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For more than 20 years, Stanford University psychiatrist Alan F. Schatzberg has been hunting for a better way to treat the most severely depressed patients.

A few years ago, he announced with considerable fanfare that he may have found it in an unlikely place -- a repackaged version of RU-486, the controversial abortion pill. It "may be the equivalent of shock treatments in a pill" without the side effects, he said in a Stanford news release.

Yet Schatzberg has more than a purely scientific interest in this particular pill.

He has a financial conflict of interest.

The 61-year-old chairman of Stanford's **psychiatry** department administers a \$600,000-a-year federal grant, part of which pays for ongoing research at the medical school on mifepristone, the key ingredient in RU-486, in depression. He is also co-founder of Corcept Therapeutics in Menlo Park, a publicly traded company that hopes to turn mifepristone into an approved treatment for depression and other psychiatric ills.

He sits on the company's board of directors, chairs its scientific advisory board and is one of its largest shareholders. And because the company has an exclusive license from Stanford for Schatzberg's discovery, the university also stands to profit from Corcept's work.

Such conflicts are surprisingly common in the high-stakes world of academic medical research. But what makes Schatzberg's case unusual is that two other top research psychiatrists have publicly attacked his work and accused him of shoddy science.

Schatzberg's conflict is a lesson in how hard it can be for a leading scientist at a major medical school to disentangle his outside financial interests from his academic role.

The Stanford professor says he has done everything required under the rules: He's disclosed his corporate ties to the university and the government. He has identified them in published papers and lectures. And he's kept a distance from RU-486 depression research on campus even while administering federal grants that pick up the costs.

"The reality is when people invent something at a university and they may in fact get a royalty, they've

created some conflict," Schatzberg said. "But conflicts only materialize with success, when there might be a benefit."

But two independent experts on medical statistics, asked by the Mercury News to review key papers co-written by Schatzberg about the effects of RU-486 on depression, agree with his critics: The studies published to date, they say, are not properly analyzed.

Schatzberg defends his studies as solid preliminary research and says the criticisms fail to grasp the importance of publishing promising early findings in drug development.

"We're trying to do something to help very badly ill patients and if it's successful the field will be advanced," he said. "I didn't come into this because of business. What motivates me is to help people."

The stakes for Schatzberg, his company, the university and severely depressed patients are huge. Corcept estimates that 3 million patients could benefit from the drug. Schatzberg, whose family has paper profits of nearly \$12 million from Corcept stock, could reap millions more if the company's treatment is approved.

Unusual dispute

As its tongue-twisting name implies, the American College of Neuropsychopharmacology is dedicated to research that probes the workings of the brain. Schatzberg is a past president.

Members try not to miss its annual meeting, typically held in December in a warm climate. It was at the 2004 meeting in San Juan, Puerto Rico, that Schatzberg's critics publicly unveiled their critique of his work in the form of a poster -- really a scientific paper in outline form, pinned to a board in an exhibit hall.

The contents were explosive.

The poster, by Drs. Bernard J. Carroll and Robert T. Rubin, systematically picked apart the conclusions in three published studies of RU-486 in depression, two by Schatzberg and his colleagues, one by an independent group.

But in a departure from the usual give and take of scientific debate, the poster quoted positive public statements about the drug by Schatzberg and other researchers and juxtaposed those statements against the individual's financial interest in Corcept.

There, for example, was Schatzberg saying RU-486 may be "the equivalent of shock treatments in a pill" and a statement pointing out that he owned 3 million shares of Corcept stock. The point was hard to miss: Researchers with a financial interest were expressing "considerable enthusiasm" for a treatment of questionable effectiveness.

The poster was seen by many of the top brain scientists in the country, people whose opinions matter deeply to Schatzberg as well as his critics. Carroll, former head of **psychiatry** at Duke University and now semi-retired in Carmel, recalls that people came up to him during the session, slapped him on the back and said, "It's about time somebody said this."

But he and Rubin soon learned that other members, Schatzberg among them, were furious. A lawyer for Corcept says the ACNP admonished Carroll and Rubin for their conduct. Both Carroll and Rubin say they were faulted for making their criticisms public, not for the content of the presentation.

Even now, Schatzberg can hardly contain his anger. "Those that are critical," he said, "ought to be careful about impugning others."

