

The Boston Globe

Lure of riches fuels testing

'To wash people out from their medication, to take away at kind of treatment, that to me is inhumane.'

By Robert Whitaker, Globe Correspondent, 11/17/98

Third of four parts

During the first three weeks she spent in Fairview Riverside Hospital in Minneapolis, Susan Endersbe, a 41-year-old woman struggling with schizophrenia and suicidal impulses, obtained care and medication that made her feel much better.

Her mood lightened. By May 26, 1994, she was telling nurses that she felt she'd be ready to leave soon.

But the very next day, she was referred to psychiatrist Faruk Abuzzahab, an encounter that put her on a path that led to her death.

Abuzzahab, a past president of the Minnesota Psychiatric Society and onetime chairman of its ethics committee, had a contract with Abbott Laboratories to test the experimental antipsychotic drug Sertindole. What he earned has not been disclosed, but such contracts typically pay physicians much more than regular health insurance reimbursement, creating a powerful incentive to put patients into commercial research trials.

Endersbe's death offers a peek into the financial side of corporate-funded research of new drugs for the mentally ill. While the development of new antipsychotic drugs has brought new hope for schizophrenic patients and allowed many to live successfully in the community, the clinical testing of these medications is also big business, with the pursuit of money often in conflict with good patient care. The result, in schizophrenia research, is a landscape tarnished by the greed of some rogue investigators and repeated instances of patients being harmed.

"The abuses are there," said Dr. Morris Goldman, associate professor of psychiatry at the University of Chicago School of Medicine, who investigated Abuzzahab's transgressions. "A big part is the dollars involved. "

There are "people drawn into this field because they are interested in dollars," Goldman added. "They are very profit-conscious. And that combination of a lot of money, plus the added ethical dilemma you face in human research, that is a bad combination. And there are particular risks with psychiatric patients, with the whole issue of informed consent. It can really go wrong."

When Abuzzahab enrolled Endersbe into his drug trial, he later admitted to state investigators, he ignored study criteria that excluded patients who were suicidal. And as soon as she stopped taking the venlafaxine that had controlled her symptoms, she quickly worsened, state investigators reported.

Endersbe repeatedly told nurses that she intended to kill herself. Devils were now struggling for her mind, her brother said. Her complaints were recorded in nurses' notes, but Abuzzahab presented a rosy picture in his research records for Abbott. Endersbe was experiencing no side effects from the drug, he wrote, so he kept her in the trial.

For nearly two weeks, until June 8, Endersbe received no antipsychotic medication. Then, on June 11, when she had been on the experimental drug for three days, Abuzzahab granted her a day pass to leave the hospital unaccompanied. She went to her apartment to gather some keepsakes, slipped the key back under the door, and walked straight to the Franklin Avenue Bridge. Just as she had said she would, Endersbe clambered over the railing and leapt to her death in the Mississippi River.

"For nearly 20 years, my sister was managing to win the battle for her survival, and when she went on a drug study, there were supposed to be safeguards in place to protect her," said her brother, Edward Endersbe. "Not only were they not in place, they neglected to have the usual safeguards that she would have had if she stayed on as an inpatient" outside the drug trial.

"And to wash people out from their medication, to take away any kind of treatment, that to me is inhumane," he added. "If they did that to someone with a physical illness, I would think it would be criminal."

Troubling questions about patient safety

People with schizophrenia, studies have shown, are at greatest risk of suicide during a relapse, at the beginning of an acute psychotic episode, and when they are discharged from the hospital. Taking part in a drug trial often exposes them to all those factors.

In the 1990s, three antipsychotic drugs for schizophrenia have been brought to the market: Zyprexa (olanzapine), Risperdal (risperidone), and Seroquel (quetiapine). Abbott Laboratories also submitted an application for Serlect (sertindole) - the drug Susan Endersbe was given - but withdrew it after a Food and Drug Administration advisory committee questioned its safety.

