Revised January 20, 2004

Introduction:

My name is Allen Jones. I am a "whistleblower" who has sought the protection of the federal courts to tell the following story.

I am employed as an Investigator in the Commonwealth of Pennsylvania Office of Inspector General (OIG), Bureau of Special Investigations. In November of 2002, I entered a Civil Rights lawsuit against OIG officials to preserve my right to speak out on issues of vital public interest involving pharmaceutical industry influence on the treatment of mental health patients in state institutions.

As an OIG Investigator, I attempted to expose evidence of major pharmaceutical company wrongdoing. The industry was influencing state officials with trips, perks, lavish meals, transportation to and first-class accommodations in major cities. Some state employees were paid honorariums of up to $2,000 for speaking *in their official capacities* at drug-company sponsored events.

As I attempted to explore and surface these facts I met stiff resistance by OIG officials. I was told that pharmaceutical companies are major political contributors and that I should not continue my probe. The more I attempted to delve, the more I was oppressed by my supervisors. I was effectively threatened with loss of job, career and reputation if I continued to investigate the pharmaceutical companies.

In the words of the OIG manager who curtailed my investigation and participated in overt threats against me: **"Drug companies write checks to politicians – they write checks to politicians on both sides of the aisle".**

I was removed from the drug investigation, forbidden to inquire further, and assigned to menial duties. However, I continued the investigation on my own as a private citizen.

The "Model Program" being implemented in Pennsylvania with drug industry hard-sell, misinformation and inducements has just been recommended by President Bush's New Freedom Commission as a model program for the entire country.

The "Model Program" is the Texas Medication Algorithm Project" (TMAP-pronounced T-Map) and it began in Texas in 1995.

TMAP is a Trojan horse embedded with the pharmaceutical industry's newest and most expensive mental health drugs. Through TMAP, the drug industry methodically compromised the decision making of elected and appointed public officials to gain access to captive populations of mentally ill individuals in prisons and state mental health hospitals.

The pharmaceutical industry bypassed governmental safeguards and medical review by creating and marketing TMAP as a "treatment model" that was instituted in various states as an *administrative* decision by a select few politically appointed officials.

The treatment model accepted by these state officials had a fundamental requirement rooted deep within it: Doctors must first treat their patients with the newest, most expensive drugs patented by the pharmaceutical companies. The state doctors treating mental illness could choose which patented drug to use, but effectively could not choose to use less expensive generic drugs unless and until the patented drugs failed.

Drug companies marketed their newer, patented medications as safer and more effective than the older, generic brands. These drugs, they said, not only better treated the symptoms of mental illness, they did so without the troublesome side-effects often seen with conventional medications.

However, these new "miracle" drugs did not live up to their hype. They have proven to no better than generics. Most importantly, most of the new drugs have been found to cause serious, even fatal side-effects, particularly in children. It is a statistical certainty that many lives have been lost and many others irreparably damaged.

The drug companies involved in financing and/or directly creating and marketing TMAP include: Janssen Pharmaceutica, Johnson & Johnson, Eli Lilly, and Austrazeneca Pfizer, Novartis, Janssen-Ortho-McNeil, GlaxoSmithKline, Abbott, Bristol Myers Squibb, Wyeth-Ayerst Forrest Laboratories and U.S. Pharmacopeia.

Janssen Pharmaceutica operates a specialty sales division devoted to public sector marketing. Janssen was the most aggressive of the companies in developing this model and in directly compromising and influencing public officials. All of the other companies mentioned contributed funding to the effort.

The patented mental health drugs embedded within this model program include: Risperdal, Zyprexa, Seroqual, Geodone, Depakote, Paxil, Zoloft, Celexa, Wellbutron, Zyban, Remeron, Serzone, Effexor, Buspar, Adderall, and Prozac, all manufactured by the above companies.

Drug industry money guided TMAP from conception through development and expansion to other states. The growth of TMAP began with misleading science. It grew and expanded with the aid of compromised public officials at all levels of our government.

This is a story of an unhealthy alliance between politics and the pharmaceutical industry (Pharma). It is a story of the betrayal of our society's most helpless citizens.

Pharma has woven an elaborate marketing scheme from scant evidence and copious illusion. Illusion has become operative "truth". Operative "truth" has become clinical practice. Clinical practice has become Roulette – and the "House" (Pharma) always wins.

I will show you how TMAP became implemented in Pennsylvania. It is a story that cost me my career. First I will tell you about the development of TMAP and why the drug industry found Texas to be the ideal place to begin this project.

 : Smoke and Mirrors

The Texas Medication Algorithm Project

A Texas Primer:

Texas is uniquely suited for the pharmaceutical industry to develop a marketing scheme of the depth and proportion of TMAP.

The industry needed to create an aura of legitimacy and a body of favorable data to advance its marketing aims. It needed universities, prisons and hospitals. The industry also needed a friendly Legislature to initiate such an extensive program.

Texas is a notoriously political state, and this politicism extends to the state universities, state hospitals and prisons, where regents and administrators are routinely replaced by new gubernatorial administrations.

In Texas, 150 representatives, 31 Senators and the Lieutenant Governor all earn $7,500 per year and meet for 140 days every two years. In 1997, 1,662 registered lobbyists representing 2,034 clients earned $210 million dollars and spent many millions more to influence these legislators. Many of these lobbyists, and many of these millions, represented pharmaceutical companies.

Texas has the largest prison system in the United States, with nearly 150,000 inmates in correction and detention facilities at any given time. Likewise, it has a crowded mental health hospital system..

The Texas Legislature, meeting for 140 days every-other year and outnumbered by well financed lobbyists by 10 – 1, can be expected to pass legislation and support programs based on reasoning that is separate from their personal understanding of the issues involved.

Newspaper columnist Charles T. Bowen, in an article "Quick Note; Silent Vote; No Gloat." In ***The Tampa Tribune***, 21 April 1997, described how one former Texas legislator, Tom Robbins, was annoyed that his colleagues seemed to pass legislation that they had not even read, let alone understood. To prove a point he introduced a resolution to honor Albert de Salvo. The language of the resolution stated in part: “

> *“This compassionate gentleman's dedication and devotion to his work has enabled the weak and the lonely throughout the nation to achieve and maintain a new degree of concern for their future. He has been officially*

recognized by the state of Massachusetts for his noted activities and unconventional techniques involving population control and applied psychology."

The Resolution passed with a unanimous vote.

Albert de Salvo was, of course, the Boston Strangler.

To augment the efforts of the pharmaceutical industry lobbyists, pharmaceutical manufacturers contributed heavily to the individual political campaigns of the Texas governor, senators, representatives and judges.

According to the National Institute on Money in State Politics, the pharmaceutical industry contributed zero contributions to individual politicians in Texas in 1994. During the 1998 election year, pharmaceutical manufacturers made a total of 251 contributions totaling $152,000 to individual candidates for Texas state office. In 2002, the total was 419 individual contributions by drug makers totaling $384,735.

Additionally, the pharmaceutical industry employed 297 lobbyist in Washington D.C. alone (600 lobbyists by 2003). The industry spent 236 million dollars in their lobbying efforts between 1997 and 1999 alone. The annual expenditures have risen steadily since that time.

This accounts only for reported hard-money contributions. The amount of soft money contributions is unknown and unknowable.

At the same time, pharmaceutical manufacturers were pouring millions of dollars into Texas universities.

Texas Governor George W. Bush supported Texas **Mental Health Parity** legislation in 1997 that required private industry to provide increased insurance coverage for mental health treatment, including mental health drugs.

Texas passed legislation expanding Medicaid coverage of mental health drugs to persons who would not otherwise qualify under Medicaid guidelines. Budget increases were made to pay for mental health drugs for the Texas mental health and prison systems.

During Bush's presidential campaign, he cited his support of TMAP along with his most recent state budget recommendation for an additional 67 million dollars to pay for still more mental health drugs.

TMAP opened the doors of the Texas prison system, juvenile justice system and Texas state mental health hospitals to the unlimited influence of major pharmaceutical companies in expanding the usage and marketing of their most expensive drugs.

How?

TMAP essentially utilized pseudo science to create the *appearance* of drug safety and effectiveness. TMAP purchased scientific influence in the propagation of data to suggest that newer, patented drugs were safer and superior to generic drugs.

CONTEXT:

TMAP arose during a period of decreased Food and Drug Administration (FDA) oversight and vastly increased sophistication in pharmaceutical industry marketing practices. These practices aggressively pursued favorable public and professional "opinion" through media promotion, and biased reporting of drug trial results.

The industry flooded the psychiatric profession, and psychiatric professionals, with money and salted medical journals with reports by "researchers" who were the direct beneficiaries of drug industry funding.

Award winning science journalist Robert Whitaker, in his book *Mad in America,* outlines the pharmaceutical industry influence on the science and promotion of the Atypical Antipsychotics (new schizophrenia medications). In Whitaker's words:

> "*By the late 1980s the pharmaceutical Industry's storytelling apparatus had evolved into a well oiled machine. The creation of a tale of a breakthrough medication could be carefully plotted. Such was the case with the Atypicals, and behind the public façade of medical achievement is a story of science marred by greed, deaths and the deliberate deception of the American public"*

Whitaker cites Marcia Angell in a 2000 New England Journal of Medicine article:

> "*The ties between clinical researchers and industry include not only grant supports, but also a host of other financial arrangements. Researchers also serve as consultants to companies whose products they are studying, join advisory boards and speakers bureaus, enter into patent and royalty arrangements, agree to be the listed authors of articles ghostwritten by interested companies, promote drugs and devices at company-sponsored symposiums, and allow themselves to be plied with expensive gifts and trips to luxurious settings"*

Whitaker found the factors of biased review and deceptive reporting to be particularly relevant to the advancement of Atypical antipsychotics. Via the Freedom of Information Act he gained access to FDA raw data on the Atypical drug trials. Whitaker learned that the trials, and the FDA's review of the trials, did **not** support industry claims that the Atypicals were safer or more effective than existing generic drugs. In fact, in the approval letter to Janssen regarding their drug Risperdal, the FDA specifically stated:

> *"We would consider any advertisement or promotion labeling for RISPERDAL false, misleading or lacking fair balance under section 502 (a) and 502 (n) of the ACT if there is a presentation of data that conveys the impression that Risperidone is superior to haloperidol* (a generic antipsychotic) *or any other marketed antipsychotic drug product with regard to safety or effectiveness."*

Whitaker noted "while the FDA had the authority to stop Janssen from making false claims in its ads, it had no control over what academic physicians, who had been paid by Janssen to conduct the trials, reported in their medical journals or told the press."

The same applied to doctors, academics and practitioners within the range of influence of Janssen money. Janssen needed a mouthpiece.

Enter TMAP

TMAP began in 1995 as an alliance of individuals from within the pharmaceutical industry and the Texas state university, mental health and corrections systems. Start-up funds included a 1.7 million dollar grant from the Robert Wood Johnson Foundation; a Johnson&Johnson related foundation. Johnson&Johnson owns the pharmaceutical companies Janssen Pharmaceutica and Janssen/Ortho McNeil.

(According to the non-profit group Texans for Public Justice, http://www.tpj.org/index.jsp Robert Wood Johnson IV, heir to the Johnson & Johnson fortune, raised over $100,000 for George W. Bush's 2000 presidential campaign. Johnson has raised over $200,000 for Bush's 2004 campaign.)

The group's goal was to develop a model mental health treatment program for incorporation into public mental health and prison systems. This model program would ensure that newer, expensive medications would be heavily used.

But the drug industry had a problem: Clinical trials simply did not favor their new products. Alternative justification for favoring these drugs would have to be developed.

"Expert Consensus Guidelines"

This consortium sought to "legitimize" the medications recommended in the model program's "drug menus". The group elected to utilize "Expert Consensus Guidelines", rather than clinical studies or drug trials to form these recommendations.

Essentially, TMAP opted to "establish" new drugs as the best drugs for various illnesses by surveying the opinions of doctors and psychiatrists of TMAP's own choosing**. No hard science, no patients, no study review, and no clinical trials** – just the "Expert Opinions" of persons TMAP elected to survey.

The "Expert Consensus" process became TMAP's standard mechanism for creating the *appearance* of superiority for certain drugs and it was employed repeatedly from 1996 to 2003.

The doctors who were surveyed included persons who had already published articles favoring the new drugs. The survey included doctors with strong ties to the drug industry.

They included Dr. Jack Gorman. According to a March 13, 1999 *New York Post* article by Greg Birnbaum, Gorman resigned his position as the number two official of New York's

Psychiatric Institute after it was disclosed that he received over $140,000 from drug companies in a single year between April 1, 1997 and March 31, 1998.

During that time Gorman received speaking fees, travel, board memberships and consulting deals from Janssen, Johnson&Johnson, Eli Lilly and Pfizer, among others. Gorman received $12,000 from Pfizer while he was heading research into Pfizer Drugs.

Twelve other Institute researchers were found to be profiting from similar drug company payments including the head of the Psychiatric Institute's *Patient Protection Panel*, which was charged with ensuring patient safety in drug trials.

The institute was found to have conducted Prozac experiments on children without advising parents of risks. It also conducted non-therapeutic research on children with the dangerous drug fenfuranine, which was subsequently been removed from the market due to deadly side effects.

From a pool of such candidates, TMAP drew their "Expert Consensus" panels.

TMAP formulated the questions to be posed to these physicians and formulated the structure of the responses permitted. No input aside from the survey questions was solicited. A total of only **fifty-seven** doctors and psychiatrists responded to the medication survey.

TMAP <u>independently</u> analyzed the resultant responses.

TMAP concluded that the Atypical antipsychotic medications **Risperdal**, produced by Janssen Pharmaceutica, **Zyprexa** produced by Eli Lilly, and **Seroqual**, produced by Austrazeneca, are the drugs of choice for all first, second, and third-line treatments of Schizophrenia.

TMAP concluded that all newer, patented anti-depressants were superior to generics.

TMAP concluded that the patented bi-polar drugs were superior to generic drugs.

