Yale-Lilly Experiment: Adolescents Rx Toxic Drug for Presumed Mental Illness They Do Not Have

PRINT

Wednesday, 03 May 2006

When the Times refers to an experiment as "bold and controversial" the reporter is sanitizing the fact that the experiment is UNETHICAL—it violates medicine's cardinal rule "First, do no harm."
The New York Times reports: "In recent years, psychiatric researchers have been experimenting with a bold and controversial treatment strategy: they are prescribing drugs to young people at risk for schizophrenia who have not yet developed the full-blown disorder."

The article goes on to describe an experiment reported in the American Journal of Psychiatry (AJP) in which adolescents were treated with a toxic drug for a mental disorder that they did not actually have. [1]

This experiment is akin to performing mastectomies on women who are at risk of—but do not have—breast cancer. Because the treatment involves risk, great care must be taken to ensure the risk of the disease exceeds the risk of treatment. The risk of breast cancer in women has been quantified, and patients are able to weigh this risk against the risks and benefits of surgery.

Despite the fact that antipsychotic drugs entail serious risks of irreversible harm, no such assessment is offered for this trial.
The experiment, sponsored by Eli Lilly, was conducted at Yale University (and 3 added sites, 1997-2003). Sixty adolescents who did not meet any criteria for a diagnosis of mental illness, were prescribed the antipsychotic drug, Zyprexa (olanzapine), raising serious ethical concerns. The speculative premise underlying this experiment is not supported by ANY scientific evidence.

The principle investigators, led by Dr. Thomas McGlashan of Yale, speculated—without evidence and without a validated tool for detecting schizophrenia in unsymptomatic individuals--that Zyprexa would be effective in delaying or preventing presumed psychosis and symptoms of schizophrenia. Indeed, the authors of this belated report obliquely acknowledge this limitation:
“the study addressed an essentially new clinical entity, which required designing new “prodromal” assessment instruments and a new definition of psychosis onset.” [1, p.797]

However, the authors neglect to inform readers what their “new definition of psychosis onset” is.
They acknowledge recruitment problems compounded by “the variable fraction of patients with true versus false positive prodromes.” In other words, many adolescents were falsely assessed as at risk of psychosis. The investigators don’t disclose what the inclusion / exclusion criteria were. We would venture to guess that no journal other than in psychiatry would publish a clinical trial report that failed to provide such fundamental information.

The report lags three years behind completion of this (admittedly) underpowered, small trial, most likely because the sponsor was reluctant to publish the negative finding: the experiment failed to demonstrate a significant benefit of Zyprexa, and 54.8% of adolescents prescribed Zyprexa compared to 34.5% on placebo refused to complete the study (the 20% difference indicating substantial intolerable safety problems with the drug). [1]

The investigators fail to report the adverse events. Disclosing only that adolescents on Zyprexa had acute weight gain—averaging 13% increase in body weight in one year—which they acknowledge may pose a long-term risk for “metabolic syndrome.” (See below American Heart Association) Another highly significant reported finding: “It is striking that all of the olanzapine patients whose symptoms converted to psychosis did so within the first weeks of the clinical trial. These patients were among the most symptomatic.” [1, p. 798]

But the authors demonstrate feats of mental acrobatics when they offer implausible explanations for this disturbing finding in an effort to deny the possibility that the drug is to blame:
“It is possible that some patients were already psychotic but unable to communicate this until, paradoxically, they received sufficient olanzapine to convey effectively their state of mind….some of these patients may have been on the cusp of psychosis and were not medicated rapidly or sufficiently enough to forestall conversion.” [1]
The plausible alternative hypothesis is that the drug itself may have pushed them into psychosis.

The drug’s severe adverse effects were well-known to Eli Lilly and were (or should have been) known to the investigators. Zyprexa’s action blocks multiple brain receptors causing a laundry list of adverse effects—some of which are lethal. At the time of the drug’s approval, the FDA noted that the pre-marketing clinical trials of Zyprexa were “fundamentally flawed,” test design was biased, as was the patient pool. [2] Zyprexa’s safety profile in pre-marketing trials (lasting 6-weeks) showed the drug caused severe adverse effects in 22% of patients.

