university researchers give control to drug companies

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A Shadow Of Doubt

Medical schools give too much control to drug firms when testing medications, critics say

By Mark Horvit

Star−Telegram Staff Writer

The studies had all the right credentials.

Their lead authors were prominent academicians. The research was conducted at respected medical schools, including two in Texas.

They came to the same conclusion: New antidepressants are safe and effective for children and teen−agers.

Doctors prescribe millions of the pills, which parents give to their children. It hasn't gone well for some of them. While many doctors say

children in their care are helped, there have been reports of suicide attempts and other violent acts blamed on the pills.

Whether the drugs are responsible remains a point of contention, as does the question of how much they help those younger than 18.

But there's little question that studies conducted at universities that could cast doubt on the popular pills were shelved, while favorable results were promoted.

In the past few months, hard questions have been raised about some top−selling drugs. The roles of federal regulators and big pharmaceutical companies have come under heavy scrutiny.

But some are also asking whether academic medical centers do enough to prevent themselves from being used as marketing tools by one of the world's most profitable industries. Among the concerns:

· By setting the rules by which the drug studies are conducted, companies can stack the deck on the outcome.

· Research for a single study is usually spread among many academic institutions, and companies may limit, delay or prohibit individual researchers' access to the overall results.

· University researchers put their names on journal articles for which they haven't seen all the results or which company employees had a heavy hand in writing.

· Academic experts have stood by while companies kept unsuccessful results from the public.

A simple motivation can give companies the upper hand, said Dr. Drummond Rennie, deputy editor for the Journal of the American Medical Association.

"Money," Rennie said. "Money for yourself, money for your unit, money for all the people you employ on other research, money for travel. Money is a very, very powerful influence here."

Texas public medical schools and other academic institutions received more than $200 million in research funding from pharmaceutical and biotech companies between 2001 and 2003, according to an examination by the Star−Telegram. Some researchers who conduct those studies have pulled in tens of thousands of dollars a year in consulting contracts and speaking fees from the same companies.

University officials say that the money is only a small percentage of their overall research funding −− which was close to $3 billion in that three−year period −− and that academicians bring objectivity and oversight to the studies. Industry officials say that the federal Food

and Drug Administration oversees many facets of the process and that academic experts can play significant roles in shaping the research.

"The argument that we're doing things and conducting trials on our own is really wrong," said Alan Goldhammer, a vice president for Pharmaceutical Research and Manufacturers of America.

Many universities have strengthened their hand in working with drug companies, said Dr. David Korn of the Association of American Medical Colleges. But institutions still sometimes cede too much control, he said.

"They are supposed to stand for objectivity and dispassion and accurate, high−quality science and accurate reporting of science," said Korn, of the association's research division.

"And I think they can't have it both ways. If they're going to stand for that reputation, then they can't be trading it away for research contracts from drug companies."

Mixed results

Even before the debate on the safety of antidepressants for children and teens made headlines last summer, FDA reviews were coming to an important conclusion about the drug studies:

Most failed to prove the medications work.

But doctors usually had no way to know that. Instead, they heard about successful studies trumpeted in respected journals. Those articles featured the names of top university researchers −− some of whom had also been involved in unsuccessful trials that weren't seeing the light of day.

Consider how Paxil, one of the new−generation antidepressants, was tested in children and teens.

Three large clinical trials were funded by GlaxoSmithKline, or GSK, the maker of Paxil. Researchers at numerous universities participated.

In the first trial, the drug failed to meet the main goal researchers had set to measure its effectiveness. But because it met some secondary goals, researchers −− including two from Texas schools −− deemed it effective for adolescents, and an article was published in a major medical journal.

The two other trials failed to show that Paxil, when tested against a placebo, or sugar pill, was effective. Neither has been published.

An internal GSK memo shows how the company handled such mixed results. An employee discusses the need "to effectively manage the dissemination

of these data in order to minimize any potential negative commercial impact." The document, obtained by the New York attorney general for a lawsuit, also says "it would be commercially unacceptable" for GSK to state that Paxil's effectiveness had not been proved.

But when an FDA reviewer looked at the Paxil trials together, that's exactly what he determined.