TMAP concluded that "Expert Consensus" established these drugs to be safer, more effective, better tolerated and relatively free of side effects when compared to the older, generic, medications.

TMAP then formulated separate "algorithms" (flow charts) and drug menus for the treatment of schizophrenia, depression and bi-polar disorder. All of the new, patented drugs were incorporated into the TMAP algorithms.

State doctors following the algorithms were and are ***required*** to use these drugs. The ***administrative*** decision of a State Mental Health Program to adopt TMAP brought with it the ***clinical*** decision to use the recommended drugs on all patients in the state system. A state doctor may choose which patented drug to use, but he may not choose to use a generic drug until at least two, often three, patented drugs have failed.

In order for a state doctor to use a generic drug as first or second line treatment, that doctor must set down his or her rational in writing, effectively assuming liability for deviating from the state-sponsored requirements.

Janssen Pharmaceutica funded the "Expert Consensus Guidelines" survey and analysis.

Eli Lilly and Austrazeneca were also funding the project by the time the initial results were published in 1996. Pfizer, Novartis, Ortho-McNeil, GlaxoSmithKline, Abbott, Bristol Myers Squibb, Wyeth-Ayerst Forrest Laboratories and U.S. Pharmacopeia have since joined them.

All of these drug companies have patented drugs in one or more of the TMAP "menus".

The larger mental health treatment community did not share TMAP's bold and aggressive endorsement of Risperdal, Zyprexa, and Seroqual for the first three stages of the treatment of schizophrenia.

At the time TMAP was developed, there were other guideline and algorithm projects in existence or in contemporaneous development. These projects employed actual science and a comprehensive analysis of state-of-the art methodology and practice in the treatment of Schizophrenia. Their outcomes, and recommendations, did not echo or support TMAP's "Expert Consensus Guidelines". (Attachment 1 – Other Schizophrenia Algorithms and Guidelines)

Consensus or Confusion

In January of 1999, in the *Journal of Practice in Psychiatry and Behavioral Health*, Peter J. Weidman M.D. published an article entitled "Guidelines for Schizophrenia: Consensus or Confusion?" that compared the Port guidelines, the APA guidelines and the Expert Consensus guidelines.

Dr. Weidman, who himself participated in the TMAP "Expert Consensus" process had this to say about the Guidelines three years later:

"**Weaknesses of the Expert Consensus Schizophrenia Guidelines:"**

> *"The most important weakness of the EC Guidelines is that the recommendations are based on opinions, not data. History shows that expert's opinions about "best" treatments have frequently been disproved, and there is no assurance that what the experts recommend is actually* ***the*** *best treatment. One danger here is that clinicians or administrators may misinterpret "current consensus" as truth.*
>
> *Another limitation involves the development of the survey itself. Treatment options are limited to those items appearing on the questions, and it was not possible to cover all situations. Another problem is potential bias from funding sources. The 1996 Guidelines were funded by Janssen (makers of Risperidone [Risperdal]) and most of the guideline's authors have received support from the pharmaceutical industry. This potential conflict of interest may create credibility problems, especially concerning any recommendations supporting the use of atypical antipsychotics."*

The National Institute of Mental Health (NIMH) launched a multi-year study in 1999 to address the issue of Atypical vs. generic antipsychotic drug usage. The *Clinical Antipsychotic Trials of Intervention Effectiveness* (CATIE) project is a carefully controlled and monitored project involving over 10,000 schizophrenic patients.

CATIE has independent investigators, co-investigators and collaborators involved in a multi year clinical trial designed to determine precisely the kind of information that TMAP claims to have determined with their "expert consensus" process. The CATIE study is genuine science as opposed to selective opinions.

Independent clinical trials and studies in Europe have been far less supportive of the Atypicals and far more scientific in examining the true benefits and dangers of the drugs. In 2000 the British Medical Journal published the results of a multi-year study by Dr. John Geddes, who examined the results of independent clinical trials involving over 12,000 patients and examined the effectiveness and dangers of the Atypical and Typical antipsychotics in clinical, scientific head-to-head trials. The results:

> *A. "There is no clear evidence that atypical antipsychotics are more effective or are better tolerated than conventional antipsychotics. Conventional anti-psychotics should usually be used in the initial treatment of an episode of schizophrenia unless the patient has previously not responded to these drugs or has unacceptable extrapyramidal side effects"*
>
> *B. Conventional drugs should remain the first treatment, although atypical antipsychotics are a valuable addition to treatment options, especially when extrapyramidal side effects are a problem.*

The British Study was funded by the British Department of Health, and included no drug company funding.

In a New York Times Article entitled *Leading Drugs for Psychosis Come Under New Scrutiny*, Erica Goode reports on the results of a study by Dr. Robert Rosenheck, Director of the Department of Veterans Affairs Northeast Program Evaluation Center. Rosenheck found that Zyprexa cost the V.A. $3,000 to $9,000 more per patient, with no benefit to symptoms, side effects or overall quality of life.

(For an excellent review of the status of drug industry clinical trials in this country during TMAP development, see Attachment # 2 by Vera Hassner-Sharav entitled *"CONFLICTS OF INTEREST".)*

TMAP "Science"

With the support of Governor Bush and members of the Texas Legislature, the "Expert Consensus Guidelines" and resultant algorithms were adapted and sixteen Texas prisons, juvenile facilities and mental hospitals were made available for pilot projects for the TMAP algorithms.

With the doors of the Texas prisons and mental hospitals open to TMAP, TMAP personnel were free to "mine" patient records in a process called "Retrospective Analysis." Essentially they could research files of those patients who had previously been treated with the newer medications and report on those cases that offered favorable results Additionally, TMAP personnel were responsible for monitoring the usage of the drugs, gathering raw data, analyzing data and formulating reports. (In Pennsylvania this included experimentation with dosage levels and new symptoms.)

Not surprisingly, TMAP "research" confirmed the "Expert Consensus". TMAP, funded by the drug companies, found **Risperdal**, **Zyprexa** and **Seroqual** to be safer and more effective than generic drugs for the treatment of schizophrenia.

TMAP "research" found **Paxil, Zoloft, Celexa, Wellbutron, Zyban, Remeron, Serzone, Effexor, Buspar, Adderall,** and **Prozac,** to be safer and more effective than generic drugs for the treatment of depression.

TMAP "research" found **Depakote** to be more efficient than generic drugs for the treatment of bi-polar disorder.

Undaunted by a rising independent body of contrary findings, and with their own retrospective and clinical analysis in hand, TMAP began referring to their algorithms as being "Evidence Based" and "Evidence Based Best Practices".

Members of TMAP began publishing widely. Co-Directors and staff of TMAP traveled widely, at the expense of pharmaceutical companies, to tout the wonders of the new drugs and to expand their guidelines and algorithms to other states – and to other nations. As early as 1997, TMAP members were traveling to China, Japan and other nations to sell the TMAP agenda.

The principal TMAP spokesman is Dr. **Steven Shon**, who has lauded TMAP and pursued TMAP development under several titles at both state and national levels.

By 1999 the TMAP program was officially adapted by the Texas Legislature, which has passed several bills endorsing the project and funding the project's ever-increasing drug costs. These funding measures included expanding Medicaid eligibility to families whose income would not otherwise meet guidelines, in order that they could continue on the expensive medications upon discharge from institutions.

In 1997-98, TMAP, with pharmaceutical industry funding, began working on the Texas Children's Medication Algorithm Project. (TCMAP). An "Expert Consensus" panel was assembled to determine which drugs would be best for the treatment of mental and emotional problems in children and adolescents.

The panel consisted almost exclusively of persons already involved in TMAP or associated with TMAP officials. A survey was not necessary. These persons simply met and decided that the identical drugs being used on adults should also be used on children. There were no studies or clinical trial results whatsoever to support this consensus.

One of the members of the children's "expert consensus panel" was **Graham J. Emslie, M.D.**, Professor and Chair, Division of Child and Adolescent Psychiatry, University of Texas Southwestern Medical Center, (a TMAP site) and Director, Bob Smith Center for Research in Pediatric Psychiatry, Dallas, TX.

The website http://www.cspinet.org/integrity/index.html which links drug company money to researchers, lists the following drug company involvement by Emslie**: "Consultant to GlaxoSmithKline, Forest, and Pfizer. Receives research support from Eli Lilly, Organon, Religion, and Wyeth-Ayerst. Member of the speaker's bureau for McNeil. ("Experience in the use of SSRIs and other antidepressants in children and teens")"**

These drug makers all manufacture TMAP depression medications, including Paxil, Prozac, Remeron, Wellbutron and Effexor.

The panel also included **Dr Karen Dineen Wagner**. In the Aug. *27 Journal of the American Medical Association*, Wagner reported on a **Pfizer-funded** study conducted by Wagner and colleagues at the University of Texas Medical Branch in Galveston. Wagner reported that the **Pfizer** SSRI Zoloft was safe, effective and well tolerated in children.

Increadibly, this claim was made in the wake of UK bans on the use of Paxil and Effexor (SSRI's) in children, when both the FDA and the British Committee on Safety in Medicines announced that they were re-examining *all* SSRI clinical trial data.

An article by Fred Gardner in *Drugnews*, published on September 3, 2003 critiques the report and offers the following information about Dr. Wagner:

"Dr Wagner has received research support from **Abbott, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Organon, Pfizer, and Wyeth-Ayerst; has served as a National Institute of Mental Health consultant to Abbott, Bristol-MyersSquibb, Cyberonics, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Novartis, Otsuka, Janssen, Pfizer, and UCB Pharma; and has participated in speaker's bureaus for Abbott, Eli Lilly, GlaxoSmithKline, Forest Laboratories, Pfizer, and Novartis."**

The article states:

> "*What we have here is a case study in how pharmaceutical companies respond to warnings that their products cause harm. Earlier this summer British health authorities advised against treating children and teenagers with Paxil because it triggers suicidal thinking and actual suicide attempts. Zoloft (which is Pfizer's name for a chemical called "sertraline") affects the same receptor system, and is evidently just as dangerous."*
> http://mail.psychedelic-library.org/show.cfm?postid=4258&row=29

In an article in *The Guardian* on Wednesday October 1, 2003 entitled *Scientist in rethink over drug link to suicide*, Sarah Boseley, health editor reported:

> "*The scientist who led the latest trial of an antidepressant drug given to children, which claimed that it was effective and safe, has conceded to the*

Guardian that the drug's potential to cause suicidal thinking needs to be investigated.

Last month the Journal of the American Medical Association published results from two trials of children treated with Pfizer's antidepressant drug Lustral, known in the US as Zoloft.

Seventeen children who were given the drug were pulled out of the trial because of side effects, compared with five who were given a placebo. Only 10% more children improved on the drug than improved on a placebo.

The researchers nonetheless concluded "the results of this pooled analysis demonstrate that sertraline (Lustral) is an effective and well-tolerated short-term treatment for children and adolescents with major depressive disorder".

The lead author of the study was Karen Wagner of the department of psychiatry at the University of Texas. She was also one of the authors of studies of a similar antidepressant, Seroxat, which was banned for use in children in June by the UK licensing body, the medicines and healthcare products regulatory agency.

The MHRA said a re-analysis of the data from the Seroxat trials showed an increase in the numbers of children who became suicidal on the drug. The studies that Dr Wagner and colleagues carried out on Seroxat in children had also concluded that Seroxat was effective and well tolerated.

Asked whether she still believed both drugs were safe, after the MHRA ban on Seroxat and the inquiry that has now been launched by the US regulator, she replied: "I think it requires further investigation and looking at the entire database of these medications. With regards to paroxetine [Seroxat], it is being investigated."

In 1998, without any published trial data and based on the "consensus opinion" of Emslie, Wagner and others, TCMAP began widespread usage of these SSRI's and other drugs on children within the Texas state Juvenile Justice system and state Foster Care System.

By some accounts, antidepressant drug prescriptions for children in the United States has increased over 500% from 1999 to 2003, with tragic results. Example:

Paxil was one of the wonder drugs recommended by the TCMAP "expert consensus" panel and prescribed in treatment of children when the drug was brand-new and relatively untested.

Since then, Paxil has been linked to a myriad of violent and deadly side effects in adolescents. Lawsuits have named Paxil as factors in murder, suicide, debilitating disease and school shootings. Additional cerebral and cardiac problems have been linked to the drug. In June of 2003, the FDA issued a warning that Paxil should not be prescribed to persons under 18 due to the alarming number of suicides by children on this drug.

The FDA "Talk Paper, report # T03-43, June 9, 2003 says, in part:

> *The Food and Drug Administration (FDA) said today it is reviewing reports of a possible increased risk of suicidal thinking and suicide attempts in children and adolescents under the age of 18 treated with the drug Paxil for major depressive disorder (MDD).*
>
> *FDA is recommending that Paxil not be used in children and adolescents for the treatment of MDD. There is currently no evidence that Paxil is effective in children or adolescents with MDD, and Paxil is not currently approved for use in children and adolescents.*
> *Three well-controlled trials in pediatric patients with MDD failed to show that the drug was more effective than placebo. The new safety information that is currently under review was derived from trials of Paxil in pediatric patients.*
>
> *Following its review of the same data, the UK Department of Health issued a Press Release on June 10 stating that paroxetine (Paxil)(brand name Seroxat in the UK) must not be used to treat children and teenagers under the age of 18 years for depressive illness because UK authorities have concluded that there is an increase in the rate of self harm and potentially suicidal behavior in this age group, when paroxetine is used for depressive illness.*
>
> *More information about today's statement is available at*
> http://www.fda.gov/cder/drug/infopage/paxil/default.htm

The TCMAP-recommended drugs **Effexor, Prozac** and **Serzone**, and others, likewise accumulated a deadly side-effects profile. These drugs have also been linked to violence and mayhem in young persons. Serzone was withdrawn from European markets and received "black box" warnings in the United States when it was conclusively linked to a high incidence of deaths from liver failure. The use of Effexor in children was banned UN the UK in August of 2003.

