

## Psychiatrist criminally indicted: Promoting off-label use of drug for depression!

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The New York Times reports that a Maryland psychiatrist, Dr. Peter Gleason, was handcuffed and arrested in March and charged with criminal promotion of a drug "for purposes other than those approved by the federal government."

This will be an interesting test--giving lawyers a field day: the case demonstrates how pharmaceutical companies circumvent federal law prohibiting companies from promoting the use of drugs off-label (for uses not approved by the FDA). The purpose of the law is to protect the public from untested drugs whose safety has not been proven.

When doctors prescribe a drug off-label for a patient, that patient becomes a guinea pig in an uncontrolled unapproved experimental drug trial. The drug may prove to be lethal.

The F.B.I. news release about the indictment, compared Dr. Gleason to a "carnival snake-oil salesman";

Daniel Troy, former FDA chief counsel, continues to represent pharmaceutical company interests, now legitimately, as a partner in the law firm, Sidley Austin. Troy told the Times that "the government appears to be overreaching in going after Dr. Gleason and may chill a common and legitimate form of medical discussion. This is a very, very scary development";

For an industry not noted for abiding by "truth in advertising" laws, drug companies have flouted the law prohibiting the marketing of off-label drug uses. Since 2000 drug company giants have paid hundreds of millions of dollars in fines to settle federal criminal cases over off-label prescriptions: For example, Pfizer pleaded guilty to criminal promotion of Neurontin, a drug approved only for use as an adjunctive medicine in the treatment of epilepsy. The company promoted Neurontin for dozens of uses including pain and bipolar disorder. Pfizer paid \$430 million in 2004 to settle a suit brought by 28 state attorneys general. However, such fines pale in comparison to the profits drug companies garnered from multi-billion dollar sales for off-label uses. Indeed, most blockbuster psychotropic drugs are prescribed for off-label unapproved uses. [1]

To circumvent the law, pharmaceutical companies hire doctors to promote drugs off-label: The Times reports that Dr. Gleason acknowledged having received \$450 to visit a doctor in the office, \$750 for speaking at a luncheon and \$1,500 for a dinner speech. He made as much as \$3,000 a day, he said. Last year alone he received \$100,000 from the Jazz Pharmaceuticals manufacturer of the drug, Xyrem.

The case is likely to bring to light the complicity between drug companies and the medical profession--its leadership, professional associations and institutions have become financial stakeholders in the drug business. These medico-industry stakeholders are acting in concert to negate the spirit and purpose of the law prohibiting the promotion of unapproved drugs. Equally appalling, as this case will demonstrate, is their complicity in the debasement of continuing medical education.

In addition to paying doctors consultant fees to promote their products, drug manufacturers underwrite physician education seminars--including those under the auspices of the American Medical Association--and most medical specialty associations. Physicians earn "continuing education" credit for attending these thinly disguised market expansion sessions and listen to company paid physicians promote unapproved uses of patented drugs.

The case may bring to light that medical associations--AMA, American Psychiatric Association, etc--are providing a subterfuge for industry's illegal marketing activities.

The AMA takes the position that "doctors should be free to prescribe drugs for off-label use." But pitching drugs for companies that pay them is not practicing medicine--it is engaging in commerce. Furthermore, Alex Berenson reports that the Accreditation Council for Continuing Medical Education--which oversees these "educational" programs loosened its rules in 2004 "so that speakers would not have to disclose whether a recommended use is on-label or off-label."

By equating experimental, unapproved, drugs with FDA-approved drugs which have been scientifically tested for safety and efficacy, the AMA is serving as industry's agent, promoting industry's marketing goals. The AMA's defense of physicians' off-label drug promotion activities overthrows the tenets of evidence-based medicine and exposes physicians to litigation--both civil and criminal.

As Dr. Gleason learned, his former benefactor, Jazz Pharmaceuticals, informed him "he would have to fact the indictment on his own: "They're just cutting me loose," he said.

1. See: <http://www.ahrp.org/infomail/04/05/16.php>

Pfizer Case Signals Tougher Action On Off-Label Drug Use By DAVID ARMSTRONG and ANNA WILDE MATHEWS, THE WALL STREET JOURNAL May 14, 2004; Page B1--includes list of drugs widely prescribed off-label. See also, Pfizer to Pay \$430 Million Over Promotion of Drug by Gardiner Harris, New York Times, May 14, 2004, C-1.