It's also the way one of the published study's authors now portrays those results. Despite her previous conclusion, Dr. Karen Wagner of the University of Texas Medical Branch at Galveston told a group of psychiatrists at a meeting last week that all three Paxil trials proved unsuccessful. Wagner declined to comment after her presentation.

The Paxil pattern held true with other antidepressants that hit the market in the 1990s. Four of the drugs had what researchers considered positive results in treating depression in minors, and the studies were published. There were at least eight unsuccessful trials, and one researcher involved with several said none of those results have been published.

So even though the FDA had not approved use of the antidepressants, other than Prozac, for anyone younger than 18, the literature only gave the impression of growing evidence that the drugs work.

"Perhaps the preponderance of failed trials in depression might have dampened some of the enthusiasm for these drugs, had that information been publicly available, but that is of course speculation," FDA epidemiologist Andrew Mosholder wrote in response to Star−Telegram questions. Mosholder re−viewed many of the drugs, both for effectiveness and safety.

Dr. Graham Emslie, a child psychiatrist at the University of Texas Southwestern Medical Center at Dallas, took part in several antidepressant studies, including two Paxil trials −− the one deemed a success, and one that wasn't.

It's important to understand, Emslie said, that an unsuccessful trial doesn't necessarily mean a drug doesn't work. Instead, the failure may indicate that the test was poorly designed, so the results may not be scientifically valid.

For example, Emslie believes many of the antidepressant trials failed because they were modeled on adult usage, so dosages were wrong. Emslie and numerous other psychiatrists say the drugs work for their patients.

Still, he said he's uncomfortable with the way some unsuccessful trials in which he participated have not been publicized. Recently, he presented data from one at a conference, and articles on two have been submitted for publication. While he said working with the companies delayed the process, Emslie conceded that he and other researchers

often don't push as hard to publish unsuccessful results as they do their successes.

Others are uncomfortable with how companies may limit researchers' access to results −− even when benefiting from their expertise and reputation.

Most major medical centers −− including those in Texas −− demand publishing rights for the data they gather for drug company trials.

But trials usually take place at multiple sites, and officials at one institution cannot typically demand results gathered at others. With only their own information, they usually cannot draw scientifically valid conclusions.

Emslie, who like many top researchers has been a paid consultant and speaker for several drug companies, including GSK, said there's at least one company he likely won't work with again because it refused to share data with him and other researchers.

Schools can also be hamstrung because they sign contracts giving companies a period of exclusive use of the research results. At some Texas medical schools, the delay is as long as two years. That is meant to give the company time to gather and analyze data and coordinate any published articles. But two years is too long, said Korn and others.

Several Texas university officials said they are not aware of many instances when researchers have had problems getting data.

An attorney with the University of Texas System −− which oversees several medical schools −− said that in eight years, she has received only one such complaint.

In that recent case, the UT researcher and counterparts at other participating schools banded together to get data after the company halted a trial, BethLynn Maxwell said.

Although they were initially denied, the company has agreed to cooperate, she said.

Nationally, schools' failure to require full and timely access to data is one of the major holes in the academic oversight system, Korn said.

While, as a practical matter, many schools cannot handle the mountains of data generated in multicenter studies, he said, they should demand the access they need if a study is to be published with their names attached.

"If the company handles the data, what you get is what the company gives you, which may not be a perfectly accurate reflection," Korn said.

Concerns arise

As more studies touted new antidepressants and more kids began taking them, some doctors grew concerned.

The drugs lack some of the debilitating side effects of older antidepressants; that's their primary selling point. But they carry their own potentially serious health risks for some patients, including diabetes and reports of complications associated with withdrawal.

Most troubling to some, there are indications that a small percentage of children were becoming agitated or suicidal.

Mosholder, the FDA researcher, examined all trials of new−generation antidepressants involving children and teens. Although no trial participant committed suicide, Mosholder found that almost 3 percent showed signs of suicidal thoughts or behavior, about twice the percentage of those not taking the drugs.

His findings led the FDA last year to require a prominent "black box" warning on the drugs' packaging, despite some doctors' concerns that the drugs are being unfairly blamed and patients who need them will be scared away.

For the trend to be evident, Mosholder said, it was necessary to look at all the study results combined, including unpublished trials.

To win FDA approval for a new drug, a company has to show that the medication is safe and effective. But companies can set the ground rules for researchers.