On December 10, 2003 the British Medicines and Healthcare Products Regulatory Agency, the British equivalent of the FDA, issued stern warnings against the use of 6 antidepressant drugs in persons under 18 years of age. A December 11, 2003 New York Times article by Erica Goode reports in part:

> "*British drug regulators yesterday recommended against the use of all but one of a new generation of antidepressants in the treatment of depressed children under 18.*
>
> *In a letter sent to doctors and other health professionals, the government regulators said a review of data on the safety and effectiveness of the drugs, known as S.S.R.I.'s, indicated that their benefits did not outweigh their potential risks.*

> *Their effectiveness in treating depression in children, they said, has not been sufficiently demonstrated, and some drugs have been linked with suicidal thoughts and self-harm in children and adolescents. A summary of the findings was published on the Web site of the British Medicines and Healthcare Products Regulatory Agency* [*www.mhra.gov.uk*](http://www.mhra.gov.uk)

The agency recommended against the use of six drugs: Paxil, Zoloft, Effexor, Celexa Lexapro, and Luvox.

Between 1998 and 2003, state doctors following the TCMAP guidelines routinely and regularly prescribed these antidepressant drugs to children in accordance with the TCMAP algorithm requirements.

They continue to prescribe these drugs.

Despite a nearly 500% increase in American children being prescribed mental health drugs during the past 6 years, the **New Freedom Commission** found that not enough adolescents are benefiting from mental health treatment. The NFC recommendations prominently recommend mandatory mental health screening for *all high school students*, with follow-up treatment as required.

Will the screening devices and evaluations resemble the prior tools of TMAP, NFC's recommended, "Model program"?

TMAP Expansion:

With TMAP and TCMAP in place, a Johnson&Johnson foundation provided a $300,000 grant to fund the implementation of the *Texas Implementation of Medication Algorithms Project* (TIMAP) for the sole purpose of exporting TMAP and TCMAP to other states. Janssen and those drug companies previously mentioned also funded the expansion. As of 2002, ten states, including Pennsylvania, had implemented TMAP or were in the process of doing so.

The pharmaceutical industry influence on the development of TMAP was not limited to political contributions and TMAP, TCMAP and TIMAP funding. Janssen funded efforts of the newly created Research Committee of the National Association of State Mental Health Program Directors (NASMHPD).

One Director of TMAP, himself a State Medical Director, took a prominent role in the organization. **Dr. Steven Shon**, a co-director of TMAP authored reports and articles under the NASMHPD banner in which he lauded TMAP, the TMAP algorithms and the TMAP medications.

Through NASMHPD, Janssen and other companies had the means of fostering the growth of TMAP in a very concise and effective way. By influencing only fifty key people, the pharmaceutical industry could pave the way for acceptance of TMAP in all fifty of the United States.

Janssen's influence of state Mental Health Directors was not limited to NASMHPD funded events. Janssen also formed "Advisory Boards" comprised entirely of State Mental Health Directors and regularly treated these "Advisory Board" members to trips and conferences, with all expenses paid by Janssen.

The Pennsylvania Director who oversaw the implementation of TMAP in Pennsylvania attended multi-day "Advisory Board Meetings" in Tampa, Seattle and Chicago, all during the time when PENNMAP, the Pennsylvania version of TMAP, was being developed.

The Ohio state director, Michael Hogan, and the California State Director, Stephen W. Mayberg, who are now New Freedom Commission members, also participated on this Janssen advisory board.

Janssen's influence of State Mental Health systems was not limited to deluxe treatment of state Directors. Janssen also funded trips and, through intermediaries, paid money, to other key state employees who were in a position to implement TMAP.

Janssen and Pfizer's influence on individual Pennsylvania Employees is described later.

Meanwhile, back in Texas:

By 1998 The Texas MHMR network was in severe financial trouble. An article by Jerry Daniel Reed in the ***Abilene Reporter News*** on June 18, 1998 entitled "*Medications' costs forces MHMR into rationing*" described the Texas MHMR system as "choking on the costs" of "new-generation medications that treat schizophrenia, depression and bi-polar disorder."

The article described the need for emergency funding to pay for these drugs and described rationing of MHMR services to the general public. One official noted, "I believe that our (Mental Health) centers are in crisis right now because they're trying to squeeze money out for these new medications". He added, "And they've diverted money from other programs that are also helpful to people with mental illness".

By early 2001, TMAP and TCMAP had bankrupted the Texas Medicaid program and the budgets of the state's mental health and prison systems.

A February 9, 2001 article by Nancy San Martin, in the ***Dallas Morning News***, entitled *State Spending More on Mental Illness Drugs* reported, in part:

> *"Texas now spends more money on medication to treat mental illness for low-income residents than on any other type of prescription drug."*
>
> *'Prescription drugs are the fastest growing expense within the health care system. And the cost for mental disorder treatments is rising faster than any type of prescription drug."*

"The costs of treating schizophrenia, bipolar conditions and depression have surpassed expenditures for medications to treat physical ailments, such as bacterial infections, high blood pressure, respiratory problems and even chronic disorders, notably diabetes."

"In addition to covering nearly 40 percent of the costs of prescription drugs for Medicaid recipients, the state also spends about another $60 million annually. Most of that money goes to purchase hundreds of thousands of prescription drugs for other state-funded programs at the Texas Department of Mental Health and Mental Retardation and the Texas Department of Criminal Justice."

'This week, health officials asked for at least $657 million more to help cover Medicaid costs."

"According to a report on the state's Medicaid Vendor Drug Program, ***mental health drugs*** *made up the largest category of expenditures among the top 200 drugs in 1999. They accounted for nearly $148 million. Those costs have more than doubled since 1996."*

"For the proposed 2002-2003 budget, lawmakers have increased by $1 billion the amount of money allocated to health and human services. A significant portion of that will go for medications, officials said."

"While the growing and aging population is a contributing factor to the rise in cost in Texas, there also has been a dramatic increase in the use of "new generation" drugs such as Zyprexa, an anti-psychotic, and Prozac, an anti-depressant."

"Those who make decisions on where money is going have to consider: 'Are we going to give Texans access to newer and more effective medication, or are we going to hold the money and limit access and not provide up-to-date treatment that Texans will benefit from?'" said ***Dr. Shon*** *of the Department of Mental Health and Mental Retardation. "My advice is to think of these types of medication like you would treatment for diabetes or hypertension".*

"It's an investment in the future," he said. "The issue really is to try to get people the best medication as soon as possible. It becomes one of those, 'pay me now or pay me later' situations."

Dr. **Steven Shon** is a Director of TMAP. He did not mention this in his comments.

Prior to leaving for the White House, Texas Governor Bush recommended an additional increase of 67 million dollars in the Texas state budget for FY 2000-01 to pay for additional medications for the Texas Prison and Mental Health Systems. Bush referenced his support of TMAP during his presidential campaign and in campaign literature.

Influence continues:

The political/pharmaceutical alliance that generated TMAP is poised, via the New Freedom Commission recommendations, to consolidate the TMAP effort into a comprehensive national policy to treat mental illness with expensive, patented medications of questionable benefit and deadly side effects, and to force private insurers to pick up more of the tab.

TMAP proponents occupy positions in federal organizations that can directly promote and smooth the way for TMAP expansion. The list includes:

Substance Abuse and Mental Health Services Agency - SAMHSA:

Charles Currie, a key official in Pennsylvania when TMAP was adapted there, heads the national Substance Abuse and Mental Health Services Agency. In Pennsylvania Currie endorsed the TMAP agenda and permitted employees to solicit "educational grants" from drug companies who had a vital interest in TMAP. Currie has lauded TMAP in SAMHSA speeches and SAMHSA documents. He had a $500,000 budget in FY 2002-2003 for the express purpose of expanding TMAP.

NASMHPD

The National Association of Mental Health Program Directors continues to provide a forum for Janssen, and other drug makers, to recruit state mental health program directors. TMAP has become institutionalized in the NASMHPD agenda. TMAP officials regularly praise TMAP under the guise of NASMHPD.

The NEW FREEDOM COMMISSION:

This commission was purportedly formed to examine issues and provide guidance to the president relative to mental health treatment. I believe NFC is another "Expert Consensus" panel with a pre-set mission to create an aura of legitimacy for TMAP and to advance administration plans to implement Mental Health Parity legislation requiring private insurers, in addition to Medicaid and Medicare, to pay for expensive mental health drugs.

The NFC currently has 22 members. Simple link analysis ties 14 of these members to TMAP, directly or by close association. They are:

Charles Currie: Pennsylvania

As previously mentioned, Currie was the Deputy Secretary for OMHSAS in Pennsylvania when PENNMAP was adopted. He seemed comfortable with a great deal of pharmaceutical company influence in the state mental health system. He is reported to have approved a "slush fund" account into which OMHSAS employees solicited "educational grants" from drug companies.

Internal Janssen documents list Janssen's purpose and goal in providing these "educational grants. These grants were drawn from a promotional account for the Janssen drug Risperdal.

The stated purpose of one grant was to support "TMAP initiative to expand atypical usage and drive **Steve Shon's** expenses". Another grant lists the purpose of the grant as being "Pennsylvania OMH to meet with TMAP group" (In New Orleans). The expected "deliverable" result was "Successful implementation of PENNMAP".

Currie currently heads the federal SAMHSA agency. SAMHSA literature favors TMAP and Currie has a budget for the express purpose of fostering the growth of TMAP.

Michael F. Hogan. Ohio
Hogan is the president of the NASMHPD Research Institute, an entity heavily supported by Janssen and other pharmaceutical company grants. Hogan was the Mental Health Program Director in Ohio when TMAP was implemented there.

Hogan participated on a Janssen advisory Board along with Steven Karp, the Pennsylvania Director who implemented TMAP. He serves with Steve Shon in NASMHPD.

Rodolfo Arredondo. Texas
Arredondo served on the board of the Texas Department of Mental Health and Mental Retardation during TMAP's development. He was a member of the TMAP steering committee and is currently working with TMAP to develop algorithms for disorders co-occurring with schizophrenia and depression.

Stephen W. Mayberg. California
Mayberg was the California State Mental Health Program Director when California implemented TMAP. Mayberg is a past president of NAMHPD and the NASMHPD research institute.

Mayberg participated on a Janssen advisory Board along with Michael Hogan and Steven Karp. He serves with Steve Shon in NASMHPD.

Henry Harbin. Maryland
Harbin is a past Director of Mental Health Services in Maryland, another state listed in TMAP literature as having adopted TMAP. Harbin is now the CEO of Magellan Health Systems, the world's largest Managed Care Agency. As early as 2001, Pennsylvania officials met with Magellan to pitch TMAP as a model program. Magellan's interest in the administrative structure of TMAP is manifest.

Larke Nahme Huang
Huang was involved in the planning and formation of the National Asian American Pacific Islander Mental Health Association (NAAPIMHA). Steven Shon who is a TMAP Director and major TMAP proponent heads this recently-formed group. Haung currently serves under **Shon** in NAAPIMHA.

Randolf Townsend. Nevada
Townsend was a Nevada state Senator when Nevada adopted TMAP. In Nevada, he worked to provide extended state and insurance company funds for mental health services and mental health medications.

Anil Godbole. Illinois
Godbole had a strong partnership with the Illinois State office of Mental Health when Illinois adopted TMAP.

Robert Pasternak. New Mexico
Pasternak served as the Assistant Secretary for Special Education and Rehabilitative Services when New Mexico adopted TMAP.

Nancy Carter Speck. Texas
Speck was a coordinator at the University of Texas Medical Branch at Galveston while TMAP was being developed at that facility. Speck was also associated with the Texas Department of Mental Health during TMAP's development.

Deanna Yates. Texas
Yates was associated with universities and psychological services in both Texas and California during the time in which TMAP was adopted in those states. Yates is an outspoken proponent for legislation allowing Psychologists to prescribe medication for mental illness.

Patricia Carlile. Texas
Carlisle is a Texas native who served in HUD under the first President Bush.

Norwood Knight-Richardson. Texas
Norwood is an associate professor at facilities where TMAP was implemented. Knight-Richardson was a college friend of George W. Bush and was appointed by then-Governor Bush to the Texas drug and alcohol council during TMAP development.

Knight-Richardson is a director and shareholder in Eagle Global Logistics, a transportation company with a specialty pharmaceutical delivery division. Eagle's profits soared in 2003 with multiple contracts to ship goods in conjunction with the war and reconstruction in Iraq. Knight Richardson/Eagle have a manifest interest in pleasing Pharma and the administration.

Robert Postlehwait, Eli Lilly
Postlehwait was the head of the Neuroscience unit at Eli Lilly during the development and implementation of TMAP. It is unknown if he had any direct contact with TMAP, but Lilly's interest in TMAP is manifest.

TMAP appears prominently in New Freedom Commission publications as an example of a program that really works. I am sure Janssen would agree.

On July 22, 2003 the New Freedom Commission issued its recommendations for redesigning the mental health network in each of our fifty states. Not surprisingly, TMAP is recommended as the model program for all states to follow.

Food and Drug Administration - FDA

President Bush appointed Mark B. McClellan to head the FDA. McClellan is a resident of Austin, Texas and graduated from Texas University at Austin, a facility that played a vital role in TMAP development.

McClellan's Mother, Carole Keeton McClellan Strayhorn, is a three-time mayor of Austin, the current Comptroller of Texas and a long-time Bush family friend. As Comptroller, she has praised and pushed the TMAP program, assisting in the various funding initiatives.

Rounding out this very political family is Mark's brother, Scott McClellan, advisor and deputy press secretary to President Bush.

TMAP comes to Pennsylvania:

TMAP was "sold" to Pennsylvania by Janssen Pharmaceutica. Janssen comprised public officials who would have been in a position to raise an alarm about the legitimacy of TMAP.

The following account describes what PENNMAP is, and how it got to Pennsylvania.

PENNMAP

The Pennsylvania Medication Algorithm Project (PENNMAP) is a treatment model and regimen for the treatment of schizophrenia. It was adopted by the Pennsylvania Department of Public Welfare (DPW), Office of Mental Health and Substance Abuse Services (OMHSAS) in 2002 and fully implemented in January of 2003.

