopedic surgeon and president of the Association for Medical Ethics, noted that the Spine Journal review was an independent review.

“Is it really possible to say that a study funded by the company manufacturing the product is more independent?” Rosen said. “I don’t think so. My overall impression is that this is the fox offering to give us information on the well-being of the chickens in the henhouse.”

Krumholz said he hoped the review could be done in six months.

In June, the U.S. Senate finance committee launched an investigation into reports that doctors with financial ties to Medtronic were aware of serious complications with Infuse yet failed to reveal those problems in medical journal articles.

Citing reports in the Journal Sentinel, committee members Max Baucus (D-Mont.) and Chuck Grassley (R-Iowa) sent a letter to Medtronic demanding an extensive trail of documents, including financial records and communications between the company and doctors who have received millions in royalties and other payments.

# Bone agent linked to higher risk of cancer

Study echoes earlier report on Medtronic product

By JOHN FAUBER  
jfauber@journalssentinel.com

**Chicago** — Spine surgery patients who got a bone growth stimulating agent as part of a clinical trial were three to five times more likely to develop cancer two to three years after being implanted with the product, according to a new analysis.

The report is the latest cautionary note involving Medtronic's controversial bone morphogenetic protein-2, or BMP-2, a popular genetically engineered product used in spinal fusion surgery as an alternative to using a small amount of a patient's own bone.

The analysis led by Eugene Carragee, a Stanford University orthopedic surgeon, echoes findings in a Journal Sentinel/MedPage Today investigation last month. That story showed an elevated cancer risk in the clinical trial of the Medtronic product containing BMP-2 that is known as Amplify.

The story noted that doctors who have received millions of dollars in royalties from Medtronic had authored a 2009 paper about Amplify that failed to identify a significant cancer risk though they and the company were aware of data linking it to cancer. The royalties paid were not for BMP-2.

Doctors say Carragee's new analysis raises serious concerns about a cancer risk posed by BMP-2, which has been used in hundreds of thousands of patients since it came on the market in 2002.

"This is a provocative study that should make surgeons most concerned," said Dan Spengler, a professor of orthopedic surgery at Vanderbilt University Medical School. "I can't see a justification for its use except in extreme cases."

In response to questions on the earlier story, Medtronic and one of the authors of the paper said the cancer cases were not statistically significant. Two of the authors of the study did not respond to an email Thursday.

Medtronic spokeswoman Marybeth Thorsgaard did not address the cancer issue.

Instead she said the company was waiting for results of independent reviews being managed by doctors at Yale University. In August, Med-

## More cancer cases found in spine patients who got BMP-2

Cancer cases that were diagnosed after spinal fusion surgery among 239 patients who were implanted with BMP-2 as part of the Amplify clinical trial.

### Patients with BMP-2 fusion surgery implants who later developed cancer

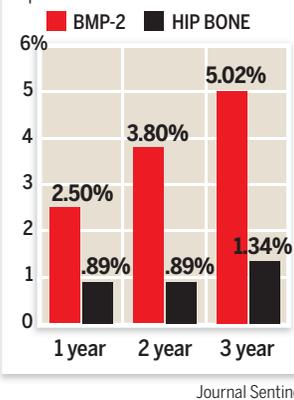
| AGE                    | CANCER TYPE                | TIME TO DIAGNOSIS AFTER SURGERY | OUTCOME                                     |
|------------------------|----------------------------|---------------------------------|---|
| <b>Female patients</b> |                            |                                 |   |
| 62                     | Stomach                    | 28 months                       | Pending                                     |
| 58                     | Thyroid                    | 38 months                       | Pending                                     |
| 45                     | Breast                     | 38 months                       | Pending                                     |
| 56                     | Thyroid                    | 48 months                       | Pending                                     |
| 40                     | Skin                       | 21 months                       | Resolved                                    |
| 42                     | Skin; melanoma (eye)       | 3 and 38 months                 | Resolved; permanent disability or condition |
| 69                     | Ovarian                    | 22 months                       | Death                                       |
| 55                     | Lung                       | 6 months                        | Death                                       |
| <b>Male patients</b>   |                            |                                 |   |
| 66                     | Leukemia (CML); skin; skin | 39 and 12 months and 5 weeks    | All pending                                 |
| 67                     | Prostate                   | 29 months                       | Resolved                                    |
| 53                     | Laryngeal                  | 8 months                        | Resolved                                    |
| 54                     | Skin                       | 55 months                       | Resolved                                    |
| 69                     | Prostate                   | 12 months                       | Permanent disability or condition           |
| 65                     | Lymphoma                   | 29 months                       | Permanent disability or condition           |
| 60                     | Pancreatic                 | 13 months                       | Death                                       |

