Psychiatrist Challenges Ethics of Yale Drug Experiment

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The ethics of this radical drug experiment is being challenged by Dr. Jerald Block, a forthright psychiatrist and experienced system's analyst. His critical appraisal, published in the Bioethics Forum, Hastings Center Report.

Ethical research on the use of medicines must carefully consider whether human test subjects are being exposed to unnecessary risk. But when the research is commercially driven, and is designed to test a radical hypothesis and an expanded use of a toxic drug in persons not diagnosed with an illness, only an academic-based high profile physician can provide the needed “authority” to lend the experiment an appearance of legitimacy.

Industry refers to such influential physicians as KOLs (key opinion leaders); they command highest fees for their services. Not only do KOLs readily obtain the backing of a prestigious university and approval of a respected academic IRB, they can obtain funds from both industry and government. And they can generate promotional buzz for the off-label use of a drug even before the trial is completed. The promotion of a medicine for "off label" use, outside of its FDA-approved indication, is something drug manufacturers are legally prohibited from doing. Only doctors have the authority to make medical judgments about whether the risks of prescribing a drug for unapproved indications are justified by the benefits.

A controversial experiment (dubbed PRIME) was initiated by Dr. Thomas McGlashan of Yale University with funding from Eli Lilly and the National Institute of Mental Health. PRIME investigators tested a speculative schizophrenia prevention theory by exposing healthy youngsters for one year to Lilly’s toxic blockbuster drug, the neuroleptic, Zyprexa (olanzapine). [1] The youngsters did not meet any diagnostic criteria for a mental condition, but the researchers declared them to be “at risk” for schizophrenia, a debilitating disease.

The ethics of this radical drug experiment is being challenged by Dr. Jerald Block, a forthright psychiatrist and experienced system's analyst. His critical appraisal, published in the Bioethics Forum, Hastings Center Report (below) highlights the global systemic failure to assess the likelihood and magnitude of the documented and foreseeable risks of harm for the young subjects.

The experiment and its speculative rationale were launched with much fanfare—as though a new treatment had been discovered. Yale established an entire research clinic–Prevention through Risk Identification, Management, and Education (PRIME). [2] Dr. McGlashan promoted the study and his speculative unvalidated theory in the media and at professional meetings much like a marketer of a new drug: In 1999, Dr. McGlashan told The New York Times—without a shred of evidence—that “80 percent if not more of the damage is done before the disorder appears." [3] In 2000, the WSJ reported that Dr. McGlashan justified the experiment stating: “The idea is to use schizophrenia drugs ‘as a preventative as well as a palliative.’" [4] In 2002, the Boston Globe reported: “McGlashan presented hopeful new results at the American Psychiatric Association's annual meeting in Philadelphia. "There is evidence to suggest that intervention in this stage can have a preventive effect," McGlashan said. [5]

From 1997 to 2003, sixty previously healthy youngsters were enrolled in the experiment: of whom half were exposed to Zyprexa (olanzapine), a drug so toxic it was approved only for use in adult patients diagnosed with schizophrenia. Later it was approved for short term treatment of bipolar disorder in adults. None of the youngsters met the diagnostic criteria of either condition for which the drug was approved. Absent a diagnosable condition, and absent any evidence to support the assumption that a drug can prevent schizophrenia, these healthy youngsters were exposed to a toxic drug on the basis of speculations.

Psychiatrists have long resisted conducting or even examining studies that tested the outcome of non-drug treatment. But the few studies that have been done, have shown better outcome results for people with newly diagnosed symptoms of psychosis when treated without medication. [6] By contrast, documented evidence links the toxic drugs used to treat psychosis with severe harm.

Zyprexa induces irreversible, debilitating chronic physical and mental dysfunction: the drug triggers metabolic syndrome—a cluster of life-threatening diseases leading to stroke, high blood pressure and cholesterol levels leading to cardiovascular disease, hyperglycemia, and insulin-resistant type-2 diabetes. Metabolic syndrome increases the risk of coronary heart disease. A reasonable benefit / risk assessment by a physician not financially tied to drug manufacturers would have led to reject the use of drugs in the youngsters recruited by Yale.