The results of the clinical trials submitted to the FDA, obtained by the Globe through Freedom of Information requests, raise troubling questions about the safety of schizophrenic patients enrolled in commercial drug trials:

Among 12,176 patients from the US and abroad who had participated in trials for all four drugs at the time the data was submitted to the FDA, there were 88 deaths, including 38

suicides. [The figure includes deaths up to 30 days after patients left the trial.] That is an overall death rate of 1 of every 138 volunteers.

The suicide rate for the clinical trials is two to five times higher than the norm. In the medical literature, annual suicide rates for schizophrenia patients range from two to five deaths per 1,000 people. The annual suicide rate in the trials, on a time-adjusted basis, was close to 10 per 1,000.

In trials for the three approved drugs - Zyprexa, Risperdal, and Seroquel - 60 percent of the 7,269 patients who received the experimental drug dropped out before the end of the study period, typically six to eight weeks. Patients dropped out because the drugs didn't work, because of side effects, and sometimes because they refused to continue.

No one has made a detailed study of the mortality or suicide rates of subjects in schizophrenia drug trials. When queried, a half dozen psychiatric researchers expressed varying responses to the numbers collected by the Globe. Some thought they were remarkably high. Some argued that the majority of the people entering the trials had been chronically ill with schizophrenia, and thus a number of suicides and deaths could be expected. And some researchers begged off; they did not know what to make of the statistics.

Researchers seduced by lure of lucrative rewards

The research enterprise that has produced new neuroleptic drugs for schizophrenia has paid off, of course, in important ways. The standard drugs used from the 1950s to the early 1990s typically made patients feel like zombies and caused major side effects that disrupted muscle control. The antipsychotic drugs that have reached the market in recent years [Risperdal, Zyprexa and Seroquel] are less sedating and appear to have fewer harmful side effects.

Desperately ill schizophrenics have turned to clinical trials for early access to these new drugs, and many of those patients attest to the attentive care that they received from researchers conducting the trials.

But there are powerful financial factors at work that can tempt researchers to enroll mentally ill patients into drug trials even when it will not serve the patients' interests.

Antipsychotic drugs are considered a major and fast-growing market for the pharmaceutical industry. In 1997, US sales topped \$1.5 billion, double the figure from two years earlier. Pharmaceutical companies developing antipsychotic medications know that every day shaved from the testing process can get them to the market a day sooner, and each day earlier to market represents \$1 million to \$2 million in additional sales per drug. The companies need to get patients into their trials quickly, and they will pay researchers handsomely for doing so. But they also expect the researchers to deliver. Researchers who do not meet their patient quotas are not likely to get a contract for the next project.

"The pressures are enormous," said Newell Unfried, executive vice president of the Alliance for Multispecialty Research, a group of leading for-profit research centers. Increasingly, he added, performance reviews "are being drawn up by pharmaceutical companies on every physician in clinical research on their patient recruitment. There is pressure to get these patients."

In fact, the drug-testing industry today is a highly competitive, profit-driven enterprise. Only about 25 percent of drug trials are conducted in nonprofit academic medical centers. The rest are conducted by community physicians who contract with drug makers or by for-profit companies whose sole focus is conducting drug trials.

Physicians who do commercial drug research full-time regularly report generating more than \$1 million in annual revenues, and profits exceeding \$300,000.

In the 1990s, a Providence-based company, Clinical Studies, built a nationwide chain of research centers focusing on drugs for Alzheimer's disease, schizophrenia, and other neurological disorders. The founders sold it in 1997 to a physician-practice management company for stock valued at \$85 million. Hoping to make similar scores, venture capital groups have poured more than \$100 million into start-ups seeking to duplicate Clinical Studies' success.

In this environment, researchers know that the "product" they deliver is patients who can be enrolled in trials and kept there until they complete the study protocol. Physicians often earn bonuses for meeting patient-recruitment goals.

Critics say the monetary incentives put researchers on a slippery slope, particularly when it comes to testing schizophrenia drugs. Their financial interests push them to recruit patients aggressively, yet the trials expose the patients to numerous risks.

But Dr. Stanley Cheren, a Brookline psychiatrist who conducts commercial drug trials on a full-time basis, insists "there are a number of things that keep you sober and honest - your own conscience.

