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Studying Drugs in All the Wrong People

How the costly race to enroll subjects in psychiatric research trials is harming patients and compromising treatme

By Gabriella Rosen | Thursday, September 6, 2012 | 2 comments

One evening in the emergency room, I was asked to evaluate a patient requesting admission to the psychiatric unit. Gia was waiting for me, looking pale but fit. (All individuals identified only by their first name have been assigned pseudonyms, and their identifying details have been changed.) She had heard that the hospital was recruiting inpatients for a study of bipolar disorder and wanted to participate. She described herself as moody—upbeat for a few hours, then down, then happy again.

Image: FERRAN TRAITE SOLE

“How do you feel right now?” I asked.

“Okay,” she shrugged.

Psychiatric diagnosis is as much an art as a science, and it relies largely on a physician's observations and a patient's self-reports. Gia's calm, even speech, her pleasant demeanor and her relaxed manner were not in keeping with a bipolar diagnosis, nor were the symptoms and history she related. At the same time, all was not well—her lab work and vital signs revealed several abnormalities, including low blood pressure, anemia and troubling results on liver tests.

“Are there any medical conditions you forgot to mention?” I asked, puzzled. “Or medications?” I ran through an exhaustive list of symptoms—itchiness, weight loss, light-headedness. At last, when I asked about possible chemical exposures in her line of work, Gia produced a stack of business cards.

“Your employers?” I held seven or eight cards. The names included several nutritional and biomedical companies. “What do you do for them?”

“I try things. Drugs. Pills. Products.”

Gia took these drugs for money. Yes, she said, she had participated in psychiatric studies before. I expressed concern about her lab results and asked if she could

recall more details about the pills she had taken. She said she was not sure how many different experimental agen system at that moment. I shuffled and reshuffled the cards in my hand.

"So ..." Gia said, breaking the silence. "Is there room in the study?"

Researchers involved in psychiatric drug development know patients like Gia well. They ask to join studies in whic belong, motivated by the monetary compensation. The question is not why such individuals wish to take part but v want to enroll them. Testing a drug for bipolar disorder—or any other ailment—on people who feign the condition And yet these subjects are enrolled in trials, over and over again. The reasons why reveal a troubled system, one ir reward researchers for recruiting as many subjects as they can. As a result, studies can produce suspect findings, v doctors' treatment decisions for countless others.

Some of these trials fail altogether, and it may well be because the wrong patients are enrolled. The corresponding drug development—currently on the order of $1.8 billion to bring a single new drug to market—carries downstrea health care consumers and taxpayers. The problem is particularly acute in psychiatry because the subjective natur makes it comparatively easier to enroll the wrong patients. As this country undertakes a historic, and expensive, o national health care system, we cannot afford to miss this piece of the puzzle.

When Quantity Trumps Quality

Ten years ago, when I first entered medical school, the pharmaceutical industry was barely on my radar. I would s briefcases emblazoned with various companies' logos, perhaps stopping in at sponsored luncheons to grab a tuna back to the wards. That was about it. The medical research in which I participated as a student was, to my knowle entirely by the government. Only years later did I realize how anomalous such publicly funded research was fast b

Today less and less drug research is conducted in academic settings, and a still smaller sliver is not industry-spons estimated 70 percent of clinical researchers were affiliated with academic medical centers, but by 2006 only 36 pe to the Tufts Center for the Study of Drug Development. Even within academic institutions, 36 percent of the grant come from industry.

In the past few years the federal government has enacted various regulations to combat the worrisome influence o companies on medical practice [*see box on opposite page*]. The extent of their influence on medical research, how appreciated. Within psychiatric research, the harmful effects of industry-sponsored incentives for subject recruitn and patient well-being are especially pernicious.

Here is a typical scenario for a psychiatric drug trial: A pharmaceutical company wants to test a compound that ha reduce depressive behavior in mice. First, it needs to demonstrate with small trials that the compound is safe for i The next step is to give it to a large number of depressed patients and see if it helps. The subjects are randomized t potential new drug or a comparison pill, which may be an existing treatment or a placebo—a sugar pill. The resear professionals running the study do not know who is getting which pill. At the end of a prearranged time period, th assessed, and the numbers are crunched to see if the drug helped patients more than the placebo or existing treatr

A major hurdle during this process is that study subjects are in short supply. "Where there used to be 50 schizoph must be thousands now, and they're scrambling over each other to do these things," says Joseph McEvoy, a schizo

and Duke University professor. The profitability of psychiatric drugs fuels the drive for new products. In 2010 anti antidepressants were among the top-five highest-selling classes of drugs, generating $16.9 billion and $16.1 billion year, according to consulting group IMS Health.