Previously healthy youngsters were exposed to the drug’s life-threatening risks because the researchers presumed they exhibited undefined “prodromal symptoms” of schizophrenia.

As Dr. Block (and others) point out, “psychiatrists are not yet able to accurately predict who will manifest schizophrenia. Unfortunately, the prodromal symptoms are also remarkably common, diffuse, and unspecific, especially when one considers that the patient is usually young – adolescence is a period of life that is normally marked by

tumultuous changes in personality.”

Indeed, the authors (who include the Vice-President and Chief Medical Officer of Eli Lilly, Dr. Alan Breier) acknowledge that the psychological diagnostic test instrument they used had a high false positive rate: “In prior studies, 46% to 80% of those tentatively labeled "prodromal" never developed schizophrenia after up to two years of observation. [7] More than half of the youngsters treated with Zyprexa in the PRIME experiment were exposed to the hazardous effects of this neuroleptic for a disease they did not have on the basis of two speculative theories with obvious commercial appeal, but without ethical or scientific justification.

The authors now acknowledge in their published report that the experiment had failed—Zyprexa did not prevent schizophrenia and they acknowledge that scientific confirmation for their “prodromal” speculations was lacking. Thus, they had resorted to reliance on “virtual” reality: “In this article, ‘the prodrome to onset of psychosis’ refers to a virtual syndrome that is validated only after the onset; thus, the term ‘prodromal’ here means ‘putatively prodromal.’” [7]

By conducting such a study, Dr. Block charges, “psychiatry may have crossed into ethically questionable territory. Regardless of the actual findings, though, the study never should have been performed.”

Every doctor involved in the approval process, the execution, and the published report—knowingly violated medicine’s cardinal rule: “First do no harm.” [8] The IRBs who approved the experiment violated federal regulations mandating that “risks to human subjects are minimized” and that procedures used “do not unnecessarily expose subjects to risk.” [45 CFR 46.111] In the published report the investigators acknowledge that the drug-induced weight gain during the year study—13% of their body weight—may put “these young people [ ] at higher long-term risk for the metabolic syndrome, but they do not display this during the first year of treatment.”

When we learned of this experiment, in 2000, we filed a complaint about the ethics of exposing healthy youngsters to the risks with the federal Office of Human Research Protection. The OHRP letter of determination found the investigators and the Yale institutional review board (IRB) in violation of federal regulations. Of note, the Yale IRB was chaired by a prominent KOL in bioethics whose influence on national bioethics advisory committees has shaped current medical ethics policies, and his opinions lend support to current IRB decision-making practices.
http://www.hhs.gov/ohrp/detrm_letrs/dec00e.pdf

OHRP found that Yale's IRB failed to comply with rudimentary federal informed consent requirements: “there was some confusion regarding informed consent documents that were misplaced or not signed." Furthermore, the consent documents failed to disclose the risks: "It appears that the informed consent documents reviewed and approved by the IRB to this research project failed to include an adequate description of the reasonably foreseeable risks and discomforts, as required by HHS regulations at 45 CFR 46.16(a)(2).”

Among numerous misrepresentations in the informed consent document cited by OHRP:
"If you are randomly assigned to receive placebo you will be at risk for receiving inactive treatment which could result in a worsening of your condition." The investigators apparently forgot that the subjects of this speculative experiment did not meet the criteria of any diagnosable condition—the psychiatrists merely hypothesized "prodromal symptoms." Indeed, the OHRP letter notes the inappropriateness of that statement: "Given that the efficacy of olanzapine in preventing progression of a prodromal state to schizophrenia has not been established and is being assessed by this research…” The informed consent document further misinforms: "While the clinical goal is to help you feel better and more in control of your life, it is possible that you will feel worse. This is a risk of your clinical condition, not a risk of being in the study." OHRP notes, “This statement appears not to take into account "feeling worse" due to olanzapine side effects."

