

The conclusions were clear: Women who took hormone therapy drugs were at increased risk for breast cancer, heart disease, stroke and blood clots.

The findings were so strong that researchers stopped a clinical trial in 2002, five years early, because it would have been unethical to continue giving the drugs to women.

But that same year, the University of Wisconsin-Madison's School of Medicine and Public Health began a medical education program for doctors that promoted hormone therapy, touted its benefits and downplayed its risks.

For the next six years, thousands of doctors from around the country took the online course that was funded entirely by a \$12 million grant from Wyeth Pharmaceuticals, which makes the hormone therapy drugs used in the study, Prempro and Premarin.

The university received \$1.5 million of that total, and university faculty received money as well.

Even after the course was no longer available, the Web site and course material remained on the Internet, accessible to consumers and doctors. The university dropped the site Jan. 15, one day after the Journal Sentinel began questioning UW officials about the propriety of the program.

The influence of drug companies on doctors -- and, by extension, medical schools -- is coming under increased scrutiny, with critics saying programs like the UW one are essentially marketing exercises.

Now, prompted by questioning from the newspaper, the university is investigating the course to see whether it met the standards of the medical school, said its dean, Robert Golden.

"We expect all of our educational activities to follow the highest standards," he said.

The course material was developed largely by DesignWrite, a New Jersey-based firm paid by Wyeth.

The company is being investigated along with Wyeth by a U.S. senator looking into the practice of ghostwriting in scientific articles as a way to market hormone therapy drugs.

Together, Wyeth, DesignWrite and UW formed the Council on Hormone Education -- the name of the educational organization stamped on course material for the class.

Thirty-four of the 40 council member physicians have financial ties to Wyeth, including the course director, Julie Fagan, a UW doctor and associate professor of medicine.

"It is pure, undisguised marketing," said Anthony Scialli, an adjunct professor of obstetrics and gynecology at Georgetown University's School of Medicine.

Drug companies are "funneling money through universities for advertising and trying to disguise it as education," said Scialli, who is also a member of PharmedOut, an organization of doctors opposed to universities using drug money.

His take has been echoed by others, including the Senate Finance Committee, which reported in 2007 that pharmaceutical firms have taken control of these programs to get favorable presentations of their products, grab market share for expensive brand-name drugs and encourage doctors to write prescriptions for off-label use.

The UW course is a prime example of these practices, said Jerome Kassirer, a distinguished professor at Tufts University School of Medicine and former editor of the New England Journal of Medicine.

The Journal Sentinel asked several doctors, including Jacques Rossouw, chief of the Women's Health Initiative branch of the National Institutes of Health, to review course material. The initiative is the largest clinical trial of hormone therapy drugs.

He said the views expressed in the course are not those of the general scientific community and are not suitable for a university medical education course.

"There is a history of this kind of thing from Wyeth," Rossouw said. "The materials regurgitate lines that I have heard and read many times, and I have come to believe (though I do not know) that this is part of an overall marketing strategy to the profession. It is not good science because it fails to strive for any kind of balance."

Raymond Gibbons, a professor of medicine at the Mayo Clinic and former president of the American Heart Association, said he also found material relating to heart disease one-sided.

He noted that the materials inappropriately gave observational data equal weight to rigorously done, randomized clinical trials.

"It's a lot of post hoc analysis," he said. "I don't see the other side of the argument."

Studies show risks

For years, doctors thought hormone therapy reduced the risk of heart disease and stroke while also relieving menopausal symptoms, such as hot flashes, night sweats and genital atrophy.

But beginning in 1998, some of those myths started unraveling.

Rigorous studies involving thousands of women showed that hormone therapy increases the risk of heart disease, stroke, breast cancer, blood clots and dementia. They also showed quality-of-life benefits are short-lived.

In May 2002, a major clinical trial that was part of the Women's Health Initiative was suspended because medical investigators were worried they were subjecting women to too much risk.

Despite the risks, the Food and Drug Administration approved the use of hormone therapy for the treatment of menopause symptoms, though only at the lowest possible doses and for only short periods of time.

In the fall of 2002, just months after the health initiative was stopped, the Council on Hormone Education launched its first UW hormone therapy medical education course.

"There were millions of women impacted by that information, and physicians and women really needed to have that information," said Doug Petkus, spokesman for Wyeth. "We felt we were providing a service to them by helping them . . . understand the significance."

Over the next several years, Wyeth poured \$12 million into the course.