Source: FDA records

Journal Sentinel

## More cancer two to three years later

Spine surgery patients who got BMP-2 had a significantly higher risk of developing cancer than those who got a graft of their own hip bone.



Journal Sentinel

tronic said it would spend \$2.5 million to hire the Yale researchers to do an independent review of the safety and effectiveness of the product.

That followed news in June that a U.S. Senate committee had launched an investigation into reports that doctors with financial ties to Medtronic were aware of serious complications with BMP-2 yet failed to reveal those problems in medical journal articles.

The Senate Finance Committee said it opened the probe after reports in the Journal Sentinel.

### Statistics

The new BMP-2/cancer analysis was presented Thursday at the North American Spine Society's annual meeting in Chicago.

The clinical trial it focused on involved 239 patients who got the high-dose Amplify product and 224 who got a conventional graft of their own hip bone.

Among those who underwent follow-up about three years after the surgery, 5% of those who got Amplify, or 12 patients, were diagnosed

with a new cancer, compared with 1.3%, or three patients, who got a graft of their own hip bone. The difference was statistically significant.

After two to three years of follow-up, Amplify patients were four to five times more likely to develop at least one new malignancy, the analysis found. Viewed another way, one extra patient would be expected to develop cancer out of every 20 to 25 treated with Amplify.

The cancer numbers and ethical questions raised about conflicts of interest drew criticism from surgeons attending the presentation:

“Who do we believe?” asked John Jacquemin, an orthopedic surgeon from Cincinnati. “When the literature comes out, what’s real and what is not?”

Jacquemin said he was especially troubled by allegations of bias in papers written by doctors with financial conflicts.

“That scares me and troubles me,” he said.

Jerry Knirk, an orthopedic surgeon from New Hampshire, said he was concerned that most funding for medical devices comes from corporations.

“Money corrupts,” he said.

The authors of the 2009 paper mentioned the cancer link only in a table accompanying the paper. The text itself never addressed the concern of whether BMP-2 might fuel cancer.

It was written by six physician authors. The first three authors of the paper — or entities they are associated with — received about \$10 million from Medtronic, mostly in royalties, in 2010 alone. The royalties were for other products, not for BMP-2.

While the authors failed to warn of the cancer concern, the Journal Sentinel found a full airing of the cancer question in more than 1,000 pages of U.S. Food and Drug Administration records. That information included FDA reports and information filed with the agency by Medtronic as part of its application to win approval for Amplify.

At a 2010 Amplify hearing, for example, an FDA staffer said “the primary statistical

concern is an apparent association with malignancy.”

Since coming on the market in 2002, BMP-2 has become popular in spinal surgery. By stimulating bone growth, it can eliminate the need to harvest a small amount of a patient’s own bone for use in a spinal fusion surgery.

The product was approved for a narrow use after an earlier clinical trial showed it worked about as well as a standard hip bone graft in a specific kind of spinal fusion surgery. But doctors quickly began using BMP-2 in other, unapproved ways, known as “off-label” use. That helped fuel annual sales of \$700 million.

### **FDA ruling appealed**

With the Amplify trial, Medtronic was seeking additional FDA approval for a different BMP-2 spinal fusion product. The FDA has refused to grant approval, a decision Medtronic is appealing. Doses of BMP-2 similar to what was used in the Amplify trial are commercially available.