Despite the difficulty of recruiting subjects, many doctors continue to take part in this process in the hope of devel treatments down the road. Academic physicians are also often compelled by the need to publish papers: their job d past two decades, however, a third motivation—direct profit—has come strikingly to the fore. Industry-sponsored variety of financial incentives to accelerate the recruitment of trial subjects. Investigators may receive direct paym $10,000 to $30,000 per patient enrolled, according to McEvoy. Competitive enrollment, in which multiple sites v patients as they can before a study is full, also encourages haste. Recruiters may even receive bonuses after they ha number of patients. The process can become a kind of a race, with new monetary rewards at every turn. Investigat enroll more patients, not better ones, as quickly as possible.

“There's a lot of concern about this [recruitment issue]. Substantial bonuses are paid for each patient who's actual study, so you're giving people incentives to fudge,” says Paul S. Appelbaum, a Columbia University professor of law past president of the American Psychiatric Association. “It is understandable why you might be seeing enrollment truly eligible for the study.”

With such enormous sums hanging in the balance, it would be tempting to enroll everyone you know. Quantity rat becomes the goal.

Room to Fudge

Although financial incentives exist in a variety of research fields, psychiatry is uniquely vulnerable to the problem subject selection. This is because of the imprecision of psychiatric metrics. To be admitted to a study of anticholes person's lipid profile must meet particular thresholds. No such laboratory tests exist for psychiatric disorders. “Th determine whether or not a patient is truly hearing voices, for example,” says John M. Kane, an Albert Einstein Co professor who researches schizophrenia.

To minimize subjectivity, doctors use rating scales to verify that a psychiatric patient has a given disorder. For stu disorder, say, researchers often use the Young Mania Rating Scale to assess the severity of the “up,” or manic, half questionnaires rely heavily on self-reporting; a savvy subject could exaggerate his or her way into enrollment. The enough wiggle room for the evaluating physician to tip the balance, too.

The mismatch between a patient and a trial can be subtle—the patient may carry the correct diagnosis but not be a diagnosis may seem slightly off. Other times, however, the claims can strain credulity.

Jack, a doctor who trained at a well-regarded academic hospital, recalls a teaching session in which a psychiatrist Eileen. Eileen had been admitted to the ward the night before as part of a study. In the interview, she spoke of her her feelings of abandonment, her frequent crying spells. She sat slumped in her chair, did not make eye contact, sp conveyed a sense of hopelessness. It did not take a professional to apply the word “depressed.”

After the session, the group discussed her case. Jack asked Ann, the resident treating Eileen, to which study Eileen

"The bipolar study," Ann said. "Of acute mania."

The psychiatrist, visiting from another hospital, rolled his eyes. The exuberance of mania was as far from Eileen's could be.

In other cases, the patients themselves, such as Gia, wish to enroll in studies in which they do not belong. "What I patients who want money, who aren't even mentally ill," says Helene, an inpatient psychiatric nurse who has work and private hospitals. "They brag about what other studies they've done. I see no symptoms of anything. They're c money." When she expresses hesitation about the appropriateness of a patient for a given study, she says, researcl half smile and walk away.

Failed Trials, Stalled Drugs

One outcome of studies populated by inappropriate subjects is that the drugs in question may fail to pass the test: more effective than a placebo or other current treatments. Failed trials have a far-reaching impact. Patients who n from the drug will never receive it. Pharmaceutical companies must make up the wasted money by raising prices f According to a report in 2003 by the U.S. Department of Health and Human Services, pharmaceuticals represent health care expenditure and the largest source of cost increases among federal health care programs.

Within psychiatry, trials fail at astounding rates. Half of all antidepressant trials, for example, do not pass muster. poor results for a number of possible reasons, but in psychiatry, the main problem is that the drugs are not showi placebos. This could be because the new compounds are worthless. But there are signs that something else is goin decades the number of psychiatric subjects who appear to be getting better on placebos has been increasing. High rates make it difficult to tell if a drug works: if half of all the patients who take a sugar pill get better, significantly take the drug must improve for it to look effective.

A growing body of studies has directly implicated inappropriate subject selection as a cause for the rising placebo studies compare subject evaluations done by disinterested researchers with those of researchers who have incenti Investigators with a financial stake have been shown to deem patients significantly more ill than scientists not mo When subjects are later evaluated for improvement, the participants in the financially motivated groups appear to across the board.

To understand how this affects placebo rates, let us imagine a potential subject, Paul. To be eligible for a depressic given an 8 out of 10 rating on a depression scale. Even though Paul is really only a 6 out of 10, the researcher rates enroll. Any subsequent ratings that show Paul is a 6 will look like improvements—but in fact, he was always a 6. Ir of the pool will be taking a placebo; hence, patients such as Paul will appear to be getting better—even on a sugar p

Much of the data on subject enrollment comes from companies with a financial interest in the findings. Called cen companies, these contractors employ off-site physicians to remotely evaluate psychiatric subjects via video. They pharmaceutical companies more accurate assessments than on-site researchers. A 2010 paper funded by MedAva of such companies, for example, found that MedAvante's raters excluded more subjects than did local raters at the lower placebo response rates. In other words, when subjects were more objectively selected, the placebo response

Some experts question whether these studies can be trusted because of their origin. It is an important considerati

data add up. McEvoy concurs: “My belief is that this [high placebo response rate] is almost entirely related to subj “Twenty or 30 years ago you would find large placebo-drug differences. [Patients taking] placebo would get worse active drug would get a lot better because they actually put the right people into the trial.”