This model was incorporated into OMHSAS as an ***administrative*** decision to accept and implement a self-contained approach to the ***medical*** treatment of schizophrenia and related conditions.

The centerpiece of this model is a set of algorithms that, together with text guidelines, guide a clinician in prescribing medications to schizophrenic patients and in changing or adjusting medications. Algorithms are basically flow charts, or graphs, that illustrate step-by-step movements in a process. (Attachment # 3 is a sample algorithm)

The centerpiece of the algorithms is a formulary of approved and required medications. A formulary is like a menu in a restaurant, but it lists medications instead of food. It is a list of what medications a doctor may choose from. If a drug is not on the menu, it cannot be used.

The menu also stipulates the order in which classifications of drugs can be used. To carry the restaurant analogy further, the "appetizer menu" must be used first. In the drug formularies, "the appetizer menu" is that list of drugs that must be used first, second and often third, before moving on.

The PENNMAP schizophrenia formulary has a restrictive, proprietary, "appetizer menu" consisting exclusively of new, patented and very expensive drugs. These drugs are referred to in literature and throughout this report as "Atypical Antipsychotics", or "Atypicals". This refers to a new classification of schizophrenia drugs developed from the early 1990s through the present day. These drugs will occasionally be referred to as "SGAs", or Second

Generation Antipsychotics. This report focuses on the Atypicals **Risperdal, Zyprexa and Seroqual**.

The older drugs, first appearing in the 1960's are referred to as "Typical Antipsychotics", or "Typicals". All of these drugs are available in generic form today. These drugs will occasionally be referred to, in the bibliography section of this report, as "FGAs", or First Generation Antipsychotics.

The designation of PENNMAP by OMHSAS as the required treatment methodology for all schizophrenic patients required that *all schizophrenic patients* coming in contact with the state hospital system be treated with Atypicals, *regardless* of patient history and regardless of past or current success with Typical medications.

During the phase-in of PENNMAP hundreds of mental patients had their medications switched ***in the absence of medical need or indication*** to comply with an administrative decision. This was an unethical practice instituted without regard for the rights of patients and in the absence of meaningful consent.

Contrast this with what happened in Massachusetts when state doctors were found to have switched the medication of only four patients for non-medical reasons: A Boston Globe article by Ellen Barry published on November 10, 2003 (Attachment # 4) addresses the issue.

Barry found that four patients were switched, without informed consent or medical need, to the Janssen drug Risperdal to make them eligible for a Janssen drug trial. One of the patients nearly died from the experience. When other staff complained about the ethics of the move, a state agency investigated and confirmed the switch. Result?

1. The drug trial was halted.
2. The doctor's conduct is being reviewed by the Massachusetts Board of Registration in Medicine.
3. All Massachusetts state hospital doctors are required to undergo re-certification in the ethics of medical research
4. Dr. Douglas Hughes, the facility medical director resigned on September 29, 2003. Douglas disclosed having received $30,000 in speaker's fees from Janssen in 2003.

In Pennsylvania, a wholesale change in medications, which is a ***clinical*** matter, was implemented as a result of an ***administrative*** decision made by a relatively few administrators within OMHSAS.

All of these OMHSAS administrators were subjected to, and willingly accepted, concerted and pervasive influence on their decision-making by the drug manufacturers, including Janssen, who have Atypical medications represented in the algorithms.

The Atypicals were adopted because of drug manufacturers' claims that they were safer, more effective and produced fewer side effects than the Typical Drugs. Claims of greater effectiveness and safety were not supported by the clinical trials leading to FDA approval of the Atypicals.

In reality, the Atypicals entered the market with significant warnings and are evolving a side effect profile that includes serious and life threatening conditions in an alarming number of patients. In fact, the Food and Drug Administration (FDA) data established that one of every 145 persons enrolled in clinical trials for these drugs *died* as a result of adverse reactions to the drugs.

These side effects include, but are not limited to:

Suicide, Diabetes Type 1 and Type 2, Diabetes Mellitus, Hyperlipidemia, Convulsions, Neuroplectic Malignant Syndrome, Pancreatitis, Necrotic pancreas, Hyperglycemia, Tardive Dyskinesia, Stroke, Hypertension, Cardio Arrhythmia, Cardiomyopathy, Hyperlprolactinaemia, Obesity Somnolence and Amenorrhoea.

People are dying of these side effects at alarming rates. The FDA is far behind its European counterparts in issuing strong warnings for Atypicals, but has recently issued warnings regarding suicide, stroke and diabetes.

Persons on Atypicals have been found to commit suicide at rates two to five times more frequently than the schizophrenic population in general. Older persons in particular are victims of stroke when taking Risperdal. Adult onset Diabetes has been found to occur ten years earlier and in far greater frequency in patients treated with Atypicals than in the general population.

There is evidence that drug manufacturers were aware of the emergence of these side effects when PENNMAP was "sold" to Pennsylvania. In fact, drug companies had been sued successfully as a result of some of these effects years prior to PENNMAP. Many of the side effects had in fact been identified in clinical trials prior to the drugs receipt of FDA approval.

An independent researcher, Dr. David Healy, studied Federal Drug Administration (FDA) raw data on the Atypical schizophrenia drug Zyprexa and concluded that it was among "the deadliest drugs ever to gain FDA approval".

The *Journal of the American Medical Association*, Nov 26, 2003 edition pages 290:2693-2702 reports on a study by Yale researchers who followed 309 schizophrenic patients at 17 Veterans Affairs hospitals nationwide. Of those, 159 received Zyprexa and 150 took Haldol, a generic antipsychotic.

This 12-month double-blind study found no statistically or clinically significant advantages of Zyprexa for schizophrenia on measures of compliance, symptoms, or overall quality of life, nor did it find evidence of reduced inpatient use or total cost."

This study is meaningful in that, unlike drug company controlled clinical trials, this study examined the drugs' effects on patients' lives and functioning: it monitored symptom reduction, adverse effects, and also patient quality of life, patient satisfaction, and maintenance costs.

The study revealed that neither Zyprexa nor Haldol were superior to the other. Zyprexa did NOT reduce hospitalizations as has been claimed. No cost benefit was found to offset the high cost of Zyprexa. Acute weight gain in patients taking Zyprexa puts them at increased risk of diabetes and other health problems. The major difference between the older and newer antipsychotic drug is the cost. Zyprexa costs $3,000 to $9,000 more per patient per year than Haldol.

More than 80 percent of schizophrenics in the VA system now take atypical antipsychotics, with 38 percent on Zyprexa. In fiscal year 2003, the VA spent $208.5 million on Psychotropic drugs, including $106.6 million on Zyprexa.

The study results were reported in the Wall Street Journal on November 26, 2003. http://online.wsj.com/article/0,,SB10697854598899400,00.html

Journalist Robert Whitaker, via the Freedom of Information Act gained access to FDA data on the drug trials for the Atypicals Risperdal, Seroqual and Zyprexa. Whitaker found that:

1. One in every 145 patients who entered the trials *died*, and yet those deaths were never mentioned in the scientific literature.
2. The trials were structured to favor the Atypicals and most of the study reports were discounted by the FDA as being biased.
3. One in every thirty-five patients in Risperdal trials experienced a serious adverse event, defined by the FDA as a life threatening event or one that required hospitalization.
4. Twenty-two percent of patients in Zyprexa trials suffered serious adverse events
5. The Atypicals did not demonstrate superior effectiveness or safety over Typical antipsychotics.

It is important to note that a drug company does not have to prove that a new drug is safer or more effective than an old drug to gain FDA approval. Essentially, the manufacturer has to demonstrate that the drug is proved to yield better results than placebo in a statistically significant number of patients in short-term trials (6-8 weeks).

With these results at their disposal, and in the presence of other independent studies questioning the drug company claims regarding the safety and effectiveness of the Atypicals, Pennsylvania's OMHSAS Administration went resolutely forward with the implementation of PENNMAP.

Why?

The answer leads to the same pattern of drug industry influence and political intervention that created the Texas Medication Algorithm Project. The following is an account of the ***known*** drug industry influence on ***known*** members of the Pennsylvania OMHSAS administration, leading to the adoption of PENNMAP.

KEY PENNSYLVANIA OMHSAS ADMINISTRATIVE EMPLOYEES AND THEIR ASSOCIATION WITH DRUG MANUFACTURERS

Charles Currie
Deputy Secretary
Office of Mental Health and Substance Abuse Services

Currie was appointed by Governor Ridge to a key position within the Pennsylvania Mental Health system even though Currie lacked medical credentials. His highest degree is a MSW. Currie did have administrative experience and political connections.

Currie approved a slush fund and an off-the-books account that formed the basis of the initial OIG investigation. Currie approved the receipt of pharmaceutical company "educational grants" intended to promote the TMAP agenda. The OIG received reports that drug company sales reps frequently and openly made gifts of meals and sporting event tickets to officials and state hospitals during Currie's tenure.

Currie seems to have been very tolerant of drug company influence in Pennsylvania. The decision to implement PENNMAP was made during his tenure.

Currie's involvement was discovered at the same time I was being removed from the OIG investigation. I do not know, but seriously doubt, that Currie was interviewed concerning his contacts/affiliations with drug companies.

It seems, however, that Currie was intimately involved with the importation of TMAP into Pennsylvania as PENNMAP.

Following the start of the PENNMAP implementation process in Pennsylvania, Currie was appointed by President Bush to head the national Substance Abuse and Mental Health Services Agency (SAMHSA).

In that capacity, Currie has worked to further the expansion of TMAP, which is listed as one of his prime initiatives. SAMHSA had a $500,000 budget in FY 2002-03 for the express purpose of aiding TMAP development.

Currie also serves on President Bush's New Freedom Commission, which seeks to expand the role of the insurance industry in more fully funding mental health services, including mental health medications.

Steven J. Fiorello
Director of Pharmacy Services
Office of Mental Health and Substance Abuse Services

An April 2002 "Faculty Bio" in a Janssen publication describes Fiorello as being "responsible for the formulation of policies and procedures for drug use for ten state hospitals and facilities including the development and implementation of the PENNMAP project".

Fiorello describes himself as the "Point Man" in Pennsylvania for any drug company wishing to have their product placed on the state drug formulary. He is the Chairman of the Pennsylvania Formulary Committee that approves or disapproves drugs for the state "menu".

Known Fiorello interactions with drug companies:

Fiorello solicited "educational grants" from pharmaceutical companies totaling at least $13,765.

Part of this amount was spent to bring **Steven Shon** to Pennsylvania to "sell" the TMAP agenda.

Part of this amount was spent on trips to New Orleans for Fiorello and OMHSAS Psychiatric Services Manager; Dr. Robert Davis's to meet with TMAP representatives and marketing representatives of Janssen Pharmaceutica.

While in New Orleans, Fiorello was treated to lavish dinners by the Janssen Sales representatives and attended Janssen entertainment venues.

Along with Dr. Fredrick Maue, Chief, Clinical Services Division, Pennsylvania Department of Corrections, Fiorello did a presentation on PENNMAP at a Janssen sponsored event in Hershey, PA on April 17, 2002. He was paid a $2,000 honorarium for the presentation, which he delivered in his official state capacity. Fiorello noted that Maue was implementing a similar program in the state prison system.

A Janssen sub-contractor, Comprehensive NeuroSciences, (CNS) arranged the Hershey event for Janssen. A Janssen sales representative attended the event. Documents indicate that CNS, as Janssen's sub-contractor and Janssen personnel themselves, prepared and reviewed Fiorello's presentation materials. CNS sent Fiorello Janssen slides from the previous year to use as a model. This Janssen involvement was in direct violation of AMA regulations and FDA *Guidelines for Industry*.

Comprehensive NerouSciences is a high-sounding name for an events-management company that facilitates educational seminars for pharmaceutical companies. The two CNS employees involved in Janssen Pharmaceutica events in Pennsylvania worked out of their homes and their cars. They work on contract with the companies to do for the pharmaceutical companies what the companies cannot legally do for themselves.

At the request of Pfizer, Fiorello traveled to Maryland with Pfizer Representatives as a consulting pharmacist. There he met with his counterpart in the Maryland Department of Mental Health. The purpose of the meeting was to discuss TMAP and PENNMAP.

Fiorello traveled three times to Pfizer World Headquarters in Manhattan, at Pfizer's invitation, to participate on an "advisory counsel" with "an elite group of pharmacists".

Pfizer paid all of Fiorello's expenses including lodging at the Millennium Hotel in Manhattan. Fiorello was paid an honorarium of $1,000 in addition to expenses for each "advisory council" appearance.

Fiorello traveled to Philadelphia in late 2001, at the request of Janssen to do a PENNMAP presentation to community based managed care service providers to promote PENNMAP outside of the Pennsylvania State Hospital system. Fiorello went to Philadelphia as a pharmacy consultant to Janssen.

At the request of Janssen Pharmaceutica, Fiorello conducted "retrospective analysis" of patient records within the Pennsylvania State Hospital system. He essentially "mined" the patient records for information favorable to Janssen and compiled a "study report". Fiorello was then treated to a trip to New Orleans to present his "report" to pharmacists from across the nation. All expenses were paid by Janssen.

During the implementation phase of TMAP, Fiorello gathered data regarding off-label experimentation with dosages of Atypical medications that were higher and/or lower than the FDA approved dosages listed in the Physician's Desk Reference (PDR), which is the authoritative prescribing guide for doctors. He also gathered data on usages of the medications for symptoms for which the drugs were not approved for usage.

Fiorello gathered this information into a computerized data collection system that was provided, at least in part, by pharmaceutical companies. Fiorello relayed, to the drug companies, the medication data and results drawn from the affected patient's records.

The Pennsylvania OIG limited its investigation to Fiorello's honorariums. The matter was treated as an issue of possible employee misconduct related to non-reporting of outside employment income on code of conduct forms.

Steven J. Karp DO
Medical Director.
Office of Mental Health and Substance Abuse Services DPW

Karp was recruited from private industry by Charles Currie to fill the position of Medical Director in OMHSAS.

Karp is a supervisory level above Fiorello and, according to Fiorello, authorized the slush fund account and approved expenditures.