During the 6-week trials, adverse effects included:
Cardiac & Hypotension - 10% to 15%; Serious weight gain - 50% had gained 7% of their body weight; Parkinson-like motor dysfunction - 11.7%; Akathisia - 7.3%; FDA data reveals that the drop-out rate was 65%. There were 22 deaths of which 12 were suicides. The number of attempted suicides has yet to be disclosed.

Indeed, internationally acknowledged expert psychopharmacologist, Dr. David Healy, has pointed out that the rate of suicide, death, and suicide attempts linked to Zyprexa in pre-marketing clinical trials was “greater than any other psychotropic drugs in history.” [3]

In fact, FDA's summation of the safety data submitted by Eli Lilly warned, that, given olanzapine's broad action on multiple receptor types, "no one should be surprised if, upon marketing, events of all kinds and severity not previously identified are reported in association with olanzapine's use." [2, p. 281] That dire prediction is being corroborated by the drug's casualties. Since its marketing, Zyprexa has been shown to significantly increase the lethal risk of metabolic syndrome which is manifested in obesity, hyperglycemia, cardiovascular disease, diabetes, and pancreatitis. Patients are dying.

In fact, Eli Lilly settled a lawsuit filed by 8,000 consumers of Zyprexa who developed diabetes for $700 million, rather than risk public disclosure of the documented evidence showing the magnitude of this drug's severe hazards in open court.

This dubious drug experiment was sponsored by Eli Lilly and several Lilly employees are listed as authors. It is the worst example of unethical market expansion through "disease mongering." Subjects were recruited through advertisements for an experiment designed to expand the market for the drug beyond severely ill patients disabled by schizophrenia or manic-depression (bipolar) for whom it was approved—no matter how harmful the consequences might be.

In April 2000, we filed a complaint with the federal Office of Human Research Protections (OHRP), about the ethics of this dubious experiment citing:

1. the shaky basis for the psychiatrists' conjecture that the children would develop schizophrenia because one of their siblings has the disorder when the scientific evidence does not support it.
"The risk of schizophrenia for the general population is 1%, for siblings the risk increases to 8% to 15% - in other words there is a 90% likelihood that these children will not develop schizophrenia. Even for those who already exhibit early signs ("prodromal symptoms"), the estimated risk for developing schizophrenia is highly variable (25% to 50%), given the absence of scientifically accurate tools for interpreting psychiatric "symptoms."

2. FDA data showing evidence of the severe effects of Zyprexa. [See: http://www.ahrp.org/Initiatives/YaleComplaint.php]

Our complaint led to an investigation by OHRP whose letter of determination (December 12, 2000, addressed to Yale's Provost) states that the informed consent documents reviewed and approved by the Yale institutional review board (IRB): "seriously breached federal regulations."

OHRP indicates that in its response the Yale IRB claimed "some confusion regarding informed consent documents that were misplaced or not signed."

The OHRP letter further states that the Yale IRB-approved informed consent forms: "failed to include a complete description of the procedures followed and identification of any procedures which were experimental;" and misrepresented the risk "of worsening symptoms due to olanzapine side effects" by falsely stating "it is possible that you will feel worse. This is a risk of your clinical condition, not a risk of being in the study." See: http://www.hhs.gov/ohrp/detrm_letrs/dec00e.pdf

The negative results of the experiment and the high drop out rate were predictable inasmuch as evidence of the drug's intolerable effects and hazards had been noted by FDA reviewers at the time of the drug's approval for adult schizophrenia—not for presumed "prodromal" symptoms in adolescents.

Given the absence of a diagnosable illness; the uncertainty surrounding an ill-defined, "prodromal" assessment which often results in "false-positives," should have precluded its approval. All the more so, given the documented evidence of immediate and long-term risks posed by the drug. Yet, the Yale University IRB, one of the most prestigious institutions in the U.S. approved it. The Yale IRB was chaired (between1979-2000) by one of the most influential authoritative bioethicists, Dr. Robert Levine. See: http://cira.med.yale.edu/about_us/bios.asp?PID=1003

This experiment encapsulates the prevailing utilitarian culture and ethical relativism that engulfs academic medicine demonstrating how the symbiotic relationship between academia and the drug industry has resulted in institutional betrayal of moral, professional, scientific integrity, and public trust.

