The light flickered on for Shalmah Prince one day in 1994. Sitting in a doctor's office, she spotted an article in U.S. News & World Report on human radiation experiments conducted in the 1950s. Her mind, she said, raced back to a wrenching experience from her past.

She had been in an experiment of some type. Had she too been used? Prince, a portrait artist who suffers from manic depression, also known as bipolar disorder, dug into her medical history and documented a chilling story.

In 1983, she had been in an experiment in which investigators withdrew her medication, did nothing to intervene as she became increasingly manic, and then injected her with apomorphine, a chemical that other researchers had tested to see if it could provoke psychosis. Prince became so delusional that she had to be placed in leather restraints, a descent into madness that didn't fully subside for 10 days.

"I was never the same person again," Prince said. "My perception of myself and who I was completely changed. I had a sense of shame and embarrassment. Who would have ever thought that doctors would create psychosis like that?"

Prince's story provides a window into a troubling corner of psychiatric research that continues to this day. She is one of more than 2,000 mentally ill patients who over the past 25 years have been ushered into a disturbing series of experiments by psychiatric researchers exploring the biology of psychosis. In their published accounts, doctors have told of injecting mentally ill patients with drugs designed to exacerbate their delusions and hallucinations. In prestigious journals, they have described studies in which they withheld effective antipsychotic medication from desperate patients who stumbled into hospital emergency rooms. In precise, clinical terms, they have reported how they deliberately stopped giving medication to stabilized schizophrenic patients to see how quickly they became sick again.

These studies were designed to gain knowledge that might lead to improved treatments for schizophrenia and related illnesses. But the experiments offered no possibility of therapeutic benefit to the subjects and exposed them to some measure of psychic pain and risk of long-term harm. Moreover, this controversial line of experimentation has been marked by repeated instances in which researchers failed to fully disclose the risks to the mentally ill patients and obscured their true purposes. Those are the very themes of the story Shalmah Prince pieced together:

On Jan. 14, 1983, fearing the onset of a manic episode despite the lithium she had been taking for two years, Prince went to University Hospital in Cincinnati seeking help. Her medical records show that she arrived well-groomed, in control of her emotions, and thinking fairly clearly. Standard procedure would have been to test the lithium level in her blood and adjust the dosage, but that's not what happened.

Prince signed a consent form that said she was agreeing to take part in a study designed to "clearly diagnose her illness." In their research protocol, however, the psychiatrists said the purpose of the study was to explore "schizophrenia subtypes," based on the patients' response to apomorphine. The consent form didn't mention any risks associated with stopping the medication, even though Dr. David Garver, who ran the study, later acknowledged in a sworn deposition that without medication, the research
subjects might "have a delusion that they were capable of flying, leap out a window, [and] injure themselves."

"They assured me they were there to treat me," Prince recalled. "And I just wanted to be kept safe. I knew that I didn't have insurance and that I was extremely vulnerable. I needed help and a regular doctor was $150. So I was really stuck."

Without her lithium, Prince quickly deteriorated. By the fourth day she was wildly manic, yelling and threatening suicide. She also "got in the face" of another patient, she said, and he started beating her. Still, she was given no medication.

On the fifth day, researchers injected her with apomorphine. Her manic and delusional behavior soared. During the next three days, when her friends and family visited, they found her in restraints, a humiliation that has never left her. "Everything they did to me was for the purposes of their research," she said, her voice tinged with bitterness even today. "As my medical record shows, when I went into the hospital I was calm and cooperative. I was just worried and vulnerable. I came out thinking I was crazy, and my parents thinking I was crazy, and my friends thinking I was crazy. My family and I believed that every psychotic feeling and behavior was natural to me, rather than caused by their experiment."

The final blow came when she got a hospital bill. Prince was asked to pay nearly $15,000 for the experience.

Attorney Ken Faller, who defended Garver and his coresearcher, Dr. Jack Hirschowitz, in a lawsuit brought by Prince, sees her experience differently. "No one disputes that patients ought to be given information concerning meaningful risks," he said. "In her particular case ... we don't believe that there were significant undisclosed risks involved."

Although the judge in Prince's lawsuit said he found the facts troubling, he dismissed Prince's case, saying she should have filed her complaint within two years of the experiments. Faller also said that the hospital forgave more than three-quarters of her bill. "She did receive treatment and the treatment benefited her to this day," he said. "She was a sick person when she went into the hospital and she came out seemingly in pretty good shape."