Karp was aware of Fiorello's association with Janssen.

Karp was aware of the gathering of patient information and the dissemination of that information to the drug companies.

Known Karp affiliations with drug companies:

Prior to state service, Karp frequently gave presentations for drug companies for which he received honorariums and expenses.

In December of 2000 Karp was appointed to the advisory board of *Mental Health Issues Today*, (MHIT) a Janssen publication. Janssen contracts with Parexel International Corporation to produce MHIT. Janssen funds the project, but Parexel writes the checks.

New Freedom Commissioner Michael Hogan served on this same "advisory board"

As a result, Karp was invited, at Parexel's expense to attend periodic " advisory board meetings". In 2001 Karp attended a meeting at the Mayflower Park Hotel in Seattle Washington on June 23-25. Janssen, via Parexel, provided airfare, lodging and sustenance in Seattle and reimbursed Karp for his expenses in getting to the BWI airport.

Karp also attended a meeting at the Hyatt Regency Westshore in Tampa, Florida on November 17-19, 2001. Again, Janssen, via Parexel, covered his expenses.

In June or July of 2002 Karp again attended an Advisory Board Meeting in Chicago with all expenses paid by Janssen, via Parexel.

As a result of Karp's participation in these meetings, he was quoted in *Mental Health Issues Today* articles and achieved a degree of notice in his profession. Janssen, via Parexel, funded the publication and distribution of the articles.

A list of attendees at these functions indicates the membership is exclusively comprised of state mental health directors.

Karp also belongs to the National Association of State Mental Health Program Directors (NASMHPD) along with **Steven Shon** and NFC commissioner Michael Hogan. The growth of this organization paralleled the development of TMAP and was likewise heavily subsidized by Janssen. The group has actively sought, and accepted grants from other drug companies to fund their conferences and publications.

Members of this organization are directors of all of the states that have implemented TMAP.

The OIG management tightly restricted the scope and depth of questions I was permitted to ask Karp.

I was forbidden to interview Karp regarding his knowledge of the treatment of schizophrenia in the PA corrections system or his knowledge of drug company involvement of commonwealth employees other than Fiorello.

Robert H. Davis, MD
Psychiatric Physician Manager
Medical Services Division
OMHSAS

Davis works under Karp in the Medical Services Division.

Known Davis affiliations with Drug Companies:

Davis attended two functions in New Orleans with Fiorello. Expenses were paid with Janssen funds. Davis attended the dinner meetings with Fiorello and the Janssen Representative.

Davis participated in Fiorello's above-described retrospective analysis of patient data, the formulation of a "study report" and the dissemination of information to drug companies.

Davis was not interviewed by the OIG, as the focus of the inquiry was strictly limited to Fiorello. I was not permitted to question Davis concerning any other drug company affiliations or his role in data gathering and data transmission to drug companies.

Fredrick Maue
Chief, Clinical Services Division
Pennsylvania Department of Corrections

Maue is Karp's counterpart in the Department of Corrections.

Known Maue affiliations with Drug Companies:

In April of 2002 Maue did three presentations at Janssen-funded events sponsored by Janssen's contractor Comprehensive NeuroSciences. They included the one with Fiorello described above.

The other two were held in Sacramento California and Orlando Florida. According to CNS, Maue received a $2,000 honorarium plus all expenses for each of the presentations.

There is abundant anecdotal evidence that Maue and the Department of Corrections were involved with the receipt of drug company funds and the implementation of a medication algorithm long before the OMHSAS. Maue in fact introduced some of the state employees and pharmaceutical company representatives.

I was expressly forbidden from pursuing this lead and was not permitted to request documentation on Maue that would have been easily obtainable from existing sources. I was not even permitted to determine if PENNMAP or a similar project was in use within the Department of Corrections.

The Pennsylvania Office of Inspector General Turns it's Back

The vast majority of the information in this report is the product of my individual investigative efforts as a private citizen.

However: ***the entirety of the information contained in the "Key Employee" section was part of the OIG record when I was removed from the case.*** If not destroyed, the evidence remains in the OIG file.

In the face of pervasive evidence of corruption and improper influence, the OIG limited its investigation to a single employee who was the lowest ranking employee identified as being involved in the matter.

I was removed from the investigation when I refused to hide or ignore clear fact and compelling evidence that would impact on the pharmaceutical industry and that industry's political contributions.

In the words of the OIG manager who curtailed my investigation and participated in overt threats against me: **"Drug companies write checks to politicians – they write checks to politicians on both sides of the aisle".**

I was forbidden to contribute to the final OIG report on and was forbidden to review a copy. The report was silent on the issue of drug company misconduct. The drug companies were not cited for wrongdoing and no further investigation into the drug companies or the legitimacy of PENNMAP was done.

Here are some of the issues the OIG chose to overlook:

Janssen Pharmaceutica may have violated AMA Guidelines, FDA Guidelines, Federal Health and Human Services OIG guidelines and federal anti-kickback laws in that:

1. Janssen made direct payments of money to state officials for representing Janssen products. The remuneration was far in excess of "reasonable value" ($2,000 for ½ day presentations) and was made to officials who were in a position to influence the state drug formulary.

2. Janssen provided trips, entertainment and meals directly to the persons who were in key positions to accept or reject Janssen's product in the state formulary.

3. Janssen influenced, to the point of control, the content and materials in which Janssen had provided "educational grant" funding.

4. Janssen selected speakers for "educational grant" funded symposiums and paid travel expenses and honorariums to these speakers.

5. Janssen, through these symposiums and through direct contact with Pennsylvania officials, encouraged doctors to prescribe drugs in dosages that were not FDA approved.

6. Janssen, through these symposiums and through direct contact with Pennsylvania officials, encouraged doctors to prescribe medications for non-FDA approved indications.

7. Janssen conspired with commonwealth employees to obtain data generated from the non-FDA approved activities.

8. Janssen funded travel and expenses for commonwealth employees to represent Janssen in the employee's official state capacities.

9. Janssen's cooperation with other drug manufacturers in the advancement of TMAP has clear Anti-Trust and Racketeering implications.

In addition to the drug company impropriety, the OIG had solid evidence that employees in addition to Fiorello had engaged in the same conduct. Yet Fiorello was the only one investigated and recommended for prosecution.

Information provided to the OIG clearly established that state employees were experimenting on mental health patients and reporting the results to drug companies, yet this was not even mentioned in their report.

Additional Costs

I was not permitted to obtain census data from the state mental hospitals or the Department of Corrections regarding the numbers of schizophrenics being served in Pennsylvania. My best estimate based on tangential data is that there are approximately 9,000 schizophrenics in the state's prisons and mental hospitals at any given time.

Based on average length of stays, it is believed that at minimum, an additional 4,000 persons will cycle through the systems in any given year, taking their prescriptions for Atypicals with them, resulting in an estimated 13,000 persons affected.

At an average cost of $6,000 per patient, Pennsylvania could spend **78 million dollars,** for the medication of institutionalized schizophrenics alone in 2003.

It is important to note that state mental hospitals and prisons have a flow-through population. Patients treated at these facilities will leave the facilities with prescriptions for the medications they were treated with while institutionalized. Most will rely on Medicaid or Medicare to pay for the drugs. This is "patient recruitment and retention" in pharmaceutical industry terms.

The costs to Pennsylvania government will grow annually, and exponentially, as patients are "recruited" through the prisons and state hospitals.

Ohio, with a population of 11.5 million, one million fewer residents than Pennsylvania, implemented TMAP in 1999. In 2002 Ohio spent 145 million Medicaid dollars on the TMAP atypical Schizophrenia medications alone.

I have not been able to determine how much in non-Medicaid dollars was spent on these medications.

Missouri, which embraced an algorithm program even earlier, has less than ½ of the population of Pennsylvania, approx. 5.5 million. In 2002, Missouri spent 104 million Medicaid dollars for three of the TMAP schizophrenia drugs alone. The three drugs topped the list of all drugs covered by the state Medicaid program, including cancer, HIV and heart medications.

In short, two small to medium sized states alone generated an annual Medicaid expenditure of a **quarter of a billion** dollars on three new schizophrenia drugs within three years of adopting the TMAP program.

California, now in the process of implementing TMAP spent over 500 million Medicaid dollars on the Atypicals Risperdal, Zyprexa and Seroqual alone in 2003.

TMAP literature, at various times between 1996 and the present, lists TMAP programs in the following states: Texas, California, Colorado, Nevada, Illinois, Kentucky, New Mexico, New York, Ohio, Pennsylvania, South Carolina, Maryland, Missouri, and Washington D.C. The discussion of TMAP in the New Freedom Commission report presents a smaller list.

Several states have adopted the depression and bi-polar algorithms as well as algorithms for ***children.*** The Texas Medication Algorithm Project has already generated many billions of dollars in sales in the United States.

If we extrapolate the Ohio and Missouri costs for a 17 million population, based on a national population of 250 million Americans, the annual costs to the Medicaid programs would be approximately **3.7 billion dollars per year** to treat schizophrenia alone. That is over **ten million dollars per day** just in ***Medicaid*** expenditures for schizophrenia drugs.
The costs of TMAP algorithm drugs for depression and bipolar disorder are likely to be at least double that figure, possibly far more.

Thirty million dollars per day can buy a lot of political and professional influence.

Ironically, in 2003 the Texas Legislature voted to cut $22 million from its budget for medications for prisoners who were released from the Texas state prison system. The costs were simply growing out of control.

Human Toll

My best effort at correlating dollars spent with deaths from drug side effects suggests that people may be dying from side effects from the schizophrenia drugs alone at the rate of at least one death for each one million dollars spent on these drugs. The actual numbers may reflect a much higher death rate.

FDA data indicates that one of every 145 patients enrolled in clinical trials of the schizophrenia drugs ***died*** of side effects. In some trials, 22% of participants were hospitalized with severe adverse reactions. At that rate alone, Pennsylvania can expect a minimum of 90 unnecessary deaths in 2003. This figure will grow steadily.

It is statistically possible that thousands of persons in the United States will die from side effects of Atypical antipsychotics in 2003.

Political Reality:

According to a *Wall Street Journal* article on 5/21/02 by Andrew Caffrey, entitled *States Go to Court to Rein in Price of Medicine,* legal action by states against pharmaceutical companies is becoming common. The States of Colorado and Nevada initiated lawsuits accusing seventeen drug companies of defrauding consumers. The Nevada suit alleges "deceptive practices" that constitute consumer fraud and says, "The drug makers, through a pattern of behavior, operated a "racketeering enterprise".

According to Caffrey, Attorney Generals in thirty-five states are looking at pharmaceutical marketing practices and the states of New York, California and Texas have also filed suits alleging improprieties in Medicaid pricing practices.

The state of Pennsylvania has been silent on the issue.

Two Investigators in the Pennsylvania Office of Inspector General are involved in a federal suit alleging cover-up of investigations into matters that are "politically sensitive", including the matters outlined in this report. The suit names the former Inspector General, his Chief Deputy and former Governor Ridge's Chief Counsel as defendants, among other high-ranking officials.

The suit is a matter of public record - Dwight McKee and Allen Jones v Henry Hart, Sydni Guido, Wesly Rish, Albert Masland, James Sheehan and Daniel P. Sattele, CIVIL ACTION No: 4:CV-02-1910, in the United States District Court for the Middle District of Pennsylvania.

The Pennsylvania OMHSAS employees listed earlier in this report are still in their jobs.

Absent external pressure, it is likely that Pennsylvania elected and appointed officials will remain silent on the issue of pharmaceutical industry fraud.

Conclusions:

Pennsylvania citizens and taxpayers are saddled with an expensive treatment model for the treatment of schizophrenics and other mentally ill persons who are in the care of the Commonwealth. This model is part of a large pharmaceutical marketing scheme designed to infiltrate public institutions and influence treatment practices. Pennsylvania is paying tens of millions of dollars for patented drugs that have no proven advantage over cheaper generic drugs.

The Pennsylvania administrators who approved the model were all receiving improper and/or illegal gratuities and perks from the pharmaceutical companies involved. The officials acted in an administrative and political atmosphere that openly allowed improper drug company influence.

Pennsylvania taxpayers may pay nearly 100 million dollars in the unnecessary purchase of patented medications in 2003 alone. This figure will grow dramatically with each passing year.

It is a statistical certainty that some of Pennsylvania's most vulnerable citizens have died as a result of this program. Deaths can be expected to continue.

Allen Jones
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Revised January 20, 2004

POSTSCRIPT

The pharmaceutical industry has methodically compromised our political system at all levels and has systematically infiltrated the mental health service delivery system of this nation. They are poised to consolidate their grip via the New Freedom Commission and the Texas Medication Algorithm Project. The pervasive manipulation of clinical trials, the non-reporting of negative trials and the cover-up of debilitating and deadly side effects render meaningful informed consent impossible by persons being treated with these drugs. Doctors and patients alike have been betrayed by the governmental entities and officials who are supposed to protect them. To the millions of doctors, parents and patients who are affected: PLEASE: suspend disbelief and realize you are on your own. Educate yourselves. The Internet has many sites that will help you. The Alliance for Human Research Protection, www.ahrp.org would be a good place to start.

The above report tells what I fear to be only a small part of a much larger story. But it is a beginning. The fuller story will require the efforts of persons with investigative resources, political authority, legal standing - and the will to use them.
AJ

OTHER GUIDELINES

The Schizophrenia Patient Outcomes Research Team (PORT) Treatment Recommendations published 1997

In 1992 the Agency for Health Care Policy and Research (AHCPR) and the National Institute of Mental Health established a Patient Outcomes Research Team (PORT) for Schizophrenia at the University of Maryland School of Medicine and the Johns Hopkins University School of Public Health.

This PORT combined the expertise of three major research centers at two universities: the Center for Research on Services for Severe Mental Illness (Johns Hopkins University and the University of Maryland), the University of Maryland Center for Mental Health Services Research, and the Maryland Psychiatric Research Center (at the University of Maryland).

The prime objective of the PORT was to develop recommendations for the treatment of persons with schizophrenia based on a synthesis of the best scientific evidence, with the ultimate goal of improving the quality and cost-effectiveness of care for persons with this diagnosis.