The published report lists the individual authors, as well as the departments of psychiatry of the following institutions: Yale University; University of Toronto; University of No. Carolina (Chapel Hill); University of Calgary; Dallas VA Medical Center and University of Texas, Southwestern Medical Center; Lilly Research Laboratories; McLean Hospital and Harvard Medical.

In 1998, a clinical trial of Zyprexa was conducted at UCLA in which the drug was tested in five hospitalized children (age 6 to 11. All children suffered adverse events: "treatment was discontinued in all five children within the first 6 weeks of treatment because of adverse effects or lack of clinically significant therapeutic response." Chasened by the drug's adverse effect on the children, the authors cautioned clinicians: "Until more encouraging data are available, clinicians should be cautious and conservative in their predictions about the potential value of olanzapine in treating preadolescent psychiatric disorders." [4]

Notwithstanding the fact that there is still no evidence of this drug's safety or clinical efficacy to support the use of Zyprexa or any other antipsychotic drug for children, psychiatrists are encouraged to prescribe these drugs anyway. Indeed, two and a half million children are prescribed antipsychotics for ill defined conditions. USA Today documents prescription drug abuse by American doctors who are harming children by prescribing these drugs irresponsibly. (A companion Infomail will be follow).

AHRP has obtained a copy of a direct to consumer advertisement by Harvard University, Massachusetts General Hospital, which is recruiting young children for antipsychotic drug experiments. The ad suggestis children's behavior may be an indication they are bipolar. Harvard psychiatrists have subjected preschool toddlers--whose mean age is 4 years old— to the hazardous effects of Zyprexa and Risperdal (risperidone). [5]

Who will protect America's children from institutionally sanctioned market expansion masquerading as medicine or science?
Who will enforce informed consent requirements ensuring that parents are (at least) fully informed about the risks of treatment?
If children are at all valued, then Congress must pass a law requiring ALL research documents involving children to be publicly posted for independent review. These should include: protocols, informed consent forms, ALL efficacy and safety data in support of claimed findings--including ALL adverse event reports.

References:
1. Thomas McGlashan, et al. Randomized, Double-Blind Trial of Olanzapine Versus Placebo in Patients Prodromally Symptomatic for Psychosis, American J of Psychiatry, May 5, 2006, 163:790–799.
2. Robert Whitaker, Mad in America, Perseus Books, 2002.
3. David Healy,Randomized Controlled Trials: Evidence Biased Psychiatry, http://www.ahrp.org/COI/healy0802.php
4. Krishnamoorthy J, King BH J. Open-label olanzapine treatment in five preadolescent children, Child Adolesc Psychopharmacol 1998; 8(2):107-13=20
5. Mick E, Biederman J, Aleardi M, Dougherty M . Open trial of atypical antipsychotics in pre-schoolers with bipolar disorder [abstract]. Acta Psychiatr Scand, (2004) 110: 29

Contact: Vera Hassner Sharav
veracare@ahrp.org

http://www.nytimes.com/2006/05/01/health/01psych.html?ex=1147147200&en=1a9efa6f722d3bf9&ei=5070&emc=eta1
THE NEW YORK TIMES
Mixed Result in Treating Schizophrenia Pre-Diagnosis
By BENEDICT CAREY
May 1, 2006

In recent years, psychiatric researchers have been experimenting with a bold and controversial treatment strategy: they are prescribing drugs to young people at risk for schizophrenia who have not yet developed the full-blown disorder.

The hope is that while exposing some to drugs unnecessarily, preemptive treatment may help others ward off or even prevent psychosis, sparing them the agonizing flights of paranoia and confusion that torment the three million American who suffer schizophrenia.

Yet the findings from the first long-term trial of early drug treatment, appearing today in The American Journal of Psychiatry, suggest that this preventive approach is more difficult to put into effect — and more treacherous — than scientists had hoped.

Daily doses of the antipsychotic drug Zyprexa, from Eli Lilly, blunted symptoms in many patients and lowered their risk of experiencing a psychotic episode in the first year of treatment, the study found. But the drug also caused significant weight gain, and so many participants dropped out of the study that investigators could not draw firm conclusions about drug benefits, if any.