In his genes

Medicine and **psychiatry** seem to be in Alan Schatzberg's genes. His father was a general practitioner in New York. His sister, brother-in-law and niece are all psychiatrists.

“When I got out of medical school in 1968,” he said, “biological **psychiatry** was just starting and I found it fascinating.”

The talk therapy pioneered by Sigmund Freud was making room for chemistry. Patients who might have spent the rest of their lives in psychiatric wards were being sent home with prescriptions, and a new generation of drugs would become billion-dollar-a-year blockbusters.

After completing his training and a stint in the U.S. Air Force, Schatzberg joined Harvard's renowned McLean Hospital, famous for its treatment of celebrity poets like Robert Lowell, Anne Sexton and Sylvia Plath.

By the 1980s, Schatzberg and a junior faculty member, Dr. Anthony J. Rothschild, had worked out a theory to explain the underlying cause of what they believed to be a distinct disease, “psychotic major depression.” These were patients who not only were profoundly depressed, but who also might believe they were being tailed by the police, that their co-workers were out to get them or that the devil was taking control of their thoughts.

The standard treatment is electroshock or a combination of drugs. But electroshock requires general anesthesia, causes memory loss and is expensive. And the drugs can cause weight gain, diabetes and uncontrolled movements.

Schatzberg and Rothschild came to believe that high levels of the stress hormone cortisol might explain what was happening to their gravely depressed patients. They speculated that a drug to block cortisol could be an effective treatment.

Ironically, this idea was partly based on earlier work by Carroll and Rubin, now Schatzberg's outspoken critics.

The main ingredient in RU-486 is mifepristone, a chemical known to block cortisol. But because of the controversy surrounding abortion, RU-486 was then impossible to obtain, said Rothschild.

In 1991, Schatzberg became chairman of the **psychiatry** department at Stanford, where he continued his work on depression. When RU-486 became available for research a few years later under President Clinton, Schatzberg and Dr. Joseph K. Belanoff, a young psychiatrist on a fellowship in the department, began testing the pill in a handful of severely depressed patients.

They were encouraged by the results of their pilot study, funded by a National Institutes of Health grant. So was the university. In 1997, Stanford applied for a patent covering mifepristone and related compounds when used to treat depression. Schatzberg and Belanoff would each be entitled to a 14 percent cut of any licensing fees and royalties paid to the university.

The university's technology licensing office, which files patents and markets the rights, made the rounds of the big drug companies. But because of the political issues surrounding RU-486, “they didn't want to touch it,” Schatzberg said. “We had a drug that could help the most severely ill people, people who are at risk of killing themselves, killing their kids, dying because of medical illness, who might be helped by a very interesting and remarkable treatment that could be an alternative . . . to shock treatments.”

The only option, he said, was to start a company, something dozens of Stanford medical researchers had done before him.

Creating conflict

With the backing of Silicon Valley biotech investors, Schatzberg and Belanoff in 1998 founded Corcept Therapeutics. The start-up obtained the exclusive license for the Stanford patents that no one else seemed to want. In exchange, the university got 10,000 shares of company stock plus annual fees and milestone payments.

Belanoff became the company's full-time chief executive officer. Schatzberg took a seat on the board of

directors and a part-time post as chairman of the company's scientific advisory board, a job that now pays him \$60,000 a year. He and his family were granted 3 million Corcept shares for \$1,000 -- today worth nearly \$12 million.

He remained head of his department at Stanford, and continued as the principal investigator on several NIH grants, today totaling more than \$1.3 million a year.

Beginning in 2000, Corcept sponsored a trial that recruited patients at six universities, including Stanford. Schatzberg, who says he played no direct role in the study, and the university had a substantial stake in the outcome of the trial -- and a classic conflict of interest.

Stanford had no conflict of interest committee at the time, so he reported his financial ties to the dean's office. After the committee was put in place in 2001, Schatzberg went before it ``to discuss in detail my research activities and my relationship with Corcept in order to ensure a clear separation of these interests."

Once the company was formed, Schatzberg decided he could no longer play a direct role in RU-486 studies in depression. But he remained principal investigator with overall responsibility for NIH grants that have paid for ongoing Stanford research on the drug Corcept hopes to market.