**Psychiatric researchers called for an accounting**

Prince's story, and scores of clinical reports of schizophrenia studies in scientific journals, evoke troubling echoes of past stains on American medicine. Perhaps the most notorious are the post-World War II radiation experiments that Shalmah Price read about and the 1932 to 1972 Tuskegee syphilis studies in which infected black men were denied treatment, blots on the remarkable achievements of US medical researchers in the 20th century.

Even as psychiatric researchers boast they are now gaining insights into the biology of psychotic illnesses, they are being asked to account for how that knowledge was gained. But unlike Tuskegee or the Cold War radiation studies, this line of psychiatric research, much of it federally funded, is ongoing. This year, according to research protocols obtained by the Globe, Yale University physicians have been recruiting people with schizophrenia for experiments in which they will hospitalize them, stop their medications, and infuse them with tetrahydrocannabinol, the psychoactive ingredient in marijuana.

Columbia University researchers have been giving amphetamine to schizophrenic patients so they can take images of their brains while they are psychotic. At the National Institute of Mental Health, in Bethesda, Md., researchers have been injecting ketamine, the chemical cousin of the notorious street drug angel dust, into unmedicated schizophrenic patients.
Deliberate withdrawal of medication for experimental purposes is an element in other active schizophrenia studies.

"I think [these experiments] are in a category that is worse than Tuskegee and the radiation experiments," said Adil Shamoo, professor of biochemistry at the University of Maryland School of Medicine and founder of the journal Accountability in Research. "There are large numbers [of subjects], and these are current practices. Do they cause harm? Of course they do."

Shamoo, who has an adult son with schizophrenia, has been a leading critic of symptom-exacerbation and medication-withdrawal experiments.

The Globe, in a three-month investigation, found a trail of both harm and deceit.

Since 1972, psychiatric researchers have used a variety of agents - L-dopa, amphetamine, methylphenidate, m-chlorophenyl piperazine, ketamine, and tetrahydrocannabinol - to deliberately provoke psychotic symptoms in more than 1,200 schizophrenia patients. In some instances, the chemicals drove the psychosis to levels the researchers called "severe."

Symptom-provocation experiments like these have been conducted by prominent researchers at the National Institute of Mental Health and at close to a dozen leading medical schools. They have drawn their psychotic subjects largely from outpatient clinics, Veterans Affairs hospitals, state mental institutions, and emergency rooms - settings that regularly provide care to the poor and uninsured. In the few studies that recorded the ethnic makeup of patients, 54 percent were minorities.

Symptom-exacerbation studies do not appear to have been conducted in Massachusetts, but prominent researchers here defend the approach.

In the '80s and early '90s, researchers conducted experiments in which they withdrew medications from schizophrenic patients whose condition was stabilized, including some living in community settings, and studied them until they had a full relapse. The prevailing view is that following a relapse, particularly the first one after a psychotic break, patients may never return to the same level of functioning. During a relapse, schizophrenic patients are also at a dramatically higher risk of self-injury and suicide.

There is evidence in researchers' sworn testimony, written correspondence, citations by the federal Office of Protection from Research Risks, and patients' own accounts that investigators have routinely failed to fully disclose the true purposes of their experiments, and withheld information about risks. The Globe's review of informed-consent forms for symptom-exacerbation studies at the NIMH and four other leading psychiatric institutions failed to turn up a single one in which the researchers directly stated that a chemical agent would be used purposely to exacerbate psychotic symptoms.

When in 1993 researchers at the University of Maryland began injecting schizophrenic patients with ketamine, the consent form said only that the experiment's purpose was "to study a medication named ketamine for schizophrenia."

OPRR, the federal agency charged with protecting research subjects, has found fault with informed consent practices of psychiatric researchers at the University of Maryland; the University of California, Los Angeles; and the National Institute of Mental Health, and has ongoing investigations of the Bronx Veterans Affairs Medical Center, New York State Psychiatric Institute, and the University of Cincinnati.

Such practices do not typify all psychiatric research. There is much experimentation that does not put mentally ill subjects at risk of harm, conducted by physicians who take pains to ensure that subjects know what they're getting into.

But there is no similar type of experimentation, in which patients' symptoms are deliberately exacerbated for research purposes only, on people of sound mind.
"We let researchers do things to people with mental illness that we would never let them do to people with physical illness," said George Annas, chairman of the Health Law Department at Boston University School of Public Health.

**Schizophrenia resists divulging its secrets**

As researchers note, schizophrenia is a poorly understood illness that has resisted giving up its secrets. It afflicts about one in every 200 adults, typically beginning in early adulthood. The disease brings on delusions, hallucinations, and bizarre thoughts (called positive symptoms) and often a striking lack of outward emotion and extreme social withdrawal (negative symptoms). It has no consistent course. Some experience an initial psychotic episode and never relapse; others relapse repeatedly as the disease becomes chronic.