In writing the recommendations, the PORT investigators graded the reliability levels of evidence used for development of Guidelines, as follows:

> Level A: Good research-based evidence, with some expert opinion, to support the recommendation

Level B: Fair research-based evidence, with substantial expert opinion, to support the recommendation

Level C**:** Recommendation **based primarily on expert opinion, with minimal research-based evidence,** but significant clinical experience.

The PORT recommendation regarding the usage of antipsychotic medications, published in 1997, noted:

"Since studies have found no superior efficacy of any antipsychotic medication over another in the treatment of positive symptoms, except for Clozapine in treatment-refractory patients, choice of antipsychotic medication should be made on the basis of patient acceptability, prior individual drug response, individual side-effect profile, and long-term treatment planning."

This research-based conclusion differs dramatically from the TMAP "Expert Consensus Guidelines" recommendations.

PORT did not receive funding from pharmaceutical companies.

The American Psychiatric Association Practice Guidelines for the Treatment of Patients With Schizophrenia: Published in 1997

The APA developed its guidelines in a process of broad and comprehensive review of scientific research into the treatment of Schizophrenia. It was headed by a work group of clinical experts who subjected their findings to widespread peer review prior to publishing their guidelines.

The psychopharmacologic recommendations of the APA Guidelines do not weight the atypical antipsychotics above the typical antipsychotics. The guidelines recommended cautious usage of the atypicals until clear efficacy and side effect profiles emerged.

The ASA Guidelines were developed without funding from the pharmaceutical industry.

The Harvard Medication Algorithm Project (HMAP):

The Harvard School of Medicine developed a Psychopharmacology Algorithm program at the Harvard South Shore Department of Psychiatry. This project began in 1997 with the goals of formulating evidence-based treatment guidelines for the treatment of mental disorders and making these guidelines available to clinicians on-line.

HMAP algorithms were created on the basis of high quality empirical studies, field trials, expert opinion, peer review and review of other guidelines. HMAP offers a free web site where any physician or psychiatrist can consult the Harvard algorithms regarding specific patients and clinical situations.

HMAP solicits continuous feed back from clinicians around the world who use the on-line algorithms. This continuous input from actual results is utilized to refine the treatment guidelines.

The current HMAP schizophrenia algorithm allows for the usage of atypical antipsychotics, but, unlike TMAP, does not require their usage. Atypicals are usually recommended for first-episode psychosis where there has been no history of success on typical antipsychotics. Persons with a history of success with typicals are not discouraged from using them.

Unlike TMAP, the HMAP algorithms provide options for usage of typical antipsychotics after the failure of a single atypical.

HMAP was developed without funding from the pharmaceutical industry.

HMAP is available on-line at http--mhc.com-Algorithms-AlgoMain

Attachment # 2

CONFLICTS OF INTEREST

Presented by Vera Hassner Sharav

14th TRI-SERVICE
CLINICAL INVESTIGATION SYMPOSIUM

Sponsored By

THE U.S. ARMY MEDICAL DEPARTMENT

And

THE HENRY M. JACKSON FOUNDATION FOR
THE ADVANCEMENT OF MILITARY MEDICINE

May 6-8, 2002

The cornerstone of public trust in medical research is the integrity of academic institutions and the expectation that universities—which rely on public funding--have a responsibility to serve the public good. Financial conflicts of interest affect millions of American people—those who are subjects of clinical trials testing new drugs and those who are prescribed drugs after their approval. Yet, the leadership paid little attention to the issue until a stream of tragic and unseemly public revelations has shaken public trust in academic research.

In January 2002, the Association of American Medical Colleges (AAMC) approved a report by its task force stating: "Financial conflicts of interest of clinical investigators---- [is] the single issue that poses the greatest threat to maintaining public trust in biomedical research." [i] The report did not address institutional conflicts of interest which create a culture that collides with the humanist tradition.

Physicians reading the current issue of JAMA[ii] will be startled to learn that a team of Harvard University professors are advising physicians NOT to prescribe new drugs to their patients because their safety has not been established—despite FDA approval. Adverse drug reactions,[iii] they acknowledge, is the leading cause of death in the U.S. They analyzed the 25-year record of drug label changes (between 1975 to 1999) as they appeared in the Physician's Desk Reference and found that 548 new drugs were approved during that period. Of these 20% required subsequent black box warnings about life threatening drug reactions, half of these adverse effects were detected within 2 years others took much longer. Sixteen drugs had to be withdrawn from the market because they were lethal.

The JAMA report provides a basis for evaluating the value and relevance of clinical trial findings for clinical care. It also provides a basis for measuring FDA's performance as gatekeeper in preventing hazardous drugs from reaching the market. They found that clinical trials are underpowered to detect uncommon, but potentially lethal drug reactions. Their design, biased selection, short duration, and accelerated approval process almost ensures that severe risks go undetected during clinical trials. The JAMA report validates the findings of a Pulitzer Prize winning investigative report in the Los Angeles Times by David Willman.[iv]

Willman uncovered evidence demonstrating the adverse consequences of the 1992 Prescription Drug User Fee Act (PDUFA), the law that brought industry money and industry influence to the FDA. The approval process for new drugs was accelerated and the percentage of drugs approved by the FDA increased from 60% approval at the beginning of the decade to 80% approval by the end of the 1990s. Willman reported that the FDA was the last to withdraw several drugs that had been banned by European health agencies. There was a concomitant precipitous rise in the approval of lethal drugs: between Januray 1993 and December 2000, seven deadly drugs were brought to market only to be withdrawn after they had been linked to at least 1,002 deaths.[v] In a follow up article, August 2001, [vi] Willman reported that the list of lethal drugs withdrawn since Sept 1997 had jumped to a dozen--9 had been approved after 1993.

None of the drugs were for life-threatening conditions, one was a diet pill, another for heartburn, another an antibiotic that proved more dangerous than existing antibiotics. The approval of these drugs illustrates the collision between corporate interests and the public interest. Corporate interests revolve around maximizing profits through the marketing of new, expensive drugs, but corporate interests collide with public safety interests. FDA's "expert advisory panels" demonstrate FDA's loss of independence. Most advisory panel members have undisclosed financial ties to the manufacturer whose drugs they recommend for FDA approval.[iv]

Corporate influence in academia:[vii]

Until 1980 a firewall existed separating industry and academia to ensure that academic pursuits were independent of commercial influence. When the Bayh-Dole Act of 1980 encouraged "technology transfer," that firewall was removed, allowing federally funded universities to patent and license inventions developed by faculty members. Researchers and institutions were free to enter into ventures and partnerships with biotechnology and pharmaceutical companies—and they did. It is estimated that of the $55 billion to $60 billion spent by the biomedical industry on research and development, large companies spend one fifth at universities, small companies spend one-half.[viii] With the flow of corporate money,

came corporate influence and control. The culture within academic institutions changed: business ethics swept aside the moral framework within which academia had functioned. Gone were such niceties as intellectual freedom and a free and open exchange of ideas, so was full disclosure of research findings. Gone was the culture of social responsibility, or a social conscience. Finally, the absence of independent, third party review has put the integrity of the process and the quality of the products in jeopardy.

The investigative series in the Seattle Times[ix] provides insight into that changed culture at the Fred Hutchinson Cancer Center during the mid 1980s. The copiously documented series examined the conduct of research and patient care in two cancer trials. It illustrates how a new entrepreneurial culture in medicine encouraged doctors to push the limits beyond what can be considered, ethical research, by subjecting patients to unjustifiable risks and increased suffering. At the Hutch a physician with a conscience who clearly did not embrace the new entrepreneurial ethos blew the whistle.

It has been said, "Doctors fear drug companies like bookies fear the mob."[x]
Researchers, whose findings collide with corporate interests, are finding out that academic freedom is no longer operational. Two high profile examples from our Canadian neighbors illustrate that researchers can face intimidation by both corporate sponsors and university administrators. In 1996 Dr. Nancy Olivieri[xi] found that a generic drug for thalassemia, manufactured by Apotex, the sponsor of the trials, failed to sustain long-term efficacy. Dr. Olivieri informed Apotex and the chair of the institution's research ethics board (REB) and moved to inform patients in the clinical trials of the risk—as is her ethical obligation. Apotex terminated the two trials and warned Olivieri of legal consequences if she informed patients or anyone else. Apotex, meanwhile had reportedly contributed $13 million to The University of Toronto.

When Olivieri attempted to publish her findings, Apotex threatened to sue her for breach of confidentiality. The University failed to defend Olivieri and the principles of research ethics or academic freedom. The University threatened to dismiss her, initiating a biased inquiry and knowingly relied on false accusations by company- funded investigators—all of which were later discredited by an independent investigation by the Canadian Association of University Teachers.[xi] Olivieri's publication of her negative findings was delayed for two years. The case is a dramatic illustration of conflicts of interest and the collision between corporate interests and the right of research subjects to be informed of any identified risks—as required by the principle of informed consent.

Another example of the clash between academic freedom and corporate interests, again involving retribution by the University of Toronto, involves Dr. David Healy,[xii] a prominent psychopharmacologist and historian of psychiatry at the University of Wales. Healy had been hired to head the Mood Disorder Program at the University's Center for Addiction and Mental Health. The program is reported to get 52% of its funding from corporate sources, and the Center received $1.5 million from Eli Lilly. After Healy criticized the drug industry in an article published by The Hastings Center, Eli Lilly withdrew its $25,000 contribution to Hastings. When Healy delivered a paper expressing his concern about the risk of suicide in some patients taking antidepressant drugs—such as Prozac-- the University rescinded his appointment. Academic freedom is but one casualty of corporate influence.

As Marcia Angell correctly observed [xiii] in her last editorial in the NEJM, corporate influence in medicine is ubiquitous, extending far beyond individual physician-researchers: its influence determines what research is conducted, how it is done, and the way it is reported. Short-term corporate goals take priority over society's long-term needs. Under corporate influence, more research is done comparing trivial differences between one drug and another, less research is done to gain knowledge about the causes of disease.

The pharmaceutical industry spends $15 billion[xiv] to buy loyalty of health care providers and allied professionals-- educators, investigators, and non-profit organizations. Drug companies shower physicians with gifts, honoraria, global junkets, and provides fees for patient referrals for clinical trials. They endow academic chairs and programs, provides grants, stock equity, patent royalty fees to researchers and institutions--even publication attribution is controlled by sponsoring companies. They make contributions to professional associations and patient advocacy groups, and sponsor their conferences.

The American Medical Association sells the rights to its "physicians' master file" with its detailed personal and professional information on every doctor practicing in the United States, to dozens of pharmaceutical companies for $20 million. [xv] That database provides drug marketers with invaluable information. Journals and the media profit from drug advertising income. Such financial inducements assure industry a fraternity of loyal allies, among them journal editors, who protect their own interests and those of their corporate benefactors. For example, the British journal, The Lancet, reported that the editor of the British Journal of Psychiatry had published a favorable review of a drug while he was receiving an annual fee of 2,000 (British pounds) from the drug's manufacturer.[xvi] Although clinical research is highly competitive, the interdependent collaborative network of stakeholders tightly controls a self-administered opaque oversight system.

The pharmaceutical industry also buys political influence in Congress and the administration. Public Citizen[xvii] reported that there are 625 pharmaceutical industry paid lobbyists in Washington, one for every congressman. Industry spent $262 million on political influence in the 1999-2000 election. That's more than any other industry. This influence ensures the industry profit enhancing legislation and reduced regulation. Since the 1992 Drug User Fee Act (PDUFA) which precipitated fast-track drug approval, congress passed the 1997 FDA Modernization Act providing industry with huge financial incentives—a six- month patent extension for drugs tested in children. These legislative initiatives are a financial bonanza for the drug industry, translating into billions of dollars in revenues—a six month patent extension can generate as much as $900 million for a single drug.[xviii].

However, the accelerated pace in research and in the drug approval process has had an enormous toll in human casualties. Adverse drug reactions are the leading cause of death in the United States—women and the elderly are at special risk.[xix] The LA Times revealed that between Sept. 1997 and Sept. 1998, nearly 20 million Americans took at least one of the harmful drugs the FDA had been forced to withdraw.[iv] A comparison of FDA's 25 year drug approval-withdrawal record analyzed by Lasser, et al,[ii] in JAMA, and the LA Times analysis of FDA's recent five year record raises alarms: 16 drugs withdrawn within 25 years, 12 within five. Most of those withdrawn drugs had been approved after 1993. The LA Times noted, "never before has the FDA overseen the withdrawals of so many drugs in such a short time."

Since 1994, reports in the press described ethical violations that undermined the safety of subjects in clinical trials, causing some to die when they might have lived.[xx] The violations occurred because a culture of expediency had replaced a culture of personal moral responsibility. Systemic ethical violations were revealed at the nation's leading research centers[xxi]—including, Duke, University of Pennsylvania, New York Cornell Medical Center, Johns Hopkins, Fred Hutchinson, NIMH, University of Maryland, and Harvard in China. The evidence demonstrates that the problem is not merely a few rogue investigators-- the problem is an entrenched insular system and weak federal oversight.[xxii] The federal Office of Protection from Research Risks (now, OHRP) was forced (temporarily) to shut down clinical trials at some of the nation's most prestigious institutions.[xxiii]

In September 2000, near the end of her term as Secretary of HHS, Donna Shalala acknowledged in NEJM, "I did not expect, or want, to complete my tenure . . . by raising questions about the safety of patients in clinical research. However, recent developments leave me little choice. . ."[xxiv] Unfortunately, the only initiative taken was to reorganize the federal oversight agency (now OHRP) under a new director who believes that education and a collaborative system of voluntary accreditation will repair the damage.[xxv] I disagree. Ethical violations such as failure to disclose risks and to protect the welfare of patient-subjects are the result of conflicts of interest—not poor education.