"Leaving that aside, you are accountable to the patient and to the patient's family, and they do raise hell when things aren't going well. The hospital staff keeps you accountable. And the third thing always lurking in the background is the FDA. If you recruit a lot of patients and do it fast, the FDA takes that as a red flag and audits your site."

However, the financial pressures and opportunities have been known to lead physicians astray. A criminal case in Georgia revealed just how far.

Dr. Richard Borison and Bruce Diamond were longtime favorites of pharmaceutical companies developing schizophrenia drugs. Borison, 48, chairman of the psychiatry department at the Medical College of Georgia in Augusta, and Diamond, 53, a pharmacologist on the school's faculty, had demonstrated time and again a knack for

bringing psychotic patients quickly into trials funded by drug companies. Eli Lilly, Janssen, Zeneca, Novartis - they all came knocking.

As faculty, Borison and Diamond were supposed to get approval from the medical school for their research. Drug-company payments for clinical trials were supposed to be sent to the school. But according to Georgia state authorities, who indicted the pair in early 1997, they began in 1989 to have the companies send payments directly to them. They opened an office across the street from the medical school, used a commercial service to do ethical reviews of their studies, and placed their staff on the school's payroll while keeping all the research funding for themselves.

From 1989 to 1996, Borison and Diamond made over \$10 million from drug trials, including more than \$4 million from schizophrenia drugs, according to the indictment and sworn testimony from their staff during an investigation by the Augusta Veterans Affairs Hospital, where Borison was chief of psychiatry. Witnesses said the two researchers focused on getting patients into the studies and paid minimal attention to their care.

To recruit the mostly male patients, they hired attractive young women, who later testified that they were paid bonuses that ran into the thousands of dollars. According to testimony, one staffer was given a Honda Accord for coaxing schizophrenia patients into trials.

To earn these rewards, workers phoned and later met mentally ill patients who were stable and living in the community and offered them \$150 to check themselves into the VA hospital so they could be in a study. Patients already in locked wards were offered cigarettes for agreeing to participate.

"When there is a possibility that you are going to get a car, you're going to do whatever you can," study coordinator Angela Touhey told VA investigators.

Touhey and the other study coordinators, many of whom had no medical training, determined whether a patient belonged in a study. According to an FDA investigation, untrained staff drew blood samples and adjusted doses of the experimental drugs. Touhey said Borison and Diamond hardly saw patients during the trials. At one weekly meeting, Touhey said Diamond told the staff they weren't interested in hearing about the patients.

"Bruce told me, 'We don't care about how the patients are doing. We just want to know how many people you have enrolled in the past week or couple of weeks,'" Touhey said.

The two researchers lived high, according to Georgia authorities. They tucked away more than \$5 million in cash and securities, drove Mercedes-Benz cars, and dropped more than \$400,000 on antiques.

Borison bought medieval tournament armor from Sotheby's auction house in New York, and mahogany-paneled doors in London, for an 11,000-square-foot castle that he was

planning to build. The indictment charged that they bribed a staff member, Terri Davis, to keep quiet after a schizophrenia patient in an olanzapine trial attempted suicide.

"This whole thing was very dirty," Dr. David Hess, chief of neurology at the VA, told the hospital's investigators. "It was basically a numbers game. These patients are purely used for the greed of the researchers. That was very apparent to me what was going on."

Diamond and Borison are now behind bars. In December, 1997, Diamond pleaded guilty to theft and bribery charges and was sentenced to five years in prison, fined \$125,000, and ordered to pay \$1.1 million to the college.

After one week of testimony at his trial in October, Borison pleaded guilty to theft and a racketeering charge. He was sentenced to 15 years in prison, fined \$125,000, and ordered to pay \$4.26 million to the college.

Researcher caught falsifying records

When the Minnesota Board of Medical Practice received allegations that Dr. Faruk Abuzzahab was endangering the welfare of patients in his general psychiatric practice, it hired Dr. Morris Goldman of the University of Chicago to investigate. One of the first things he discovered was that Abuzzahab was fudging records in order to put patients into lucrative drug studies.