Carragee said only a small portion of BMP-2 use follows the protocols of how the product originally was approved by the FDA. Most of its use is in so-called off-label applications.

He noted the doses of BMP-2 as well as the carrier used in the Amplify clinical trial are commercially available and as such are used off-label by surgeons.

Carragee said he thinks BMP-2 may fuel existing cancers.

He said the theory is that as people get older they have more cancer cells in their body, which the immune system tries to keep in check.

The addition of BMP-2, especially in higher doses, may disturb that balance and allow a cancer to grow, he said.

“At higher doses in people who are older and who have less resiliency to cancer, it’s more worrisome,” he said. “I would say, why risk it?”

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John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [medpagetoday.com](http://medpagetoday.com).

# Doctors' letter to journal is silent on their payment

By JOHN FAUBER

jfauber@journal sentinel.com

Doctors who failed to identify a significant cancer risk with a Medtronic spine surgery product in their published research have refused to disclose relevant financial conflicts in a letter about that research to be published Friday in a medical journal.

Though it is believed that Medtronic had paid at least three of the doctors more than \$20 million, they told the editors of the Spine Journal, which will publish their letter Friday, that they would not reveal how much they had been paid by Medtronic from 2006 to 2009, a time period covering research papers that are the subject of Friday's letter.

The Spine Journal said its policy is to require disclosure of potential conflicts of interest, within ranges going up to \$2.5 million, for the period of papers in question, which in the case of the new letter involved papers published in 2006, 2007 and 2009.

"However, the authors refused our request for disclosures covering this time period," said an editor's note that accompanies the letter.

The note said that because of the importance of the topic an exception was made and the letter was published without the required financial disclosures.

The refusal by the doctors to reveal how much they had been paid is the latest development in the ongoing saga over Medtronic's controversial spine surgery product known as bone morphogenetic protein-2.

Last month, a Journal Sentinel/MedPage Today investigation found that those same doctors had failed to identify a significant cancer risk in a 2009 paper about a Medtronic-funded clinical trial of a high-dose BMP-2 product known as

Amplify.

The surgeons left out important data and contended that there was no significant link between the product and cancer, though they and the company had information of a significant risk at least two months before the paper was published, the newspaper found.

Then, a new analysis by independent doctors presented at a spine surgeons meeting last week in Chicago found that patients in the Amplify trial who got BMP-2 were three to five times more likely to develop cancer two to three years after being implanted with the product than those who got a graft of their own hip bone.

All of that follows a rebuke of BMP-2-related research in 13 papers published over nearly a decade and written by doctors who have received tens of millions of dollars from Medtronic. That unprecedented analysis, published in June in the Spine Journal, criticized those papers for repeatedly failing to reveal serious complications linked to BMP-2.

BMP-2, a biological agent that stimulates bone growth, was approved in 2002. It is an alternative to using a small amount of a patient's own bone in spinal fusion surgery.

The product has been used in hundreds of thousands of back surgery patients and has produced sales of more than \$700 million a year.

## Letter to Spine Journal

Prompted in part by Journal Sentinel/MedPage Today investigative reports over more than a year, in June the U.S. Senate Finance Committee launched an investigation into the failure of doctors with financial ties to Medtronic to report a variety of serious complications with the product in their published papers. Medtronic also is under investiga-

tigator judgments . . . ”

In an interview Tuesday with the Journal Sentinel, Medtronic officials said they now are looking into the issue of whether published articles failed to properly report various complications linked to Infuse.

“We are very serious about this,” said Richard Kuntz, Medtronic’s senior vice president and chief scientific, clinical and regulatory officer. “We will do a full analysis of these papers.”

Kuntz and Christopher O’Connell, an executive vice president who oversees the Medtronic division that includes Infuse, also said they will provide a full accounting of royalties and other payments to doctors who authored Infuse papers.

### **Series started in '09**

In late 2009, the Journal Sentinel began running a series of stories about the approval by the FDA of Infuse and a small group of surgeons with financial ties to Medtronic who wrote the pivotal studies about it.