An example of complicity by government officials who provide a shield of secrecy, while claiming "transparency:" On February 7, 2002, the Alliance for Human Research Protection[xxvi] requested a copy of current proposals that have been received by the Secretary of HHS in accordance with Section 407 of federal regulations (45 CFR 46. Subpart D). Subpart D protects children—who are incapable of exercising the right to informed consent--from experiments involving greater than minimal risk if there is no potential benefit to them. However, section 407 provides an appeal process to the Secretary. The regulation stipulates that nontherapeutic research with no potential direct benefit to the child, may be permitted if the Secretary, after consultation with "a panel of experts in pertinent disciplines…and following an opportunity for public review and comment" finds "the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children."

Our request was denied with the following statement:[xxvii] "Release of information would interfere with the agency's deliberative and decision-making processes. Further, each researcher has a commercial and privacy interest in the release of any information…." A similar reason was given for denying disclosure of the list of experts: "Release of expert identities associated with the review of individual protocols would interfere with the agency's deliberative and decision-making process and have a chilling effect on the ability of the agency to obtain frank and candid opinions from its reviewers." This is an example of federal officials attempting to block public access to information guaranteed under federal regulation.

The role IRBs and bioethicists have in this enterprise:

Ostensibly, IRBs were established to serve as gatekeepers to protect human subjects. But lacking independence, they actually function as facilitators for the accrual of grant monies by their parent institutions. It is not surprising, therefore, that IRBs have failed to protect research

subjects from harmful experiments or to weed out research that fails to meet scientific justification. Specifically, what conclusion is one to draw from the fact that 90% of the protocols approved by the IRB at the NIMH, apparently failed to meet either ethical and / or scientific justification? Following an investigative series in The Boston Globe,[xxviii] in 1998, the director of NIMH ordered an independent evaluation of all 89 clinical trials at the Institute. The result: 29 were suspended at once, and an additional 50 protocols were put on probation for lack of scientific justification—that's 79 out of 89.[xxix]

In "Pharma Buys a Conscience," Dr. Carl Elliott,[xxx] director of the Bioethics Center, Minnesota, (who happens to be a physician) is an insightful critical examination of bioethics. Elliott criticizes his colleagues who have been seduced by corporate financial incentives. He points out how conflicts of interest have undermined the professional integrity of bioethics. He lists ethics consultants and their corporate benefactors,[xxxi] as well as what he calls, "corporate-academic dating services" that match academic "experts" with businesses seeking expertise. He notes that corporate money and corporate influence is so entrenched at university medical centers that overt threats need not be explicitly made, everyone knows what's expected. Bioethicists are in demand because they lend the appearance of legitimacy to corporate ventures. Therefore, corporations funnel money to bioethics centers, and pay bioethicists retainers to serve on their advisory boards. But, as Elliott points out, "The problem with ethics consultants is that they look like watchdogs but can be used like show dogs."

Indeed, bioethicists have lent the seal of legitimacy to highly questionable, if not outright unethical research. Their corporate affiliations are not publicly disclosed when they render opinions in the media or on IRBs, or on government advisory panels. An institutionalized veil of secrecy shields academics who sit on government appointed advisory panels. While their recommendations affect public policy, those recommendations may also serve the financial interests of the corporations that pay them.

In 1997, I testified before the National Bioethics Advisory Commission (NBAC) about financial conflicts of interest, betrayal of trust, and the undue influence of drug companies in medicine. I pointed out that physicians who accept large payments to refer patients for clinical trials testing the safety and efficacy of new products are breaching medical ethics. The Wall Street Journal, for example, reported that doctors with academic affiliations have been paid as much as $30,000 per patient per drug trial[xxxii] in schizophrenia and Alzheimer's studies.

Following the testimonies, Dr. Harold Shapiro, chair of the NBAC and President of Princeton, indicated that the NBAC would not focus on financial arrangements of research investigators because, "after all, this is a capitalist country." Dr. Shapiro neglected to mention that he was drawing a salary from Dow Chemical Company, on whose advisory board he sat.[xxx] Such publicly undisclosed personal financial arrangements by academics who sit on public policy advisory boards are not at all unusual. The public is under the illusion that so-called "expert advisory panels" are independent, and render objective, disinterested recommendations. The public does not suspect that these panelists from academia have financial ties to biochemical companies, and therefore, conflicts of interest. No one is held accountable for formulating public policy recommendations that serve an undisclosed self-interest.

What chance does a vulnerable individual patient have as an outsider confronting a fraternity of insiders—all of whom have something to gain from his participation as a subject? The system serves its stakeholders. Revelations about the system's failure to protect human subjects from preventable harm have come to light, not because of any internal safety mechanisms, but as a result of information provided by conscientious whistle blowers and investigative press reports.

Following are my "dirty dozen" corrupt research review practices that undermine both the safety of human subjects and the integrity of research findings:

1. Efficacy by design: washout / placebo; unequal dose comparison = bias.
2. Subject selection bias: younger, healthier subjects than those likely to be prescribed treatment; randomization criteria; recruitment coercion.
3. Assessment of risk / benefit: entirely subjective, it depends who is assessing.
4. IRB evaluation and approval process: vote without examination of protocol; intimidation; IRB shopping.
5. Misleading disclosure documents = Uninformed Consent.
6. Non-disclosure: there's no benefit; newly identified risks = Uninformed Consent.
7. Suppressing adverse event reports: "don't ask, don't tell"
8. Interpretation of findings--"efficacy in expert hands is not the same as clinical effectiveness"[xxxiii]
9. Biased advisory panels: FDA panels recommend drugs that kill.
    i. Bioethics ethics: conscience for hire;
    ii. Professional guidelines, recommendations.
10. Corrupted published data: suppression of negative findings; ghost authorship.
11. Complicit government oversight officials fail to enforce, preferring to redefine the standards: Who is a human subject? What's a condition? Can children's assent be called consent?
12. Using patients as laboratory animals in symptom provocation, relapse inducing experiments.

Case 1: Placebo design: ethics vs financial stakes

Corporate influence begins with the protocol design and subject selection. For example, unequal dosage comparisons will elicit different side effects that may skew the results. Selective inclusion criteria can effectively hide adverse side effects that will later be reveled in clinical practice. Drug "washout' followed by placebo allows sponsors to manipulate the condition under which a new drug is tested. Specifically, by making patients very sick during washout, the efficacy of the new drug is likely to be inflated. Such manipulations may explain the reason that a drug's efficacy in clinical trials is not usually matched under normal clinical conditions.

The use of placebo control trials in patients for whose condition an effective treatment exists has been the subject of heated debate. The FDA has been severely criticized for its placebo control policy because it undermines patient's best interest in violation of the Declaration of Helsinki. Of particular concern is the risk of suicide in severely depressed or psychotic patients who are at increased risk when their condition is destabilized by drug "washout" and

placebo. They are at risk whether the drugs are an effective treatment or not because psychotropic drugs are associated with severe withdrawal symptoms.

Carl Elliott described his battle with the university's IRB when he challenged placebo control trials: "Tables were pounded. Faces turned scarlet. Blood pressures soared. Yet the IRB continued to approve many of the trials, over my objections and those of other members of the committee. The hospital administration eventually dissolved the IRB and reconstituted it with new membership."[xxx] Elliott explains that the reason for the explosive reaction was that "everyone's interests were involved" –not just the sponsoring drug company. These trials generated huge income for the hospital and investigators alike, some earning between $500,000 and $1 million a year.

Case 2: Biased Clinical Guidelines:

An investigative report by Jeanne Lenzer[xxxiii] in the British Medical Journal (March 2002) sheds light on the underlying factors that led the American Heart Association to "definitely recommend" a treatment that could cost more lives than the disease itself. In August 2000 the Heart Association promoted alteplase (tPA), manufactured by Genetech, as a treatment for "brain attack." The Association upgraded its recommendation of tPA for stroke, placing it in the class I category. It did so despite the fact that most controlled trials showed that such thrombolytics increase mortality rates in acute ischemic stroke. In it's annual report it described tPA as follows: "A clot-busting drug that helped revolutionize heart attack treatment, tPA holds enormous potential for the treatment of ischemic stroke, which accounts for 70 to 80 percent of all strokes. It is estimated that tPA could be used in 400,000 stroke case per year to save lives, reduce disability and reverse paralysis."[xxxiii]

The Heart Association made its bold recommendation on the basis of a single controlled clinical trial conducted by the National Institute of Neurological Diseases and Stroke (NINDS). Six other randomized studies reached the opposite conclusion. Lenzer reported the following: the NINDS study design ensured a favorable finding for tPA because the patients selected to get tPA had mild stroke scores at baseline compared with patients selected for the placebo arm who had worse strokes. Furthermore, only one fifth of those initially diagnosed were found to have stroke. This, of course put those non-stroke patients at increased risk of harm with no potential benefit. There were two observational studies reaching opposite conclusions. **The Cleveland study found that twice as many patients given tPA died compared with those that did not.**

Most suspicious of all, however, is the refusal by NINDS to reveal the raw data for that single trial. Lenzer's request under the Freedom of Information Act was rejected. Furthermore, the company vigorously opposes a head to head study comparing alteplase to streptokinase for myocardial infarction. Dr. Elliott Grossbard, a Genetch scientist, provided the company's position: "We don't know how another trial would turn out…[another study] may be good for America, but it wasn't going to be a good thing for us."[xxxiv]

The panel of experts who wrote the Heart Association's Clinical Practice Guideline recommending tPA failed to mention the catastrophic results from the Cleveland study. According to the BMJ article, eight of the nine expert panel members had financial ties to the

manufacturer, Genetech. Dr. Jerome Hoffman, the single panel member who did not have ties to Genetech wrote a dissenting opinion that was not even acknowledged by the panel. Hoffman questioned the tPA endorsement in a BMJ article, charging that the NINDS findings were artificially manipulated to exclude 95% of stroke patients.[xxxv]

Lenzer reported that Genetech had contributed over $11 million to the Heart Association and also paid $2.5 million to build the Heart Association a new headquarters. Only after the these financial conflicts of interest became public knowledge, did the Heart Association revise its class I recommendation and withdraw statements that tPA "saves lives."

The Heart Association is hardly unique: a recent report in JAMA[xxxvi] (2002) found that 87% of the authors who wrote treatment practice guidelines in all fields of medicine had financial ties with the pharmaceutical industry. In 1998 the NEJM found that 96% of medical journal authors whose findings were favorable to a product had financial ties to the manufacturer.[xxxvii] As questions have been raised about the value of mammography and other cancer screening recommendations, one grows suspicious that most highly publicized screening campaigns are launched by stakeholders with financial interests in the business. Their recommendations may turn out to be hazardous to public health.

Case 3: Subject selection bias--antidepressant drug trials:

Dr. Thomas Laughren, head of the FDA's psychiatric drug division made the following concessions at a Houston conference (2000): "there is a certain amount of myth" in the claimed efficacy of psychotropic drugs which have shown only marginal effect above placebo. "We don't know how effective they are, only that in clinical trials, they demonstrated somewhat greater efficacy than placebo." He then acknowledged: "there isn't any standard for what effect size is required to get a psychotropic drug on the market….we have never, in my experience, not approved a drug because of a finding that the effect size is too marginal."[xxxviii]

To obtain even a marginal effect above placebo, 60% to 85% of patients who are most likely to be prescribed antidepressant drugs are excluded by the eligibility criteria. That's the finding of a Brown University analysis[xxxix] of 31 antidepressant trials published from 1994 to 1998. Only 15 percent of 346 depressed patients who were evaluated in a Rhode Island hospital psychiatric clinic would have met the eligibility requirements of a standard drug trial. Such a selection process inevitably skews the results, thereby invalidating the published findings and claims about the efficacy of antidepressants. Zimmerman expressed concern: "If antidepressants are, in fact, not effective for some of these large subgroups of depressed individuals, their prescription incurs an unjustifiable exposure of risks and side effects, and alternative treatments need to be considered."

I would also argue that if the patients in clinical trials don't resemble the patients who are later prescribed these drugs—what relevance do the trials have for clinical care?

Case 4: Antidepressant drug efficacy hype:

A report in the April 10, 2002 issue of JAMA by prominent psychopharmacologists who conducted a major government sponsored, [xl] 12 -site, controlled clinical trial comparing sertraline (Zoloft), Hyperricum perforatum (St. John's wort) and placebo. The investigators acknowledged:
"An increasing number of studies have failed to show a difference between active antidepressants and placebo. Many of the presumed factors underlying this phenomenon were carefully attended to in this study, e.g, adherence to quality control by rater training, treatment adherence monitoring, inclusion of experienced investigators, and carefully defined entry criteria. Despite all of this, sertraline failed to separate from placebo on the two primary outcome measures"

Between December 1998 and June 2000, 340 Adult outpatients with major depression and a baseline total score on the Hamilton Depression Scale (HAM-D) of at least 20 were recruited and randomly assigned to receive (900 to 1500 mg) St. John's wort, (50 to 100 mg) Zoloft, or placebo for 8 weeks. Responders at week 8 could continue blinded treatment for another 18 weeks. The results of this trial states: "on the 2 primary outcome measures, neither [Zoloft] nor [St. John's wort] was significantly different from placebo." Full response occurred in 31.9% of the placebo-treated patients vs 23.9% of the [St John's]–treated patients and 24.8% of [Zoloft]-treated patients."

Clearly a dual dilemma faces those who are invested in promoting psychopharmacolgy: if they admit that the drugs don't really work, then placebo-controlled trials are ethically justified. However, absent a demonstrable benefit of the drugs, it is unethical to expose patients to the known side effects and the potential long-term risks of harm. But such an acknowledgement would undercut the financial interests of the pharmaceutical industry and all of the stakeholders who depend on corporate largesse. The prominent psychiatrists, whose names are too numerous to be listed at the head of the JAMA article, found a way to spin the negative results of the trial. In their conclusion they ignore their own findings, namely, that neither the antidepressant drug, Zoloft, nor St. John's wort were more effective than placebo. Indeed, placebo may have an edge. In their conclusion the investigators pretend that Zoloft was not part of the 3-arm trial: "This study fails to support the efficacy of *H perforatum* in moderately severe major depression."