"He would have the patient's diagnosis called one thing in the regular chart, and then the person would be put on a drug study and the person's diagnosis would be called something else to fit the criteria," Goldman said in an interview.

In July, after Abuzzahab admitted to the board that he had entered "disturbed and vulnerable" patients into drug studies even though they didn't meet eligibility criteria, and had "kept them in the study after their conditions deteriorated," the medical board suspended his license.

Among other things, Abuzzahab admitted that he cycled one woman with paranoid schizophrenia through three drug trials from 1991 to 1994, despite the fact that she did poorly on the experimental drugs and complained of being a guinea pig. Eventually she became catatonic and incontinent; she was then given standard therapies and responded well.

In another instance, the psychiatrist took a woman off clozapine, a newly approved drug that had led her to make a remarkable recovery, and enrolled her in a drug trial. The woman had previously spent 13 years as an inpatient at a psychiatric institution, but while on clozapine she had been able to go into the community and even hold a job. One day she approached Abuzzahab with questions about clozapine's side effects; he immediately stopped the drug that had helped her so much and put her into an olanzapine trial. She deteriorated until she found her way to another physician, who put her back on clozapine.

According to the state medical board, Susan Endersbe was another patient whom Abuzzahab "recklessly" entered into a clinical trial. The doctor, the medical board noted, entered her into the trial the first day he met her.

"I think a key flaw in this whole thing is the financial gain," said Edward Endersbe. "I am not a communist, but it is really disturbing to see how much this is driven by financial gain, and that it can, and does, such harm. There is no question in my mind that that is what happened with my sister. My sister very much wanted to live and to be a survivor."

Incentives encourage aggressive recruiting

Abuzzahab and Borison can be dismissed as isolated "bad apples" who unfairly tarnish the image of all researchers who conduct schizophrenia drug trials. But the economic incentives they pursued so eagerly are in play in all commercial drug testing.

Dr. Angela Bowen, president of the Western Institutional Review Board, a commercial ethics review service, said researchers are becoming more aggressive in their use of advertising to recruit patients into schizophrenia studies. Research centers that don't have any ongoing studies have even submitted advertisements for IRB approval seeking depressed and schizophrenic patients who would consent to being withdrawn from their medications, she said. The researchers apparently wanted to develop a pool of mentally ill people, already off standard therapies, who could be quickly enrolled once new drug contracts are secured.

"We, of course, don't approve those ads," Bowen said. "It boggles the mind."

Aggressive recruitment of schizophrenic patients is problematic because participating in drug trials exposes them to the risk of relapse and suffering. To determine whether a drug can curb psychosis, it must be tested in people who are actively psychotic. That scientific standard, which is endorsed by the FDA, leads straight into an ethical minefield.

One approach is for researchers to seek people who are already actively sick, either because they have stopped taking medication on their own or because the symptoms aren't being adequately controlled by medication. But many of these patients suffer from "disorganized thoughts" and some degree of psychosis, making it questionable whether they can give meaningful informed consent.

Another route is to seek stable patients who are on medication. These patients, however, must be hospitalized and their medications stopped in order for them to take part, with the expectation that their delusions and hallucinations will return. The patients must become sick again to be useful subjects.

"If you don't take people who have reestablished active disease, then you don't know what you are looking at" when you test the drug, said Robert Temple, associate director for medical policy at the FDA's Center for Drug Evaluation and Research. "That is why you have to have a washout. And once you realize that you have to do medication

withdrawal, you have already gone into what people are worried about, and that is giving a relapse."

But Temple said the profession has not "reached the conclusion that allowing people to withdraw [from medication] is dangerous to them, if they are closely monitored and well informed."

If patients become too ill when their regular drug is stopped, researchers may shorten the washout period. They then enter the active part of the study and either receive the experimental drug, a standard drug [usually Haldol], or an inactive placebo. Researchers will also use "rescue medications" if the patients deteriorate too rapidly.

"People do not have to become dramatically, floridly more psychotic in order to be ready to go into the study," said Nina Schooler, director of psychiatry research at Hillside Hospital, a division of Long Island Jewish Health System in Queens. "We are not talking about requiring dramatic psychotic relapse."