In the latest published report [7] Case 2 (reproduced below) describes a 14-year old boy randomly assigned to the placebo group: “Within 2 months all of his prodromal symptoms no longer scored in the prodromal window of severity.” Inexplicably, however, Dr. McGlashan et al., did not acknowledge they had mistakenly labeled the boy. Instead, “at discharge, he received a diagnosis of prodromal syndrome, in remission.”

If protections for human subjects were enforced to the same degree that protections for laboratory animals are enforced under the Animal Welfare Act of 1966, Yale would have lost its federal license to conduct human research—at least temporarily. The approval of this experiment by the Yale IRB (and the other sites involved) demonstrates that the ethical-scientific underpinning of the IRB system has collapsed under the weight of overriding corporate influence.

The IRBs suspended both ethical and scientific principles when they approved this high risk experiment. As Dr. Block observes, "the integrity of the controls that ensure research remains ethical" are not functioning. He goes on to say, “that a study with such glaring problems got federal funding and worked its way through one or more IRBs is alarming. What happened to the system that allowed such a trial to occur?”

The current system does not provide for accountability. There are no independent checks and balances. The sponsors, the investigators, the IRB gatekeepers, and the institutions all have a financial stake in the business of clinical trials. The subjects have no one to protect them from unjustifiable risks of harm and exploitation. OHRP, the federal agency authorized to oversee clinical trials is but a paper tiger—at most, it issues letters.

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2. Tandy J. Miller, PhD Yale University, School of Medicine PRIME Research Clinic
Yale's New PRIME Research Clinic Is at the Forefront of Schizophrenia Treatment and Research
http://www.med.yale.edu/psych/prime/part.html Text at: www.ahrp.org/cms/content/view/385/80
See also: Tandy Miller, Thomas McGlashan, Early Identification and Intervention in Psychotic Illness, Connecticut Medicine, June 2000, vol 64 at: http://info.med.yale.edu/psych/clinics/prime/pdf/ctmedicine.pdf

3. Erica Goode. Doctors Try a Bold Move Against Schizophrenia THE NEW YROK TIMES, December 7, 1999

4. Rachel Zimmerman, Radical Study on Schizophrenia May Be Expanded, The Wall Street Journal, July 2000 at: www.ahrp.org/cms/content/view/375/80

5.Ellen Barry. High school testing eyed for schizophrenia signs, the Boston Globe, May 25, 2002 page A1

6. Only seven well-designed studies since the introduction of neuroleptics (involving 623 subjects) examined the feasibility of treating first-episode psychosis without drugs. The results show that in follow up studies (1 to 5 years) between 37% and 65% of those never exposed to the drugs never needed them. See: John Bola. Medication-Free Research in Early Episode Schizophrenia: Evidence of Long Term Harm? Schizophrenia Bulletin, 2006, 32:288-296. Benedict Carey, Revisiting Schizophrenia: Are Drugs Always Needed? The New York Times, March 21, 2006 at: www.ahrp.org/cms/content/view/124/28

7. Thomas H. McGlashan, M.D. Robert B. Zipursky, M.D. Diana Perkins, M.D. Jean Addington, Ph.D. Tandy Miller, Ph.D. Scott W. Woods, M.D. Keith A. Hawkins, Psy.D. Ralph E. Hoffman, M.D. Adrian Preda, M.D. Irvin Epstein, M.D., F.R.C.P.C. Donald Addington, M.D. Stacy Lindborg, Ph.D. Quynh Trzaskoma, M.S. Mauricio Tohen, M.D., Dr.P.H. Alan Breier, M.D. Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis, American Journal of Psychiatry, May 2006, vol 163:790-799.

8. Other sites included: University of Toronto; University of North Carolina, Chapel Hill; University of Calgary, Calgary, Alta., Canada. Co-authors affiliated with universities other than PRIME trial sites: Dallas VA Medical Center; University of Texas Southwestern Medical Center; McLean Hospital / Harvard Medical School.