Symptom-exacerbation experiments were pioneered by Dr. David Janowsky of Vanderbilt University. In 1974, he reported success in developing a new tool for studying schizophrenia. He found that giving schizophrenic patients methylphenidate (Ritalin) caused "a dramatic intensification of preexisting symptoms, such as hallucinations and delusions," and that amphetamine also exacerbated their psychosis. Both drugs are known to release dopamine, a messenger chemical in the brain, and Janowsky's experiments provided indirect evidence that the biological mechanism of psychosis involved an overactive dopamine system.

His work also established the idea that psychosis-inducing drugs could be used as "challenge agents" to turn patients into models for studying psychotic illnesses. "They are uniquely human conditions and there is no animal model for developing treatments," said Dr. Stephen Strakowski, associate professor of psychiatry at University of Cincinnati Medical School, who has used amphetamine as a challenge agent. "Challenge tests are used to understand complex disorders, and without them, we would lose a significant way to do that."

In the past decade, researchers have turned to new types of psychostimulants to conduct these studies. Their findings, researchers say, may lead to better drugs. It is this prospect, they say, that justifies risks to patients, and the psychic distress they may suffer.

The researchers also say the psychotic symptoms they induce are transient, usually lasting only a few hours, and generally cause patients only modest discomfort. "What we are talking about is very short-lived increases in symptoms that patients have experienced over years and decades," said Dr. David Shore, associate director for clinical research at NIMH, where ketamine-challenge experiments are underway. "To say that increasing a particular symptom - like hearing voices for a couple of hours in somebody who has been hearing voices for 10 years - is causing [suffering] rather seems like a stretch."

Dr. Jeffrey Lieberman, who conducted methylphenidate challenge tests for more than a decade at Hillside Hospital, a division of Long Island Jewish Medical Center in New York, acknowledged that the induced symptoms are sometimes "scary and very unpleasant." Some patients get worse, he said, "but in my experience, the symptoms never exceeded the range of severity that occurred in the course of their illness previously."

Dr. Paul Appelbaum, chairman of the psychiatry department at the University of Massachusetts Medical School, said challenge studies can be justified "if the question researchers seek to answer is an important one" and the research subjects have given "good consent, adequate consent." Even the use of a drug like ketamine can be justified, he said, as long as patients have given informed consent. "The investigators [using ketamine] are quite persuasive, from my discussions, that they are not causing outrageous levels of harm," Appelbaum said.
But a different view emerges from the researchers' own medical journal reports, from people who suffer from mental illness, and from families of patients who have been in such studies. They tell of fragile minds filled with pain and suffering, and of lives made worse. The scientific literature provides a few glimpses of individual patients. This 1987 account by researchers at the National Institute of Mental Health describes a patient with bipolar disorder who was injected with methylphenidate: "Within a few minutes after the infusion, Mr. A experienced nausea and motor agitation. Soon thereafter he began thrashing about uncontrollably and appeared to be very angry, displaying facial grimacing, grunting and shouting ... 15 minutes after the infusion, he shouted, 'It's coming at me again, like getting out of control. It's stronger than I am.' He slammed his fists into the bed and table and implored us not to touch him, warning that he might become assaultive. Gradually over the next half hour, Mr. A calmed down and began to talk about his experience."

That is what outside observers could see. Those who have lived through psychotic episodes describe an interior landscape that can be filled with fear and terror as delusions and hallucinations become more florid.

"When you are psychotic, there are a lot of unusual processes going on," said Michael Susko of Baltimore, who suffered a psychotic break when he was 25 years old. He is editor of a book about schizophrenia, "Cry of the Invisible."

"You might be having death experiences, feeling like you are dying and melting," he said. "You give somebody a drug that amplifies that, you run the risk of overwhelming them. It's like a bad trip."

Franklin Marquit, founder of the National Artists for Mental Health, has suffered from a variety of mental illnesses, including manic depression, panic disorder, and obsessive-compulsive disorder. Last fall, in preparation for a hearing held by the New York State Department of Health, he gathered opinions from 25 mental health "consumers," including some with psychotic disorders, on symptom-exacerbation experiments. All objected vigorously to the idea that such studies present little danger or cause only minimal discomfort.

"Have it done to yourself and see how the symptoms are," Marquit said. "Someone who doesn't experience this traumatizing feeling, how would they know? With panic disorder, I feel like jumping off the edge of the earth at times, it is so bad. I can't imagine the rationale for exacerbating symptoms, especially a brain symptom. If a person had an arrhythmia problem, would you speed the heart up and say that it is OK because they are used to it?"