The long-awaited study, which was financed by Eli Lilly and the National Institute of Mental Health, raised more questions than it answered, experts said.

"The positive result was only marginally significant, and the negative result was clear," said Dr. Thomas McGlashan, a professor of psychiatry at Yale and the study's lead author. "This might discourage people, and legitimately so, from using this drug for prevention because of the weight gain, but hopefully it won't discourage study" of other drugs.

Critics have charged that treating people for a disorder that has not yet been diagnosed is not only premature but stigmatizing, especially for adolescents. The new study was intended in part to clarify the trade-off between the risks and the potential benefits of preemptive treatment.

"Unfortunately, the study's numbers are so small that it cannot be decisive on the key issue, which is whether it's prudent to treat people early when there are uncertainties about the diagnosis and given the effect of stigma and adverse effects," said Dr. William Carpenter, director of the Psychiatric Research Center at the University of Maryland, who was not involved in the study.

The study was plagued by recruitment problems from the beginning, in 1997. Mild, psychosis-like symptoms are rare in adolescents, and families often wait until symptoms are pronounced before seeking treatment, Dr. McGlashan said. Good candidates trickled in slowly; and the researchers added several recruitment sites along the way to increase the numbers of people in the study.

They eventually enrolled 60 people, most of them adolescents, who scored highly on a scale that assesses risk for psychosis. The scale rates severity of more than a dozen symptoms, including suspiciousness, grandiosity and bizarre thoughts. From 20 to 45 percent of

people who score high on the scale go on to develop full-blown psychosis, in which these symptoms become extreme, researchers have found.

The researchers split the participants into two groups, one that received drug treatment and one that took placebo pills. In the first year of a two-year trial, 5 of the 31 of those on medication developed full-blown psychosis, compared with 11 of 29 of those who were taking dummy pills.

But by then, more than two-thirds of the young people in both groups had dropped out, making it difficult to interpret differences between them. Some left the study without explaining why; others moved; and 10 of those on medication quit the study because they felt the drug was not working, could not make the appointments or did not like the side effects, among other reasons.

Those on medication gained an average of 20 pounds during the study. Weight gain is a common side effect of Zyprexa.

"It's a pessimistic trade-off, the weight gain and other side effects for what looks like a modest delay in the acute psychotic episode," said Dr. Steven Hyman, a professor of neurobiology at Harvard . "It's clear we need more efficacious drugs with milder side effects."

Copyright 2006 The New York Times Company

http://www.americanheart.org/images/interface/spacer.gif
American Heart Association
What is the metabolic syndrome?
The metabolic syndrome is characterized by a group of metabolic risk factors in one person. They include:

* Abdominal obesity (excessive fat tissue in and around the abdomen)
* Atherogenic dyslipidemia (blood fat disorders — high triglycerides, low HDL cholesterol and high LDL cholesterol — that foster plaque buildups in artery walls)
* Elevated blood pressure
* Insulin resistance or glucose intolerance (the body can't properly use insulin or blood sugar)
* Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor–1 in the blood)
* Proinflammatory state (e.g., elevated C-reactive protein in the blood)

People with the metabolic syndrome are at increased risk of coronary heart disease and other diseases related to plaque buildups in artery walls (e.g., stroke and peripheral vascular disease) and type 2 diabetes. The metabolic syndrome has become increasingly common in the United States. It's estimated that over 50 million Americans have it.

The dominant underlying risk factors for this syndrome appear to be abdominal obesity and insulin resistance. Insulin resistance is a generalized metabolic disorder, in which the body can't use insulin efficiently. This is why the metabolic syndrome is also called the insulin resistance syndrome.

Other conditions associated with the syndrome include physical inactivity, aging, hormonal imbalance and genetic predisposition.

FAIR USE NOTICE: This may contain copyrighted (©) material the use of which has not always been specifically authorized by the copyright owner. Such material is made available for educational purposes, to advance understanding of human rights, democracy, scientific, moral, ethical, and social justice issues, etc. It is believed that this constitutes a 'fair use' of any such copyrighted material as provided for in Title 17 U.S.C. section 107 of the US Copyright Law. This material is distributed without profit.

Close Window