Still, the essence of the process is to let the patients become sicker.

"The patient is suffering," acknowledged Cheren, the Brookline psychiatrist who conducts drug studies. "Psychosis makes a person suffer. A second [risk] is that the patient could become more violent and destructive to himself and to others. Third, people think that acute psychosis does damage to the brain, and you want to limit those periods. Multiple episodes of acute psychosis lead to poorer long-term outcomes. You want to limit all of those things as much as possible."

Stopping a schizophrenic patient's medication raises two other concerns. In normal clinical care, when a patient is taken off drugs, the recommended practice is to lower the dosage gradually, because abrupt withdrawal has been shown in numerous studies to dramatically increase the risk of relapse. Moreover, evidence is emerging that sudden withdrawal may lead to a rebound psychosis more severe than if the patient had never been treated.

"It is not simply a matter of not being treated and going back to baseline of an untreated state," said Dr. Ross Baldessarini, professor of psychiatry and neuroscience at Harvard Medical School. "There is an additional risk involved that may be due to the discontinuation itself We are trying to get people sensitized to this issue."

David Cohen, a professor of social work at the University of Montreal who has done extensive research on neuroleptic drugs, said abrupt withdrawal can also lead to flu-like symptoms, nausea, and vomiting. This, he said, is a withdrawal reaction, not just a return of previous symptoms.

"There will be new symptoms the person has never experienced before," Cohen added. "But they don't tell them the kind of suffering it will entail. They don't tell the patients

how severe these symptoms may be, and that they could be life threatening, and that they could be driven to kill themselves."

There are, of course, potential benefits for the research subjects. The primary one is that they may respond to the experimental drug, and be able to continue to get it by participating in a long-term followup study. But the mentally ill patients can expect, at least at first, to go through a difficult period.

"I know that when I was three or four days into the washout I was really struggling," said D.L., a 41-year-old woman in Illinois diagnosed with mild psychotic disorder who recently entered a trial of an experimental antipsychotic. "My symptoms increased dramatically. It was getting scary. If they had been any more severe, I know that I couldn't have handled it. I hope that if that had happened, I would not have hurt myself. But when you are delusional, it is hard to know what you are going to do."

Researchers grapple with ways to reduce patient risk

Within the psychiatric research community, there is controversy over whether drug studies can be designed to reduce the risk to patients. In Europe, for instance, researchers are reluctant to conduct placebo-controlled trials for schizophrenia. Instead, European researchers usually conduct trials that compare the experimental drug to a standard therapy.

That is also how US drug trials are typically designed for medical conditions such as high blood pressure, for which there are already effective approved drugs. But in schizophrenia research, the FDA believes that patients' reactions to antipsychotic drugs are so variable that without a placebo group, the tests cannot show whether an experimental drug is effective. That could result in ineffective drugs being approved, said the FDA's Temple.

"You have to think about the people in the trial, but you also have to think of the consequences to the community of marketing ineffective antipsychotics," he said.

Others find that justification unsatisfying.

"Can you imagine an antibiotic study that would compare the experimental drug to a sugar pill?" asked Unfried, head of the alliance of for-profit research centers. "Can you imagine that goofy study? With the result that the patient died from too much infection? In those studies, you use a standard therapy as a basis for comparison. The FDA has a role to protect people and to make sure you design the trial in such a way that you do not hurt people."

Testing violations lead to a death in California

Anyone agreeing to take part in a risky drug trial would expect attentive medical care. But that wasn't the case with Borison and Diamond. It wasn't the case with Abuzzahab.

And it was not what Jennifer Abigayle McIntyre received when she entered a trial in 1993 for Janssen Pharmaceutica's experimental drug risperidone.

After she died, an investigation by the California Department of Health found violations that took 16 pages to detail.

In the spring of 1993, Abigayle's mother, psychiatrist Judith Vukov, accompanied Dr. Robert Liberman, director of schizophrenia research at the University of California, Los Angeles, to lobby Congress to fund research on mental illness. Her daughter had schizoaffective disorder [a variant of schizophrenia], existing medications weren't helping her, and, as Liberman had told her, experimental treatments offered the best hope.