See also: NY Times report about the study and our critique, May 3, 2006 at:
http://www.ahrp.org/cms/content/view/157/31/
See also: NY Times profile of Dr. McGlashan, May 28, 2006: http://www.ahrp.org/cms/content/view/177/80

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Case 2: prodromal symptoms remitting during placebo administration
(false positive prodrome)
Benjamin was a 14-year-old boy whose parents sought help after hearing about the Prevention Through Risk Identification, Management, and Education clinic from a psychiatrist who was assessing Benjamin for attentional disorder. Benjamin was not completing his homework, was disorganized, got into &ldquo;trouble&rdquo; at school, and was not changing his clothes. Discussing Benjamin&rsquo;s development, his parents described him as a shy, quiet, &ldquo;good kid&rdquo; who did well in school. The family history was positive for schizophrenia in a maternal sibling. At intake, Benjamin scored in the prodromal range on three dimensions: suspiciousness/persecutory ideation, perceptual abnormalities/hallucinations, and conceptual disorganization. He felt at times that kids at school might be talking about him. In the past year he had begun hearing ringing in his ears, seeing colored polka dots, and smelling things that others did not notice. These experiences occurred about once a month and were perplexing but not
otherwise of concern. He talked monotonically, at times circumstantially, and occasionally lost his train of thought. He met the study criteria for the attenuated positive symptom prodromal syndrome.

Benjamin was randomly assigned to placebo, and he developed what appeared to be mild cogwheeling in his wrists,
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which remitted quickly with a dose of benztropine. Within 2
months all of his prodromal symptoms no longer scored in the prodromal window of severity. His symptoms were judged to be remitted for the rest of the year of doubleblind
treatment. He continued to improve symptomatically, academically, and socially in the second, no-treatment year. At discharge, he received a diagnosis of prodromal syndrome, in remission.

See: McGlashan TH, et al. Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis, American Journal of Psychiatry, May 2006, vol 163:790-799.

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http://ww.bioethicsforum.org/ethics-of-preventive-psychopharmacologic-treatments.asp
BIOETHICS FORUM Hastings Center Report Thursday, October 19, 2006
Preventive Psychopharmacology?
BY JERALD BLOCK
GUEST COMMENTATOR

When does research into a preventive treatment become unethical? In many areas of medicine this is a familiar question; the ethics around immunizations is solidly grounded in such thought. However, in psychiatry, wholly preventive psychopharmacologic treatments have been unusual.

Unfortunately, such research is fraught with ethical dangers. In a recent study by McGlashan et al., &ldquo;Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis,&rdquo; it seems psychiatry may have crossed into ethically questionable territory.

Preventive treatments pose difficult ethical problems for researchers. By their nature, the clinicians are treating a person who presents, for the moment, without symptoms or entirely lacking a disease. We give them care that will, hopefully, prevent them from manifesting the illness or symptoms. Unfortunately, treatments frequently have side effects and complications. Thus, we sometimes harm people when trying to prevent an illness that they might get.

It would seem the calculus between helping and harming would need to account for several variables, including these:
* How likely is it that the disease will manifest?
* How severe is the disease, if it were to manifest?
* How likely is it that the treatment will create significant side effects or complications?
* How severe are those complications?
* How long will the complications impair the patient?
* How likely is it that the treatment will prevent the disease?

In McGlashan's study, the 14 authors cooperated under a Merck and NIMH grant and conducted their research in four clinical sites in the United States and Canada. The study examined whether olanzapine (Zyprexa) could be used in patients that appeared to be &ldquo;prodromal&rdquo; for schizophrenia to prevent or delay the onset of the disease. Just as some people feel tired or irritable a day or two before getting a cold, the psychosis that is the hallmark of schizophrenia is usually preceded by a motley set of other symptoms: changes in personality such as increased anger, anxiety, restlessness, moodiness, apathy, social withdrawal, odd behavior, paranoia, and/or declining school performance are often seen by the patients, friends, and family.

Retrospectively, when diagnosing schizophrenia, these sorts of "prodromal" changes are frequently seen for several months before patients actually become psychotic. Unfortunately, the prodromal symptoms are also remarkably common, diffuse, and unspecific, especially when one considers that the patient is usually young &ndash; adolescence is a period of life that is normally marked by tumultuous changes in personality.