Schatzberg says he helped design the RU-486 studies being conducted on campus but leaves it to others to recruit patients, administer treatments and analyze results. Monitoring committees at NIH and Stanford review the studies to ensure patient safety.

However, Schatzberg acknowledges that he has considerable influence over the junior faculty members doing the studies. As chairman of **psychiatry**, he helps set their salaries and can affect their career advancement. And he continues as a co-author of the resulting papers.

Annually, he reports his Corcept holdings and his many other outside financial interests to the medical school's conflict of interest program manager. And he generally discloses his interest in Corcept, as well as other companies, when submitting professional papers or giving talks.

The med school's dean, Dr. Philip A. Pizzo, agrees that Schatzberg has played by the rules, describing him as ``a person of high integrity."

Disclosure is a key element in the university's approach to dealing with conflicts like Schatzberg's. But one study, by Don A. Moore and others at Carnegie Mellon's Tepper School of Business in Pittsburgh, suggests that disclosure can have the opposite of the intended effect.

Dr. Jerome P. Kassirer, a former New England Journal of Medicine editor, puts it this way: ``Once they've disclosed their conflicts, people feel pretty free to say whatever they want to say."

Another safeguard, put in place by Stanford in December 2002, requires that the university divest shares in companies like Corcept that have treatments being tested on campus, said Paul Costello, chief of communications at the medical school.

It did not do so until May 2004 -- a few months after Corcept went public. The university gave the proceeds -- about \$100,000 -- to Lucile Packard Children's Hospital, which is affiliated with Stanford.

However, the university continues to have a conflict: If Corcept succeeds in developing RU-486 for depression and other disorders, Stanford will get additional royalty and milestone payments. So far, Stanford has collected about \$400,000.

`Dramatic' results

Two years after Corcept was founded, Schatzberg described the results of the small NIH-funded pilot study in Stanford Report, the university's weekly faculty and staff newspaper. In four of the first five patients, the results were ``fairly dramatic," Schatzberg said.

“They stopped hearing voices and having pessimistic kinds of delusions, like they're dying or the world is ending,” he was quoted as saying. “What's interesting is that the results are not effervescent. The patients feel better and it lasts.”

The piece, which is still posted on Stanford's Web site, does not mention Schatzberg's financial ties to Corcept.

By June 2001, on the strength of these early findings, Corcept had raised \$29 million from private sources. Four months later, the results of the five-patient pilot study were published in a scientific journal, claiming “a rapid reversal of psychotic depression.”

Just before Christmas that year, Corcept filed plans with the Securities and Exchange Commission to raise as much as \$90 million in an initial public stock offering. While the company waited to issue stock, Schatzberg, Belanoff and others reported in the journal *Biological Psychiatry* the results of the larger Corcept-sponsored study of RU-486 in 30 patients at six academic centers, including Stanford. Nearly two-thirds of the subjects who received higher doses, the study said, showed “significant reductions in their psychosis” during the one-week trial.

Enter the gadflies

Bernard Carroll recalls first reading the *Biological Psychiatry* study in his home-office in Carmel, where he runs his non-profit institute, the Pacific Behavioral Research Foundation.

“The ‘spin’ was unmistakable,” Carroll said. His reaction, he said, was “sadness and dismay at the low standards evident in the report and in the editorial commentary.” That commentary, written by the journal's editors, described the work as a possible “paradigm shift in the treatment of depression.”

Later that afternoon, he got a call from his friend Robert Rubin, then a professor of *psychiatry* at Drexel University and Allegheny General Hospital in Pittsburgh. The two had become self-appointed guardians of scientific rigor in psychiatric research -- gadflies who periodically fire off salvos to journals to complain about papers that don't measure up to their standards.

They sent such a letter to *Biological Psychiatry*. They criticized Schatzberg for claiming the drug “may be the equivalent of shock treatments in a pill.” They accused the authors of “obfuscation” and the editors of ignoring the study's “fatal flaws.”

Schatzberg and Belanoff responded, saying the letter was an “ad hominem attack,” and that Carroll and Rubin had “cut and pasted snips of quotes . . . and mis-characterized what we said.”

Weighing what to do with this unusually heated exchange, the journal's editors sent the correspondence to four outside, anonymous reviewers, who split, two and two, on whether the letter and response should be published. In the end, the editors decided not to print the exchange, setting the stage for Carroll and Rubin to go public in Puerto Rico.