Later that same summer, on July 20, 1993, according to the California Department of Health and court records, Abigayle McIntyre was transferred to the research ward at Camarillo State Hospital, where doctors were treating patients with experimental protocols developed by UCLA researchers.

Abigayle signed an informed-consent form that stated she would be given a physical exam, be closely monitored, and that if her condition worsened, her treatment would be "promptly adjusted." In fact, the investigation showed, she never received a physical, nor did the staff prepare any plan for treating her psychiatric and behavioral problems.

The principal researcher, Dr. Barringer Marshall Jr., gave her a new diagnosis, chronic schizophrenia, which made her eligible for the risperidone study.

As her previous medications were withdrawn, she became more volatile, crying and screaming for hours on the phone with her mother. On Aug. 12, as part of the protocol, she was prescribed Haldol, a standard antipsychotic. Even though she began to suffer terrible headaches and her blood pressure soared, she was kept on Haldol. The protocol called for her to take the drug for three weeks before she could be switched to risperidone.

Her mother complained, but to no avail.

"Just because I am a doctor doesn't mean anything," Vukov said. "If you have a psychiatric child, your opinion is useless."

The last time the unit's staff made an entry on Abigayle's chart was Aug. 26. On Sept. 11, her mother took her out of the hospital on a day pass. At some point her daughter swallowed a large number of aspirin; she died several hours later after emergency room physicians failed to promptly diagnose the aspirin poisoning.

"I thought research was the best treatment in the country," said Vukov. "Today it is not. It is the most dangerous. Abigayle wouldn't have gotten sick like that if she hadn't been in research. She ended up outside my control and outside the control of a good doctor, who would have done something about [her illness]. She was actively neglected in research."

Messy picture often buried in a marketing glow

When a drug company submits data to the FDA, it must detail all deaths that occurred in the clinical trials, along with a full accounting of side effects, patients who dropped out of the study, and any other problems suffered by the patients.

But that often messy picture is rarely reflected in the accounts of the drug's performance that get published in medical journals.

Zeneca's Seroquel, approved by the FDA last fall, is the newest antipsychotic drug on the market. When the Globe compared the mixed results hidden in FDA files, including 14 deaths, with the glowing conclusions published in medical journals, the differences were stark.

According to the FDA's review of Zeneca's data, 80 percent of the 2,162 patients given Seroquel in clinical tests stopped taking the drug before the trial was over, even though the trials often lasted less than eight weeks. Of those who dropped out, 1,033 did so because the drug didn't help them, 398 simply refused to continue or were lost to follow-up, and 86 had to stop because of adverse reactions that included excess sleepiness, convulsions, suicide attempts, and depression.

But when articles began appearing in medical journals on the results in the summer of 1997, the authors glossed over the dropouts, failed to report on the deaths, and drew rosy conclusions. An article in the Archives of General Psychiatry hailed Seroquel as "an effective antipsychotic with a favorable safety profile"; a report in Biological Psychiatry touted the drug as "well tolerated and clinically effective in the treatment of schizophrenia."

"Most of the trial results that are published have as authors both [researchers] and people involved with the trial who work for the company," noted New York-based researcher Schooler, who Zeneca designated to be its spokesperson. "Of course people put the most positive spin possible on their results."

One result of this marketing spin is that practicing psychiatrists often say they no longer know what to believe about new drugs. Although Seroquel and the other new drugs do appear to cause fewer side effects than standard antipsychotics, there are still many questions about how they compare in efficacy.

"What gets put out is not necessarily the truth," Dr. E. Fuller Torrey, director of research for the National Alliance for the Mentally Ill, said this summer at the group's annual conference. "You'd be surprised at how much money many of my colleagues are regularly taking from the pharmaceutical industry. \$10,000 is not an uncommon amount to be given for giving a talk.... If we really hope to answer the question of new antipsychotics vis-a-vis the old ones, we're going to need something other than the pharmaceutical industry to provide funds on it."

Tomorrow: Vulnerable and unprotected

This story ran on page A01 of the Boston Globe on 11/17/98.

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