Whether symptom-exacerbation experiments and the cutoff of antipsychotic medication that often accompanies such research cause long-term harm is a thorny issue. Although these experiments have been ongoing for 25 years, the question hasn't been studied. Researchers argue that the temporary increase in psychosis does not amount to a relapse. Although they acknowledge there is a growing suspicion that acutely psychotic episodes may be toxic to the brain, causing a type of scarring of neurons, they do not believe exacerbation experiments are likely to trigger such damage.

"There is a risk there," said Dr. Stephan Taylor, assistant professor of psychiatry at the University of Michigan, who has used challenge agents to study anxiety and post-traumatic stress disorder. "My sense is that the sort of psychosis that reaches a toxic level is much more significant than what a few doses of amphetamine will produce. It's a fairly small risk."

The ultimate question, however, is how exacerbation experiments can be reconciled with a standard of good medical care that runs contrary to such practices. Psychiatrists agree that patients do best when physicians catch the psychosis at an early stage and quickly curb their delusions and hallucinations with medications. Relapse, often defined as a return of even moderate psychosis, is seen as a life-threatening event that needs to be prevented. Most clinicians believe that repeated relapses, particularly for a person early in the course of the illness, lead to a worse long-term outcome.
Moreover, critics say that the administration of symptom-inducing drugs is only part of the harm. Patients in these studies are typically taken off their medication first and may not receive effective treatment for days and even weeks, exposing them to an extended period of psychosis. A chilling example of this was detailed by University of Maryland researcher Carol Tamminga and colleagues in a 1995 article on their first ketamine experiment. One of their subjects was a 29-year-old man who at the start of the experiment was described as doing well on his medication. His medication was stopped and he was injected three times with ketamine, which caused him to become "floridly delusional." The researchers allowed his disease to progress even after the ketamine study ended.

"During a later drug-free period unrelated to this study, his clinical symptoms were that of paranoid schizophrenia," Tamminga wrote. "There were similarities between his disease symptoms and those induced by ketamine." Along with whatever harm such experiments cause, critics say that they necessarily violate the trust between doctor and patient that is vital to the healing process. "If the patients have any idea about what is being done to them, they know that they are being used as guinea pigs," said Dr. Peter Breggin, director of the Center for the Study of Psychiatry and Psychology in Bethesda and an outspoken critic of mainstream psychiatry. "If they are mentally unbalanced, and their condition is worsened by doctors for the purpose of serving the doctors' scientific careers, of course that is going to make it harder for them to trust anyone again."

The voices that are hardest to find are those that matter the most: the mentally ill patients who have been the subjects of these symptom-exacerbation experiments. Last fall, however, the mother of one patient stepped forward to tell the National Bioethics Advisory Commission, a presidential panel that advises the government on ethical issues in biomedical research, what happened to her mentally ill daughter after she apparently was given multiple doses of intravenous amphetamine.

In April 1987, Janice and Carl Becker brought their daughter Laura, 26 at the time and ill with schizophrenia, to the Maryland Psychiatric Research Center, outside Baltimore. Researchers emphasized that she would get excellent care while on the ward, Janice told the commission. A few months after Laura was admitted, researchers stopped her medications as part of a research protocol, and her condition quickly deteriorated. Twice when her mother visited, she found Laura bound with sheets to a chair, the knots so tight around her wrists and ankles that it took 20 minutes to free her. Laura's appearance changed. She lost 40 pounds. She would pace for hours on end. Alarmed and getting no answers from the staff, her parents pored through protocols, and found one describing an amphetamine study. They concluded that the amphetamine explained many aspects of her deterioration: her weight loss, the hyperactive behavior, the increased psychosis. Laura's parents never got a copy of any consent forms Laura may have signed and, to this day, do not know for sure whether their daughter signed the form for the amphetamine study.

"It was heartbreaking to watch Laura's condition deteriorate," Janice told the commission. "We had not expected that she would be required to endure such painful symptoms without medication for years. Nor had we expected that she would be given drugs that would make her psychotic symptoms worse."

Today, Laura is on her own, taking medication for her illness, living in a group home and holding a job. But her mother believes that Laura's story shows that the researchers put science first and patient care second. "The physician's creed of 'do no harm' does not apply to research physicians," Janice said from the kitchen of her rural Maryland home. "I was wrong to trust that my daughter would be protected."

Chris Hart, a spokesman for the University of Maryland, said, "Because there are issues of patient confidentiality involved, we can't comment."