McGlashan&rsquo;s team screened subjects for their study using a set of symptoms thought to be associated with the schizophrenia prodrome. They tried to select patients who were not yet psychotic but who seemed at high risk for developing schizophrenia. They then randomized their sample, giving olanzapine to one group and placebo to the other. They treated each group for one year and then observed them for another year.

Many patients dropped out of the study, and the findings were inconclusive. However, the data seemed to suggest that olanzapine might delay the onset of psychosis in those patients that are schizophrenic.

Regardless of the actual findings, though, the study never should have been performed. That it was poses a major challenge to the integrity of the controls that ensure research remains ethical. The questions above suggest four reasons why the study is so disturbing.

How likely is it that the disease will manifest? Psychiatrists are not yet able to accurately predict who will manifest schizophrenia. The psychological testing instrument the authors used in the study had a large false positive rate. In prior studies, 46% to 80% of those tentatively labeled "prodromal" never developed schizophrenia after up to two years of
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observation – they were false positives. In McGlashan's experiment, 16 of 29 subjects (55%) who were given placebo failed to progress to schizophrenia over the two years they were examined. Thus around half of those treated with olanzapine were getting the neuroleptic for a disease they, too, did not have.

How likely is it that the treatment will create significant side effects or complications? During the period of the study, olanzapine was known to be associated with several serious complications. Specifically, one should worry that, after one year of exposure at doses ranging from 5 mg to 15 mg, patients would develop metabolic syndrome or, possibly, diabetes. Also, at the time the study went to IRB, olanzapine was known to be strongly associated with large weight gains. Indeed, McGlashan's paper showed those subjects getting olanzapine gained, on average, about 19 pounds over the placebo group. Finally, olanzapine, like all neuroleptics, can significantly alter a patient's personality and/or sleep. At the doses received, personality and sleep changes would be the rule, not the exception.

How severe are those complications? Metabolic syndrome and associated diseases, like diabetes, have significant morbidity associated with them. With regards to weight gain, there is well-established morbidity and mortality risks correlated to obesity. Finally, it is unclear how the quality of one’s life will be affected during and after one year of getting daily neuroleptic. Forming and solidifying new relationships occupies much of the time in adolescence and young adulthood. As neuroleptics affect cognition and emotionality, we might expect olanzapine to influence one's ability to build relationships, for better or worse.

How long will such complications impair the patient? The median age of the subjects was 16 years. One subject was remarkably young – 12 years old. Given their young age and the chronic nature of all the complication discussed above, we might anticipate they would have a large impact over the patient's life.

Early and aggressive treatment of psychosis is probably useful in reducing the severity and length of psychotic breaks. Moreover, it seems that a patient's functioning when in remission is improved if the period of psychosis can be shortened and made less severe. Thus there is an incentive to treat psychosis early and aggressively. However, if we treat too soon, we risk catching many nonschizophrenic youngsters in our net. As antipsychiotics are hardly benign, treating these individuals for a year or longer is quite risky; doing so will cause much illness, no matter how good our intent.

If (1) the antipsychotic had fewer side effects, (2) the subjects were much older, or (3) our tests for prodromal schizophrenia were much more specific, such a protocol might be worth considering.

These are details that are worth considering. However, that a study with such glaring problems got federal funding and worked its way through one or more IRBs is alarming. What happened to the system that allowed such a trial to occur? While it is understandable and even admirable for investigators to get caught up in clinical ambition and hope to head off a tragic disease like schizophrenia, one should wonder what happened to the gatekeepers? How could one or more IRBs ignore the obvious problems with this study?

Finally, one should note that the study could affect many more people than the 31 patients immediately involved. When you have a trial with so many distinguished investigators from elite institutions appearing in a top-notch psychiatric journal, it sends the message to those reading it: prescribing neuroleptics for similar patients is alright.

The article implies that treating a troubled adolescent with a neuroleptic for a year for symptoms that are suggestive of schizophrenia's prodromal syndrome is entirely ethical. I believe we have established no such thing and that such research may legitimate what is, at present, bad practice.

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