Drug companies don't typically design clinical trials to identify uncommon risks, said Dr. Michael Fant of the University of Texas Health Science Center at Houston, who served on the FDA advisory committee that recommended the warning label. That could have been the case in the antidepressant trials, he said.

"It certainly contributed to some of the limitations in terms of what questions the studies could answer, because the studies are clearly being designed just to achieve a certain standard, and that standard is to get placed on the market," Fant said.

A shortcoming of many company−funded trials is that they pit their medicine against only placebos. Trials pitting the test drug against both a placebo and a competing pill that's known to work would be more telling, Emslie said.

But such studies could show that a competitor's product is superior, he said.

The FDA has raised concerns about how some companies design their trials.

In one study, a company pitted its new heartburn medication against a generic drug. But the new pill was prescribed in a dosage twice as strong as the generic, according to a senior FDA official.

Not surprisingly, the new drug worked better than the older, cheaper one.

Another study the FDA took issue with involved the antidepressant Zoloft.

Wagner, a child−psychiatry expert, was lead author of the study, which supported the use of Zoloft for children with major depression.

The authors reached their conclusion by combining two separate but identically designed studies, neither of which succeeded on its own.

The problem, FDA officials determined, was deciding after the studies began to combine the results. Goals are supposed to be set before the outcome is known.

Pfizer officials declined to comment about the studies. But in written testimony to a congressional committee examining the studies, a company official said the decision to combine data was made before the trials ended and results were known.

Wagner, who also took part in the published Paxil study and who has done consulting work for numerous drug companies, including Pfizer, did not respond to written questions from the Star−Telegram about specific studies.

Critics say that companies have too much power in the process and that their financial ties to some researchers increase their influence. Officials at several universities said that, on the contrary, the independence of their clinicians brings an objective eye to the design and other crucial aspects of company−funded studies.

When companies bypass academic institutions −− which has occurred with increasing frequency in recent years −− there may be far less scrutiny, said Perrie Adams, associate dean for research and a psychiatry professor at UT Southwestern.

Adams said schools have multiple safeguards intended to maintain high standards. Among them are institutional review boards, which must approve all research plans before studies can be done.

Those boards, which may review hundreds of studies a year, are designed primarily to protect the safety of patients in the trials. Part of their role involves examining the study design, Adams said, to weigh

potential benefits against any risk.

Question of authorship

In spring 2003, doctors got a special supplement with a medical journal in their mailboxes.

The publication was all about Paxil. Its 15 articles covered topics including the drug's success at treating depression, anxiety and obsessive−compulsive disorder. Not one focused exclusively on negative side effects or other shortcomings.

GlaxoSmithKline paid for it through an "unrestricted grant," implying the company didn't control content. And the funding source was explained in multiple disclaimers.

But the bold print went to the authors: respected researchers from some of America's better medical schools.

Supplements like this are an extreme example of the confluence of marketing and academia.

When a drug company is involved in a published study, university researchers are often listed as the primary authors −− the ones most responsible for the content −− with company scientists receiving second billing. But many times the company writes the bulk of an article.

"I think very few people these days who seem to be the authors of trials can in any meaningful way be said to have run the trial," said Dr. David Healy, a psychiatry professor at Cardiff University in Wales and an outspoken critic of drug companies' antidepressant research.

"It used to be, I'd draw up the protocol, get the patients, run the trial. Now, maybe I've been involved in meetings, seen and approved a pharmaceutical−company−written trial," he said. "I won't get to see the raw data at all. But I may be the first author on the paper."

Marketing can shade the content of some articles, critics say, even when the paper appears in a scholarly journal.

The Star−Telegram obtained copies of e−mails that offer a glimpse into how university researchers sometimes negotiate content with drug companies. The names are being withheld to protect the identity of the newspaper's source.

A researcher at a Texas medical school had questions about an article for which the researcher would be listed as lead author. It reported favorable results when testing a bestselling medication for a new use.

The researcher asked whether the weight gained by patients using the drug −− a known risk with such medication −− should be considered

significant.

A company official responded, "Obviously, from a marketing perspective, I hope we can avoid making this statement."

Ultimately, the published article terms the weight gain statistically significant.

When the researcher's office asked whether to expound on information about another side effect, a company employee said that was unnecessary.