According to the first newsletter published by the Council on Hormone Education, the goal of the course was "to develop and disseminate balanced, accurate, timely and consistent information about hormone therapy" so doctors could "better serve women."

Wyeth is now defending about 8,700 lawsuits, filed by more than 10,000 women, over claims that their use of Wyeth's hormone drugs caused them to develop breast cancer, stroke, ovarian cancer and heart disease.

The educational material included 16 newsletters, which included editorials and essays with titles such as "A Perspective on WHI (the Women's Health Initiative)," "Choosing the Right Therapy for Postmenopausal Osteoporosis" and "Sexual Desire Disorder in the Postmenopausal Woman."

One newsletter, titled "Don't Confuse Marketing with Science," warns doctors and women about non-commercial hormone concoctions.

"The marketing of bio-identical hormones preys on emotions . . . but clinical decision-making, in contrast, must be based on a foundation of knowledge," wrote Leon Speroff, editor of the newsletter and a Wyeth-funded researcher at Oregon Health & Science University.

Other newsletters, which included patient handouts and multiple-choice exams in the back for physicians, urged doctors to consider the bonuses of hormone therapy.

For instance, in a newsletter titled "Menopause and Quality of Life," Wyeth-funded researcher JoAnn Pinkerton wrote: "Undesirable skin changes associated with aging can have a deleterious impact on both physical and mental health. These changes include lines, wrinkles and dryness that affect Quality of Life."

"American women attach to youthful, attractive skin," she wrote, explaining that the age-induced changes are in large part the result of estrogen loss. There is no scientific consensus that estrogen supplements will reverse the aging process in skin.

The University of Virginia Health System doctor also suggested that depression, insomnia and mood issues could be the result of estrogen and other hormone imbalances.

Her conclusion: "Hormone therapy treats menopausal symptoms more effectively than any other single agent." And a physician must weigh those benefits against a woman's risk for "coronary heart disease, deep vein thrombosis, pulmonary embolism, stroke, breast cancer, and gall bladder problems, which hormone therapy may be associated

with."

Fagan, the UW course director, defended the program, saying nothing in the course material was scientifically inaccurate. However, she said the material was presented in a "more positive light" than she would have preferred.

She said she offered to participate in the course in order to tone down the material and make it as accurate as possible.

In both 2005 and 2007, Fagan received between \$5,000 and \$10,000 from DesignWrite, according to disclosure forms she filed with the university. UW was unable to produce disclosure forms for Fagan for the years 2003, '04 and '06.

Michael Platt, president of DesignWrite, said the program was developed in accordance with all regulations governing continuing medical education and was certified by UW.

"DesignWrite is proud to have assisted the University of Wisconsin and the distinguished faculty of the council," he said.

Downplaying concerns

Since the results of the first large clinical trial on hormone therapy were released in 1998, drug companies have been trying to minimize the concerns, said Marcia Stefanick, an investigator with the Women's Health Initiative.

"They are very eager to keep coming up with ways to show it isn't harmful," said Stefanick, a professor of medicine at Stanford University's School of Medicine. "There is this constant attempt to get women back into it."

With good reason: Sales of Wyeth hormone products dropped by about 65% after the first health initiative study results were released in 2002, said Wyeth spokesman Petkus. In 2008, those sales had recovered to \$809 million.

Asked if the UW course has received criticism, George Mejicano, director of UW's continuing medical education program, said: "Yes and no. It's complicated."

He said he could understand how some people might think the course amounted to marketing for Wyeth.

Asked if he would do it again, he said: "Would I do things differently? Yes, I'd do things differently."

The Council on Hormone Education is one of several drug industry- sponsored courses offered by UW, including a smoking cessation course, funded by Pfizer, the maker of a smoking cessation drug; a program on restless legs syndrome, funded by Boehringer Ingelheim, the maker of a drug that treats the condition; and a course on premenstrual dysphoric disorder, funded by Bayer HealthCare Pharmaceuticals.

Both Wyeth and DesignWrite got letters last month from U.S. Sen. Charles Grassley (R-Iowa) requesting information about the use of ghostwriters involving articles about hormone therapy.

Wyeth is responding to the letter, Petkus said. He said the articles in question were subject to peer review and were factually sound. He said the authors, not Wyeth, had control over the content.

"We are cooperating," said DesignWrite's Platt. He said DesignWrite strictly follows regulations related to its business.

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OTHER UW COURSES FUNDED BY DRUG FIRMS

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