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<http://www.nytimes.com/pages/business/index.html>

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Indictment of Doctor Tests Drug Marketing Rules

By ALEX BERENSON

At first, Dr. Peter Gleason thought his arrest was a joke.

In the early afternoon of Monday, March 6, half a dozen men in suits surrounded Dr. Gleason, a Maryland psychiatrist, at a train station on Long Island and handcuffed him. "I said, 'Well, this is a gag,'" Dr. Gleason recalled in a recent interview. "They said, 'No, this isn't,'"

Dr. Gleason, 53, was taken aback because he was arrested, and later charged, for doing something that has become common among doctors: promoting a drug for purposes other than those approved by the federal government.

But prosecutors say that Dr. Gleason went too far. At hundreds of speeches and seminars where he was rewarded with generous fees, Dr. Gleason advised other physicians that a powerful drug for narcolepsy could be prescribed for depression and pain relief. In doing so, he conspired with the drug's manufacturer to recommend it for potentially dangerous uses, the prosecutors claim.

The case has put the spotlight on the murky financial relationships between drug companies and the physicians they use to promote their medicines. Companies cannot directly advertise drugs for purposes not approved by the Food and Drug Administration. But getting drugs prescribed for unapproved uses can increase a drug's sales, so companies often skirt the rules by sponsoring seminars where doctors are paid to make presentations promoting their drugs, including the "off label" uses.

For doctors, these and other payments they receive for discussing drugs can be very lucrative. Dr. Gleason acknowledges that he received more than \$100,000 last year alone from Jazz Pharmaceuticals, which makes Xyrem, the narcolepsy drug he has promoted.

His case could establish limits on what doctors can do to help companies sell their drugs. But any precedent could be complicated by the history of Xyrem, which differs in one important way from other drugs. Because the active ingredient in Xyrem is gamma hydroxybutyrate, or GHB, an illegal street drug with a history of use in date rape and of overdose hazards, Xyrem is listed as a federally controlled substance, with distribution tightly monitored.

Some doctors who have researched Xyrem say that Dr. Gleason, in his enthusiasm for the drug, may have understated its very real risks. Still, at least one former F.D.A. official says that the government appears to be overreaching in going after Dr. Gleason and may chill a common and legitimate form of medical discussion. "This is a very, very scary development," said Daniel E. Troy, a partner at Sidley Austin and the former chief counsel of the F.D.A.

Dr. Steven Nissen, the interim chairman of cardiovascular medicine at the Cleveland Clinic, said the case could "have a chilling effect on physicians, because when we give lectures, we assume that giving an opinion about the use of a drug is not going to get us into legal difficulty." The F.D.A. and federal lawyers, he said, need to restrict criminal prosecutions to especially egregious cases of off-label promotion.

Continuing to Practice

Dr. Gleason, who is now free on bail and continues to practice medicine, insists that he is not guilty of conspiracy. He says that he was charged only after he refused to help the government build a case against the drug's maker, Jazz Pharmaceuticals — a sequence of events that court documents seem to support.

Dr. Gleason freely acknowledges that in meetings with other doctors, he advocated Xyrem as a treatment for many conditions, including depression and fibromyalgia, a poorly understood pain disorder.

In a news release about the indictment, an assistant F.B.I. director compared Dr. Gleason to a “carnival snake-oil salesman.”

But the doctor says that based on his own experience giving Xyrem to patients, he believes everything he said about the drug and that his right to express his views are protected by both F.D.A. rules and the First Amendment.

Some lawyers who have reviewed Dr. Gleason’s case, but are not representing him, say they agree.

Dr. Gleason has been trapped in the complex rules that cover what doctors and drug manufacturers are allowed to say about prescription drugs, according to Harvey A. Silverglate, a lawyer in Boston who specializes in civil liberties cases.

“What they are doing is criminalizing conduct that is not clearly criminal,” said Mr. Silverglate, who is not involved in Dr. Gleason’s defense.

Neither the F.D.A. nor the United States attorney’s office in Brooklyn, which indicted Dr. Gleason, would comment on the case. Nor would David Loftus, a public defender who took over the case after Dr. Gleason determined he could not afford a private lawyer. Jazz Pharmaceuticals, which has not been charged, also declined to comment.