“It was the suppression of our considered critique that caused us to pay increasing attention to Corcept's claims,” Carroll said.

Schatzberg, however, says the failure of *Biological Psychiatry* and other journals to publish letters from Carroll and Rubin shows that their criticisms are not credible.

“These studies were not designed to allow you to really apply statistics,” he said.

That is one of the critics' biggest complaints: They argue that all the studies of RU-486 in depressed patients published to date either do not apply statistical methods or do so incorrectly.

Carroll calls them “experimericals” -- a word he coined to describe scientific studies that create positive publicity for a particular prescription drug product.

``If there is an effect, they haven't produced the evidence," said Carroll. ``The closer you look, the more confused they appear to be, blinded to the data in their own studies because of commitment to their own therapy."

``Until I'm shown otherwise, it's a house of cards," said Rubin, now chief of **psychiatry** at the Veterans Affairs of Greater Los Angeles and a professor at UCLA.

Two independent experts asked by the Mercury News to review the three key RU-486 studies co-written by Schatzberg side with Carroll and Rubin.

University of California-San Francisco Professor of Medicine Stanton A. Glantz, the author of ``Primer of Biostatistics," found several statistical errors in the papers he was asked to look at.

``These are elementary statistical methods," he said. ``They have applied them incorrectly." The result was to ``bias their results toward reporting an effect when the data doesn't justify that. Scientists shouldn't make these dumb mistakes."

The other expert is Steven G. Self, a professor at the University of Washington, who heads the program in biostatistics and biomathematics at the Fred Hutchinson Cancer Research Center in Seattle.

Commenting on the 2002 paper in Biological **Psychiatry**, he said, ``there is no evidence at all" for a meaningful difference in the response of patients given high doses of RU-486 and those given a very low dose presumed to have no effect at all. All you have to do is look at the data, he said, to see this. ``No formal statistics are required."

Schatzberg said that applying statistical analyses to these small, preliminary case studies is ``absolutely silly." And Corcept CEO Belanoff agrees.

Schatzberg contends that Carroll and Rubin have distorted what he's said and harbor professional jealousies because their own work on cortisol did not result in new treatments. He also suggests their grievances have nothing to do with his science.

Carroll said he was briefly hired by Schatzberg as a consultant on a five-year federal grant and given a courtesy Stanford appointment. He acknowledged he was paid \$2,000 -- not the \$10,000 he thought he was entitled to. But Carroll said he is satisfied with the resolution. Rubin was passed over for a committee chairmanship of a psychiatric society when Schatzberg was president -- a position he got the following year.

Both men deny that any personal slight or dispute played a role in their criticisms of Schatzberg. Responded Carroll: ``It's a smear."

Everyone, including Schatzberg, agrees it will take large, carefully conducted studies to establish whether the drug is an effective treatment.

Eight years after it was founded, Corcept Therapeutics is pouring its money into doing just that. Corcept remains a small company, with just 11 full-time employees last year. Much of the company's work -- manufacturing RU-486, testing it in patients and developing related drugs -- is farmed out to other firms.

The company has completed two large, 200-patient trials of RU-486 in depression.

In one of those trials, four patients died, said Corcept CEO Belanoff, but three of those were in the comparison group, which was not given RU-486. The deaths, he said, were reported to the FDA, which allowed the trials to proceed. ``The real point is that these are sick people, period, medically as well as psychiatrically."

While Corcept reported positive findings in both trials, neither delivered the statistically significant results needed to win FDA marketing approval. Worse still, for a drug hailed as a replacement for shock therapy, only ``a very small number of patients" exhibited no symptoms, according to company filings.

To satisfy the FDA, the company is conducting two additional trials in the United States and a third in Europe, which could decide whether Schatzberg is finally vindicated. Results are expected later this year.

Schatzberg said he has made little money from his efforts. As part of the initial public offering in 2004, he offered to sell up to 750,000 shares of his stock at the IPO price of \$12, but demand was weak and his shares were not sold. Last year, he made \$109,000 selling some of his holdings.

But money is not what his work on RU-486 is all about, he said.

``We hope that in 2006 you're going to write a robust story about a breakthrough treatment that others have maligned," Schatzberg said. ``In the end the data will tell us if we're correct or not, and we hope we are correct."

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