**Troubling methods surface in relapse studies**

Relapse studies conducted during the '80s and early '90s are at least as troubling as the symptom-exacerbation experiments. In one line of experimentation, researchers withdrew medications from
stable patients precisely to study the biology of relapse, expecting the patients to become sick again. After their subjects’ descent into sickness could be studied, they planned to put them back on their medications.

One of the largest studies of this type was led by Dr. Daniel van Kammen at Highland Drive Veterans Affairs Medical Center in Pittsburgh. From 1985 to 1995, he conducted experiments that involved withdrawing medication from more than 150 stabilized schizophrenic patients and using spinal taps to analyze their spinal fluid. The researchers then followed the patients until they relapsed, which was defined as exhibiting worse symptoms for three days straight. During the 10-year Pittsburgh study, virtually all the schizophrenic patients either relapsed or stopped coming to the hospital and were, in the researchers' own words, "lost to follow-up."

There is considerable evidence that this relapse study put research subjects directly in harm’s way. Patients in relapse have been found to have seven times the risk of falling victim to antisocial behavior, such as assault, and 2.5 times the risk of self-injury, including wrist cutting, poisoning, and attempted hanging, according to a published study. "You do not put patients through pain and suffering, with experiments that have a high-risk design, with no benefit to their future," said research critic Shamoo, at the University of Maryland. "You just don't do that."

Van Kammen has since left the Pittsburgh VA; his coresearcher on some of this research, Dr. John Gurklis, is still there, but he declined to be interviewed.

At UCLA, researchers conducted a long-running medication-withdrawal study. Gregory Aller of Los Angeles was a subject, and his experiences led him to file a complaint with federal officials. UCLA psychologist Keith Nuechterlein began his research 15 years ago, and in an update published in 1988 he detailed how schizophrenic patients admitted to UCLA's Aftercare Clinic had been taken off medication and allowed to deteriorate into "clear" relapse. Aller, 24 at the time, became a patient at the clinic in 1988, after suffering an initial bout of psychosis. At first, he was put on antipsychotic medication, Prolixin decanoate, and thrived, earning a 3.8 grade-point average at Santa Monica College. But in late 1989, he entered a medication-withdrawal experiment led by Nuechterlein and fell into a severe relapse. He growled on buses; he lapped water out of a toilet like a dog. One evening while visiting his parents, he said he picked up a butcher knife in the kitchen and called out his mother's nickname: "Come here, Poo!"

Aller said he needed to exorcise the devil that he believed inhabited her. "It was so bizarre," said Aller, a mild-mannered man who looks younger than his 34 years. "I couldn't believe it." On Jan. 12, 1990, his parents argued with researchers that Gregory needed his medication. They detailed his psychotic behavior in a letter, but, according to the Allers, the researchers made no attempt to remedicate him. Exactly when the researchers attempted to put Gregory back on an antipsychotic drug is in dispute; what is clear is that Gregory did not resume taking medication until May 15. By then, however, the harm had been done. Gregory is doing well today, said his father, Robert, but "he never returned to his previous level of function."

UCLA clinical psychologist Nuechterlein says he cannot discuss Aller because of patient confidentiality, and the family has not given written permission waiving the confidentiality. But he justified the study as helping to determine how soon patients with early-onset schizophrenia could be taken off antipsychotic medications, and how long they could stay off. It was an important question because of the side effects of the medications available at the time. He also defended the 1988 update as a retrospective look at patients' records and measurement of relapse after the fact, rather than a study in which researchers purposely waited for patients to worsen.

In 1993 Dr. Jay Katz, professor emeritus of law, medicine, and psychiatry at Yale, reviewed documents in the Aller study at the family's request. "The patients were withdrawn from medication, indeed,
required to do so for research purposes until the needs of the study, and not those of the individual patient, had been satisfied," Katz wrote in a law journal article. By any standard, the symptom-exacerbation experiments, the relapse studies, and the patients' stories all add up to an unsettling record, one that has imposed some measure of suffering on thousands of vulnerable patients and exposed them to the risk of long-term harm, often without adequate informed consent.

Until now, it is also a record that has escaped any broad examination, despite the efforts of a handful of people to hold researchers accountable. Chief among them is Vera Sharav, founder of Citizens for Responsible Care in Psychiatry and Research, a New York-based group made up of families with sons and daughters who suffer from schizophrenia. For years, Sharav has labored to bring this research to light, digging deep into the scientific literature, hectoring reporters to write about it, and, in a variety of public forums, questioning researchers about its ethics. It is a record of experimentation, she said, that could only be done on the powerless. "That is why I am so passionate about it," she said. "It is extremely wrenching to see how easily a group regarded as misfits, or as not good enough, or as socially and economically useless, can be made into objects for other people's purposes."

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