F.D.A. rules allow doctors to prescribe federally approved drugs for any purpose, even if it is not indicated on the medicine’s label. But drug companies are tightly constrained in what they can say about their medicines. Companies can promote drugs only for their federally approved purposes — their so-called “on label” use.

“Off label” promotion by drug companies is illegal, and since 2000 drug makers have paid large fines to settle federal criminal cases over off-label prescriptions.

Pfizer, for example, paid \$430 million in 2004 to settle allegations that it had promoted Neurontin, an anti-epilepsy medicine, for pain and bipolar disorder.

Despite the F.D.A.’s constraints on drug makers, though, the companies are allowed to hire independent doctors to talk to other physicians about their medicines. Companies can also sponsor “continuing medical education” sessions, ranging from lunches to weeklong conferences, where specialist doctors tell other physicians about the latest developments in their fields — including off-label uses for drugs already on the market. For such speaking engagements, doctors can receive \$3,000 or more a day from the companies.

In other words, the F.D.A. rules allow drug makers to pay independent doctors to discuss medicines in ways that might be illegal for the companies themselves. Beyond the federal rules, guidelines by doctors’ groups give physicians wide latitude to talk about off-label use.

The American Medical Association considers continuing-education sessions valuable and believes that doctors should be free to prescribe drugs for off-label use, according to Dr. Edward Langston, a member of the A.M.A. board.

In general, though, he said, the A.M.A. believes doctors should rely on peer-reviewed research, not anecdotal evidence, when they write off-label prescriptions.

The Accreditation Council for Continuing Medical Education, which oversees the groups that create medical education sessions, loosened its rules in 2004 so that speakers would not have to disclose whether a recommended use is on-label or off-label, said Dr. Murray Kopelow, the council’s chief executive.

“The A.C.C.M.E. abandoned the distinction between off-label and on-label,” Dr. Kopelow said. Instead speakers should make recommendations based on accepted medical and scientific evidence, he added.

Dr. Gleason acknowledges that he did not follow those evidence-based guidelines when discussing Xyrem in hundreds of speeches and seminars from 2003 to 2006. The talks were paid for by the original maker of Xyrem, a company called Orphan Medical. Orphan was acquired by Jazz Pharmaceuticals in June 2005.

In one seminar cited in the federal indictment, a session last August in Denver, Dr. Gleason told doctors that “table salt is more dangerous” than Xyrem — a statement scoffed at by other experts on the drug.

#### An Aid to Sleep Quality

Xyrem’s active ingredient GHB is a fast-acting central nervous system depressant developed as an anesthetic in the 1960’s. The drug improves sleep quality, enabling narcoleptics to stay awake the next day, according to physicians who specialize in treating sleep disorders. But because GHB can suppress breathing, overdoses can cause coma or death.

“It has the potential to do a lot of good if it’s used properly, the potential to do a lot of harm if it’s used improperly,” said Dr. Martin Scharf, the director of the Tri-State Sleep Disorders Clinic in Cincinnati, who said he had studied GHB in hundreds of patients since the early 1980’s.

In 2000, after highly publicized cases in which young women died or were raped after GHB was slipped into their drinks, Congress designated the drug a Schedule I controlled substance, in the same class as heroin.

But by then, doctors had shown that GHB could treat cataplexy, a variant of narcolepsy that causes people to suffer temporary paralysis. After lobbying from doctors and Orphan Medical, Congress said that if the F.D.A. chose to approve prescription GHB, it would be designated as a Schedule III controlled substance, legal for medical use, like the painkiller Vicodin or steroids.

In 2002, after Orphan presented clinical trial data showing GHB’s effectiveness against cataplexy, the F.D.A. approved the drug, under the brand name Xyrem, as a cataplexy treatment. In 2005, the agency approved Xyrem for the treatment of all forms of narcolepsy.

To help persuade the F.D.A. to approve Xyrem, Orphan Medical agreed to make the drug available only from a single pharmacy in Missouri, which ships it to patients nationally. No other prescription drug, even other Schedule III medicines, is so tightly controlled. For now, Xyrem, which costs more than \$600 a month, is a niche product, with sales of about \$25 million last year.