Consequences for Patients

The most troubling repercussions of using inappropriate subjects are those felt by patients themselves. When a dr tested on the wrong people, there is no way to know whether it might have actually worked on the right ones. Pati the chance to try these treatments. In the meantime, subjects have needlessly been exposed to risk. Even a recent GlaxoSmithKline employees makes note of this outcome. Given that half of all antidepressant trials are failing, hal enrolled in those trials place their health in jeopardy with “no probability of a contribution to knowledge.”

The risks to study participants are numerous. Most obvious is the exposure to the experimental chemical itself, wh tested only in animals. In addition, when patients start on a new drug, they must usually stop taking the medicatio treat their conditions. As a result, their mental states may worsen, even putting them at risk for suicide. These risk patients end up in the placebo group. For this reason, placebo-controlled trials remain controversial within psychi subjects are well matched to a study. When researchers are given incentives to include as many patients as possibl careful in selecting those who can safely transition to a placebo.

A psychiatrist named Ethan, who worked in the same academic hospital as Jack, once tried to protect a patient fro placebo-controlled trial. The patient in question, a woman in her late 40s, had suffered from violent delusions for her family convinced her to get help. During her inpatient admission, the research team on that ward had approac participating in a placebo-controlled trial. Ethan felt she would suffer too greatly if she ended up in the placebo ar accordingly, only to receive a dressing down by his bosses, who needed recruits for the study. “There's a feeling of “of wanting to learn something from your superiors and also finding what they're doing is unethical.”

Another risk to patients in trials comes from the exclusion of supplemental medications. Imagine that you have a emergency room, you agree to participate in a study because you have no insurance. You are then randomized to r or a drug that *may* work. You are also informed that you cannot take even Tylenol, lest it compromise the results. commonly used adjunctive medications such as sedatives are frequently excluded. So when an actively psychotic, insomniac patient asks his doctor for something to help him calm down, the doctor is not allowed to give him the medications available. As a physician, the inability to provide relief for one's patient is heartbreaking. The inability when good, proved treatments exist is maddening. Without the incentives to rapidly recruit new patients for trials more careful to include only those for whom a trial would not be too dangerous or painful.

Patients can always refuse the invitation to be in a study, of course. But if they need the stipend or have run out of they may “elect” to participate. Is it coercion? Historically, subject enrollment might have been more literally coer prison populations. Nevertheless, many in the field worry that lower-income patients who either need the money conventional treatment are subject to a different kind of pressure. It is “coercion through lack of income,” explains Columbia professor with expertise in medical ethics. Monetary need may cloud a patient's decision making, expos greater level of risk than he or she might otherwise accept.

At the Tipping Point

The good news is that pharmaceutical companies cannot afford to continue business as usual. Their most lucrativ patent, with no adequate replacements in sight. Large-scale drug trials—phase III in the Food and Drug Administ process—fail 42 percent of the time, according to a 2006 article in *McKinsey Quarterly*, a business journal. The c astounding. Cutting Edge Information, a life sciences consulting firm, reports that the per-patient cost of running nearly doubled since 2008, from roughly $50,000 per patient to $100,000. Now figure that phase III trials involv thousands of patients each, and the financial impact of unsuccessful trials becomes clear.

As more and more trials fail, and costs soar, pharmaceutical companies will have no choice but to rethink their en The central ratings model represents one possible solution, although a fair amount of resistance to and skepticism within the field. The larger shift to rewarding good science over fast science seems inevitable now that speed has p How exactly that will work remains to be seen.

The goal of these efforts should not be to separate medical research from industry but to shape the interaction so a best science possible. “If we separate the talent and the skills of people in medical schools from the talent and skill we won't have any new products,” says Eric G. Campbell, a Harvard University professor who studies physician co Ultimately responsibility for recruiting the right patients has to lie with the researchers themselves. One of the gre physician researchers to surmount so that they can effectively police their own work may in fact be denial. “I think resistance, still, to believing that physicians can be influenced in these indirect ways,” Columbia's Appelbaum expl strong tendency within the profession to believe that we are objective, but in fact we are just like everybody else.”

With any luck, a radical restructuring of researcher incentives will soon bolster physicians looking to do the right t —patients, doctors, pharmaceutical executives, taxpayers—stands to benefit from such reinvention.

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