"We do not want to remove the focus from efficacy in the manuscript," the employee wrote.

Rennie, of the Journal of the American Medical Association, said he doesn't understand why researchers participate in studies where the drug company can heavily influence content.

"It's like saying, 'I totally trust the drug company to be disinterested in how it publishes the results,' " he said. "To which I would say, 'You've got to be joking.' "

How much difference does it make when work is funded by drug companies rather than an independent source?

Dr. John Montgomery, assistant professor of psychiatry at the University of Mississippi Medical Center, and several researchers at UT Southwestern reviewed every article about new−generation antipsychotic drugs up through March 2002. Their conclusion echoes the findings of a growing body of research.

When published studies are sponsored by drug companies, they usually come to the same conclusion: The medicine works.

Montgomery said his study did not find major differences in the quality of the studies, regardless of sponsorship. However, he said there are other ways bias can creep in.

He pointed to one study comparing Risperdal and Zyprexa −− newer antipsychotic drugs. The dosage of Risperdal was so high that it virtually guaranteed significant negative side effects, Montgomery said. The maker of Zyprexa paid for the study.

"That's just one example of how they kind of stack the odds," he said.

Proposals for change

Even most critics agree there's a need for medical schools to work with drug companies. The reality is that only the companies −− which have the most to gain −− are going to put up the millions of dollars

necessary.

And medical school researchers −− and their patients −− have much to gain from participating in trials with cutting−edge medications, school officials say.

Academic researchers could benefit from several proposed improvements.

Chief among those is an effort in Congress, supported by many educators, to require all clinical trials to be publicly registered at inception, before results are known. A federal registry exists, but it is far from complete.

Pharmaceutical Research and Manufacturers of America is creating a voluntary registry where drug companies have agreed to report study findings, regardless of outcome, said Goldhammer, a vice president for the organization. Relatively little has been posted so far, but Goldhammer said companies have until later this year to act.

Some companies are working on their own disclosure programs. GSK is building an Internet database listing results from all clinical trials, even failed ones, on products the company sells, spokesman Rick Koenig said.

But critics say voluntary industry−operated registries won't work.

Wagner said through a spokeswoman at UT Medical Branch at Galveston that she supports creating a national registry, as well as other safeguards "that will make the research process more transparent and safer without compromising the ability of scientists to do the work that leads to advances in health care."

Korn said his association and others plan to work on a set of principles and guidelines that universities should follow when conducting industry−sponsored research. He said it's up to the schools to become more demanding, such as insisting on timelier access to all the data. But he knows that will be a tough sell to drug companies.

"The companies will tell you they paid for the study and they own all the data and they can do what they want with it," Korn said.

Some industry critics say the system's flaws are too fundamental to be easily repaired.

There was once a clearer separation between industry researchers and their university counterparts, said Vera Hassner Sharav, who heads the drug industry watchdog group Alliance for Human Research Protection. The industry looked to university researchers as a "credibility bridge" to bring validity to studies, she said.

"But it turns out they're really partners," she said. "Once you have a scientist and the institution in partnership with industry, you've broken the fire wall that existed."

IN THE KNOW

Industry research funding

Texas academic medical centers received the following in research grants from pharmaceutical and biotech companies between 2001 and 2003:

· University of Texas $107.8 million M.D. Anderson Cancer Center
· University of Texas $27.8 million Health Science Center at San Antonio
· University of Texas $27.4 million Health Science Center at Houston
· University of Texas $22 million Medical Branch at Galveston
· University of Texas $16.5 million Southwestern Medical Center at Dallas
· Texas Tech University Health Sciences Center $8.1 million
· University of Texas Health Center at Tyler $3.2 million
· University of North Texas Health Science Center $2.2 million
· Texas A&M University System Health Science Center $1.1 million
TOTAL $216.1 million

· The total represents about 8 percent of all research dollars reported. The bulk of research funding comes from the federal government.

· An additional $34 million in donations was reported by five schools, with UT Southwestern accounting for $21 million of that.

· Some schools did not report a full three years' worth of data, and in some cases fiscal years are represented instead of calendar years. The figures reflect grant money awarded, not necessarily the amount spent.

SOURCES: The institutions, Star−Telegram analysis
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