Among other matters, the stories raised questions about why doctors with financial ties to Medtronic got better results in the pivotal clinical trial of Infuse than doctors in the trial who did not have financial conflicts.

Several of the stories involved Zdeblick, who has received more than \$23 million in royalties and other payments from Medtronic since 2002, was involved in the clinical trial of Infuse and also co-authored papers about the product.

Two Infuse papers co-authored by Zdeblick were published in the Journal of Spinal Disorders & Techniques where Zdeblick has been editor-in-chief since 2002.

Neither of those papers linked Infuse to a complication that causes sterility in men, though that information was known to the authors. Additionally, neither of the papers disclosed financial conflicts with Zdeblick and his co-authors.

None of Zdeblick’s royalties are for Infuse, though he has received royalties for a product that is used with Infuse. Zdeblick declined to comment for this story.

At about the same time that the Journal Sentinel started running stories about Infuse, editors at the Spine Journal began receiving complaints from doctors around the

country who were pointing out contradictions between papers published by doctors with financial ties to Medtronic and other data involving Infuse complications.

By August of last year, the problem had become so pronounced that it was brought up at a meeting of board members of the Spine Journal, said editor Eugene Carragee, a spinal surgeon at Stanford University.

In the editorial, the Spine Journal noted: “The range of critics is formidable; from Consumer Reports to the Wall Street Journal, from the Milwaukee Journal Sentinel to the U.S. Senate, from the New York Times to the Department of Justice, and so on.”

### **Cozy ties draw fire**

For years, the orthopedic surgery field has been under fire for its cozy ties to the medical device industry.

Published articles — often funded by medical device companies — have revealed scant information about the financial conflicts of authors, including a consistent failure to spell out how much royalty and consulting money authors received.

Critics say those kinds of articles have incalculable value to device-makers trying to increase sales of their products. So they say huge financial payments, which would raise eyebrows among doctors who read the articles, have been kept secret or have been revealed in such cryptic terms as to be meaningless.

The issue of the Spine Journal — nine papers and commentaries — amounts to an unheard of tell-all by a group of reform-minded orthopedic surgeons and researchers. At least one key Infuse study challenged in the new review was published in the same journal. A co-author of that study was a deputy editor of the Spine Journal at the time.

“This is really extraordinary,” said Marcia Angell, a former editor of the New England Journal of Medicine. “I’ve never seen a journal publish an issue devoted to debunking a popular treatment, and by implication, the authors of the studies that promote the treatment.”

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*This article is part of an ongoing series about how money and conflicts of interest affect medicine and patient care. John Fauber reported this story in a joint project of the Journal Sentinel and MedPage Today. MedPage Today provides a clinical perspective for physicians on breaking medical news at [medpagetoday.com](http://medpagetoday.com).*



## **JOHN FAUBER**

John Fauber has been a medical reporter at the Milwaukee Journal Sentinel since 1996. His awards include the 2010 National Headliner Award for medical/health/science writing for his ongoing “Side Effects” series on conflicts of interest at the University of Wisconsin School of Medicine; the 2010 silver Bartlett & Steele Award for Investigative Business Reporting for the expanded “Side Effects” series; the 2004 Howard L. Lewis Achievement Award for a five-year collection of stories focusing on heart disease and stroke; the 2003 American Society for Microbiology’s Public Communications Award for two stories he co-authored on prion diseases in humans and animals; and the 1992 Gerald Loeb Award for business and financial writing for the series “Adios Wisconsin” about Wisconsin corporations moving jobs to Mexico. He also was a finalist for the 2003 Pulitzer Prize for Explanatory Journalism for two stories he co-authored that were part of a five-part series on chronic wasting disease.

As a medical reporter his primary beats are heart disease, cancer and neurology. Since 2009 much of Fauber’s reporting has been devoted to the ongoing series on conflicts of interest that can compromise a doctor’s judgment.

Fauber has a bachelor’s degree in journalism from the University of Wisconsin-Milwaukee.