Dr. Gleason said he had been interested in Xyrem even before the drug was officially approved because he believed that other medicines for insomnia and depression were addictive or had serious side effects. “I immediately just started prescribing this stuff in 2002,” he said.

He prescribed the drug to about 100 of the patients he saw in his private practice in Maryland, almost always for off-label conditions like insomnia and severe depression. Xyrem seemed to work better than existing treatments, he said.

By early 2003, a sales representative for Orphan Medical, noting Dr. Gleason’s high rate of prescriptions, asked him if he would give talks to other doctors about Xyrem.

“I started doing those, and I started getting requested a lot,” Dr. Gleason said. He received \$450 to visit a doctor in the office, \$750 for speaking at a luncheon and \$1,500 for a dinner speech. He made as much as \$3,000 a day, he said.

Although he continued to see some patients, the Xyrem talks gradually became his primary source of income.

In April 2005, after a tip from a whistleblower inside Orphan Medical, the government began investigating Dr. Gleason and the company, according to an affidavit that Darren Petri, a criminal investigator for the F.D.A., filed in February in support of an arrest warrant for Dr. Gleason.

The affidavit says that a cooperating witness repeatedly taped Dr. Gleason as he discussed Xyrem, including the Denver talk where he compared Xyrem to table salt and a meeting in November where he said Xyrem was safe for children.

The indictment also charges that Dr. Gleason committed fraud against insurance companies by advising doctors to leave blank an area on the Xyrem prescription form that asked for a disease diagnosis. Dr. Gleason acknowledges that he told doctors not to offer a diagnosis but says he never told them to lie if they were asked for one.

Dr. Gleason says he did not know he was under investigation when he went to Great Neck, N.Y., on March 5 to talk to doctors about Xyrem during a lunch meeting at the office of Dr. Richard Blanck, a neurologist. The meeting had been arranged by a Jazz Pharmaceuticals salesman, Al Caronia, Dr. Gleason said.

#### An Unexpected Arrest

Dr. Blanck confirmed the meeting and said Dr. Gleason’s comments seemed typical for a sales presentation sponsored by a drug company. Mr. Caronia did not return calls seeking comment.

Afterward, Dr. Gleason says that Mr. Caronia drove him to the Long Island Rail Road station in the village center, to begin his journey home. When he stepped out of the car, Dr. Gleason says, Mr. Petri and other investigators surrounded him, bundled him into a sport utility vehicle and drove him to the Great Neck police station. Mr. Caronia was not arrested.

The federal agents said he would have to cooperate in their investigation into Jazz Pharmaceuticals, Dr. Gleason contends. “They said, ‘Who in this company roped you into this conspiracy?’”

Insisting that he had broken no laws, Dr. Gleason said he tried to persuade Mr. Petri and the others that his views on Xyrem were scientifically based. He was released later that day.

Dr. Gleason's account is at least partly supported by a letter on March 13 from Geoffrey Kaiser, an assistant United States attorney, to Lois Bloom, the federal magistrate judge overseeing the case. In the letter, Mr. Kaiser asks that the case be kept quiet because Mr. Gleason may "be willing to cooperate with this office in its broader investigation."

#### On Bail and Short on Work

The same day, Dr. Gleason was arraigned in Federal District Court in Brooklyn, where he was released on a \$150,000 bond.

It was not until three weeks later, on April 5, that the federal attorney's office announced Dr. Gleason's arrest, with the news release comparing him to a snake-oil salesman. As he awaits further hearings and trial, Dr. Gleason, who is divorced, is supporting himself by working as an in-house doctor on short-term contracts. For a brief period, he worked at a Maryland state hospital, before being let go. He said the hospital told him he had been fired because of the indictment; a spokesman for the hospital declined to comment.

Now he is filling in at various hospitals in Western states, which he did not want to identify for fear of losing the work. As for his former benefactor, Jazz, Dr. Gleason says the company told him it was now cooperating with the investigation and that he would have to face the indictment on his own. "They're just cutting me loose," he said.

For all that, Dr. Gleason said he still believed in Xyrem. "The only thing symmetrical with the efficacy and safety of GHB is the hysteria about it."

Those sorts of claims discomfort even other doctors and researchers who agree that the drug may be useful.

"He is a very smart man, and I believe he is extremely well intentioned," Dr. Scharf said. "But this is not candy. It's not a cure-all."

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