An accompanying JAMA editorial by Dr. David Kupfer,[xli] past president of the American College of Neuropsychopharmacology, also puts a spin on the findings:
"The current study on the use of St John's wort in the treatment of MDD is the second one within a year to conclude that St John's wort is not effective. These trials were conducted because, even though St John's wort is widely used for the treatment of major depression and depressive symptoms, its efficacy has not been clearly established…"

How could these prominent leaders of psychiatry draw a conclusion that contradicts the study findings? In compliance with JAMA's conflict of interest disclosure policy, a long list appends the article disclosing some of the authors' financial ties to industry —it speaks for itself.

A troubling question arises: **Why did the editors of JAMA fail to seek an independent evaluation of the research findings? Why did JAMA select a psychiatrist whose**

financial ties include membership on the advisory board of Pfizer, the drug company whose product was being reviewed? [xlii]

Case 5: Undisclosed negative data:
An editorial in the British Medical Journal by Richard Smith, "Maintaining the Integrity of the Scientific Record,"[xliii] stated: "We editors of medical journals worry that we sometimes publish studies where the declared authors have not participated in the design of the study, had no access to the raw data, and had little to do with the interpretation of the data. Instead the sponsors of the study –often pharmaceutical companies—have designed the study and analyzed and interpreted the data. Readers and editors are thus being deceived."

Even when a legitimate physician who does not have financial conflicts of interest reviews a study, there is no assurance that the process has not been corrupted. Here is an example: in 2001, Dr. Michael Wolfe was asked to write an editorial in JAMA about the findings of a six - month study testing the arthritis drug, Celebrex, on more than 8,000 patients. [xliv] The editors sent him the manuscript reporting indicating they were anxious "to rush the findings into print." Based on the data reported in the manuscript, Wolfe wrote a favorable review. When he later saw the complete data—as a member of an FDA advisory panel-- he was "flabbergasted." To his embarrassment he discovered that the study had actually been a year long, and when all the data was evaluated, Celebrex offered no proven safety advantage over two older drugs in reducing the risk of ulcers. He also learned that the study's 16 authors included faculty members of eight medical schools—they were all employees of the manufacturer, Pharmcia, or paid consultants. JAMA's editor, Catherine DeAngelis, is quoted in the Washington Post, saying: "We are functioning on a level of trust that was, perhaps, broken."[xliv] Peer review and the integrity of medical guidelines and the scientific literature have all been corrupted by the corrosive influence of industry.

Case 6: The 1997 "pediatric rule" puts children's lives at risk:
Children are being sought to serve as "risk bearing subjects" to risk their lives to test drugs. For example, the FDA approved a pediatric trial exposing 100 children to Janssen Pharmaceutica's heartburn drug, Propulsid.[xlv] FDA approved the trial and allowed babies to be enrolled even after the drug had been linked to sudden deaths. The babies who were recruited were diagnosed with gastroesophageal reflux—a condition hardly considered life-threatening. Doctors say that most babies outgrow the problem by their first birthday. Among the casualties was a 9-month old infant, Gage Stevens. He was recruited by researchers at the University of Pittsburgh. According to press reports the parents only learned about the risks associated with Propulsid from an Associated Press report AFTER their baby was dead.

The LA Times reported that Propulsid's danger to the heart was identified as early as January 1995, when FDA's senior gastrointestinal expert informed Janssen executives that recent adverse-reaction reports showed their drug was prolonging the QT interval, perhaps resulting in deaths. The British Medicines Control Agency (BMCA) had warned against any use of Propulsid in infants since 1998, and cautioned against prescribing it to children up to age 12. The consent form given to the parents falsely indicated that the FDA had approved Propulsid for children. The parents said the doctor conducting the clinical trial was adamant that Propulsid was the best treatment for their child. The parents said they would never have

consented, had they known of the previous deaths. The mother was quoted by CBS News, exclaiming: "It's like giving you chemotherapy for a toothache…the benefits just don't outweigh the risks. I mean, it's reflux! It's not something that's (going to kill him)."[xlvi] The final blow was delivered when the baby's parents learned from the autopsy report that Gage's esophagus did not show any signs of "significant inflammation or other hallmarks of gastroesophageal reflux."[xlvii] In other words, the baby didn't have the condition for which he was entered as a subject into a fatal clinical trial.

A spokesman for Janssen (a Johnson & Johnson subsidiary) indicated that the company did not promote Propulsid for use by children. However, the LA Times reported, the company acknowledged that it did make two "educational grants" to the North American Society for Pediatric Gastroenterology and Nutrition. The society's literature advised doctors that Propulsid could be used safely and effectively in children.
FDA did not pull the drug off the market even as the death toll rose. In December 2000, the LA Times reported that overall Propulsid has been cited as a suspect in 302 deaths. FDA administrators now concede that the agency failed to contain Propulsid's fatal risk. In comments to an FDA advisory committee in June 2000, FDA's Dr. Florence Houn said: "The labeling probably was not effective." In the end, it was not government intervention that forced Janssen to stop marketing Propulsid in the U.S., it was litigation. I question the wisdom of a policy that encourages the use of children in drug trials BEFORE the safety and efficacy of the drugs have even been established in adults.

Case 7: Children exposed to risks in psychotropic drug trials:

Psychotropic drugs are being tested in children despite the acknowledged risks of harm. Psychotropic drugs are advertised as normalizing a "chemical imbalance" in the brain. In fact, they do the opposite: they induce profound changes in the central nervous system with demonstrable physical and neurological impairments.[xlviii] Dr. Steven Hyman, former director of NIMH, an expert on the mechanisms by which psychoactive drugs work, explained that, whether abused or prescribed, the mechanisms by which psychoactive drugs work are the same.[xlix] Hyman stated that antidepressants, psychostimulants, and anti-psychotics created "perturbations in neurotransmitter function."[l] The drugs' severe adverse side effects are symptoms of the drugs' disruptive effect on the neurotransmitter system and on brain function.

In 2001 Dr. Benedetto Vitiello, NIMH's director of Child and Adolescent Treatment and Preventive Interventions Branch acknowledged the impact of FDAMA: "pediatric psychopharmacology has recently seen an unprecedented expansion…clinical trials in youths has more than doubled in the last few years."[li] Indeed, children as young as three are being recruited to test mind-altering drugs that may affect their developing brain. Parents are being offered financial inducements to volunteer their children for drug trials. The foremost problem with prescribing or testing psychotropic drugs for children is the absence of any objective criteria for diagnosing children with pathological behavioral problems to justify pharmacologic intervention. Vitiello acknowledged "diagnostic uncertainty surrounding most manifestations of psychopathology in early childhood."[lii] Vitiello also acknowledged the possibility of long-term harm: "The impact of psychotropics on the developing brain is largely

unknown, and possible long-term effects of early exposure to these drugs have not been investigated."

Eli Lilly's highly touted new anti-psychotic, Zyprexa,[liii] reveals much about the collision between corporate interests and the health and safety of children. In clinical trials averaging 6 weeks, Zyprexa was tested in 2,500 adults. The drug was linked to serious, in some cases life-threatening side effects requiring hospitalization in 22% of those tested.[xxviii]Acute weight gain of 50 to 70 lbs is usual, and with it the increased risk of diabetes. FDA data (under FOIA) reveals a 65% drop out rate, and only 26% favorable response. **During those 6 week clinical trials there were 20 deaths, of which 12 were suicides.**[liv] David Healy, who found a suicidal link to antidepressants (Selective Serotonin Reuptake Inhibitors) in his research says, as far as he can establish, the data from these trials "demonstrate… a higher death rate on Zyprexa than on any other antipsychotic ever recorded." [lv] In 2000, FDA approved Zyprexa for short- term use only, in bi-polar patients.[lvi]

Yet, children aged six to eleven were recruited for clinical trials to test the drug. According to their published report, UCLA investigators tested Zyprexa on children who were not even diagnosed as having schizophrenia. The children were diagnosed as having a variety of questionable psychiatric disorders, including ADHD.[lvii] According to the published report, all the children in the trial experienced adverse effects, including sedation, acute weight gain, and akathisia (restless agitation). The trial was terminated less than six weeks after it had begun.

Controversy surrounds a Zyprexa trial at Yale University. In that experiment, 31 youngsters aged 12 to 25 who have not been diagnosed with any psychiatric illness are being exposed to the drug for one year. The stated rationale given by the researchers (who are under contract with he sponsor) is their speculation that these children may be "at risk" for schizophrenia. Since there are, as yet, no objective tests or biological markers for the illness – they hypothesize without evidence, merely on the basis of conjecture. The shaky basis for their conjecture is that assumption that the children may develop schizophrenia because one of their siblings has been diagnosed with the disorder.

The risk of schizophrenia for the general population is 1%. For siblings the risk increases from 2% to 15% - in other words there is 85% likelihood that these children will never develop schizophrenia.

Given the absence of scientifically accurate tools for interpreting psychiatric symptoms, psychiatrists cannot as yet accurately diagnose schizophrenia much less predict which children will get it. **Is it ethical to expose healthy children to risks of drug- induced pathology on such speculation?** The Wall Street Journal aptly noted that such a study "raises the question of whether the drug companies are mainly interested in "creating" a new illness that requires drug treatment."

Conflicts of interest in clinical trials result in deadly medicine:

Conflicts of interest have corrupted the soul of the American university, the ethics of medicine, the integrity of the scientific record, and the safety of patients who serve as human subjects in pre- and post-marketing clinical trials. Adverse drug reactions in FDA-approved

drugs are the leading cause of death in the United States.[ii], [iii] The JAMA report advises physicians against prescribing new drugs "unless they represent an important medical advance" because newly approved drugs are likely to be unsafe—even lethal. The JAMA report corroborated the findings of the LA Times earlier report: in some cases FDA approved new drugs despite pre-marketing evidence indicating potential danger. In his editorial in JAMA, FDA's Dr. Robert Temple attempts to disavow agency responsibility, while acknowledging: "Premarketing trials in a few thousand (usually relatively uncomplicated) patients do not detect all of a drug's adverse effects…and sometimes the postmarketing discoveries cause the drug to be withdrawn."[lviii]

Why did the FDA's track record of protecting the public from unsafe drugs worsen since 1993? The answer is undue corporate influence and a tainted drug testing and approval process that has compromised the safety of both clinical trial subjects and patients in clinical care. The absence of independent, third- party reviewers has undermined the safety of the drug development and approval process. A tainted process has led the FDA to approve deadly drugs that killed patients while enriching those drugs' manufacturers. The LA Times reported that seven lethal drugs that were ultimately withdrawn between 1997 and 2000, generated $5 billion in sales. It remains to be seen how the American public will react to the revelation that new drugs are less safe than old drugs. How will Americans respond to the revelation that when they take a new, FDA-approved drug, they are essentially testing the drug's safety? Public trust is not likely to be restored until the integrity of the process and the institutions is restored through independent unbiased review. When the condition is life-threatening, or when the new drug offers a significant advance over existing treatments, the risks may be justified. But no one should have to die from a heartburn drug or a diet drug.

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[iii] Lazarou J, Pemeranz B, Corey PN. "Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies," JAMA, 1998, 279: 1200-1205. See also, Wood AJ. The safety of new medicines: the importance of asking the right questions. *JAMA.*1999, 281:1753-1754.

[iv] Willman, D. "How a New Policy Led to Seven Deadly Drugs" Los Angeles Dec 20, 2000, Front page, http://www.latimes.com/news/nation/reports/fda/lat_fda001220.htm.

[v] The seven drugs (and the number of suspected deaths they caused) are: Lotronex (5 deaths), Redux (123 deaths), Raxar (13 deaths), Posicor (100 deaths), Duract (68 deaths, including 11 liver failures), Rezulin (391 deaths, 91 liver failures), Propulsid (302 deaths) . The figure is based on adverse drug reaction reports submitted to the FDA which is estimated to reflect 10% of actual adverse drug reactions. See Willman, 2000.

[vi] The five additional drugs withdrawn between 1997 and Aug 2001 are: Raplon, Hismanal, Seldane, Pondomin, and Baycol. See, Willman, D. "Drug Tied to Deaths Is Pulled" Los Angeles Times, Aug 9, 2001, Front page

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[x] Harold Elliott, a psychiatrist at Wake Forest University, quoted by Carl Elliott, Ref 30

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[xiv] Dembner, A. "Drug firms woo doctors with perks: Billions spent in bid to gain brand loyalty" The Boston Globe, 5/20/2001 Front page.

[xv] Stolberg, SG and Gerth, J, "MEDICINE MERCHANTS / Tracking the Doctors, " The New York Times, November 16, 2000, at: http://www.nytimes.com/2000/11/16/science/16PRES.html?printpage=yes. This comprehensive master physician list gives this industry the most powerful marketing tool in the world. "Overall spending on pharmaceutical promotion increased more than 10 percent last year, to $13.9 billion from $12.4 billion in 1998."

[xvi] "Just how tainted has medicine become?" Editorial, The Lancet, Vol. 359, Number 9313, April 6, 2002

[xvii] Public Citizen Report. The Other Drug War: Big Pharma's 625 Washington Lobbyists, July 23, 2001, http://www.citizen.org/congress/drugs/pharmadrugwar.html.

[xviii] Zimmerman, R. "Drug Makers Find a Windfall Testing Adult Drugs on Kids," The Wall Street Journal, Feb 5, 2001.

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University of Illinois, Chicago (involved all Federally supported research); University of Alabama, Birmingham; and University of Texas Medical Branch at Galveston. See OHRP website. Letters of determination. Online at: http://ohrp.osophs.dhhs.gov/detrm_letrs/lindex.html

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[li] Vitiello, B " psychopharmacology for young children: clinical needs and research opportunities," Pediatrics, Oct 2001, Vol. 108 Issue 4, p983, 7p. Quote, p. 987 (estimated).

[lii] Vitiello, quote, p. 983.

[liii] Zyprexa was approved by the FDA in 1996 for adult schizophrenia.

[liv] Whitaker, R. Mad in America, Perseus Books, 2001, p. 281.

[lv] Dr. David Healy, "Testing psychotropic drugs in children," April 30, 2002, see: www.researchprotection.org.

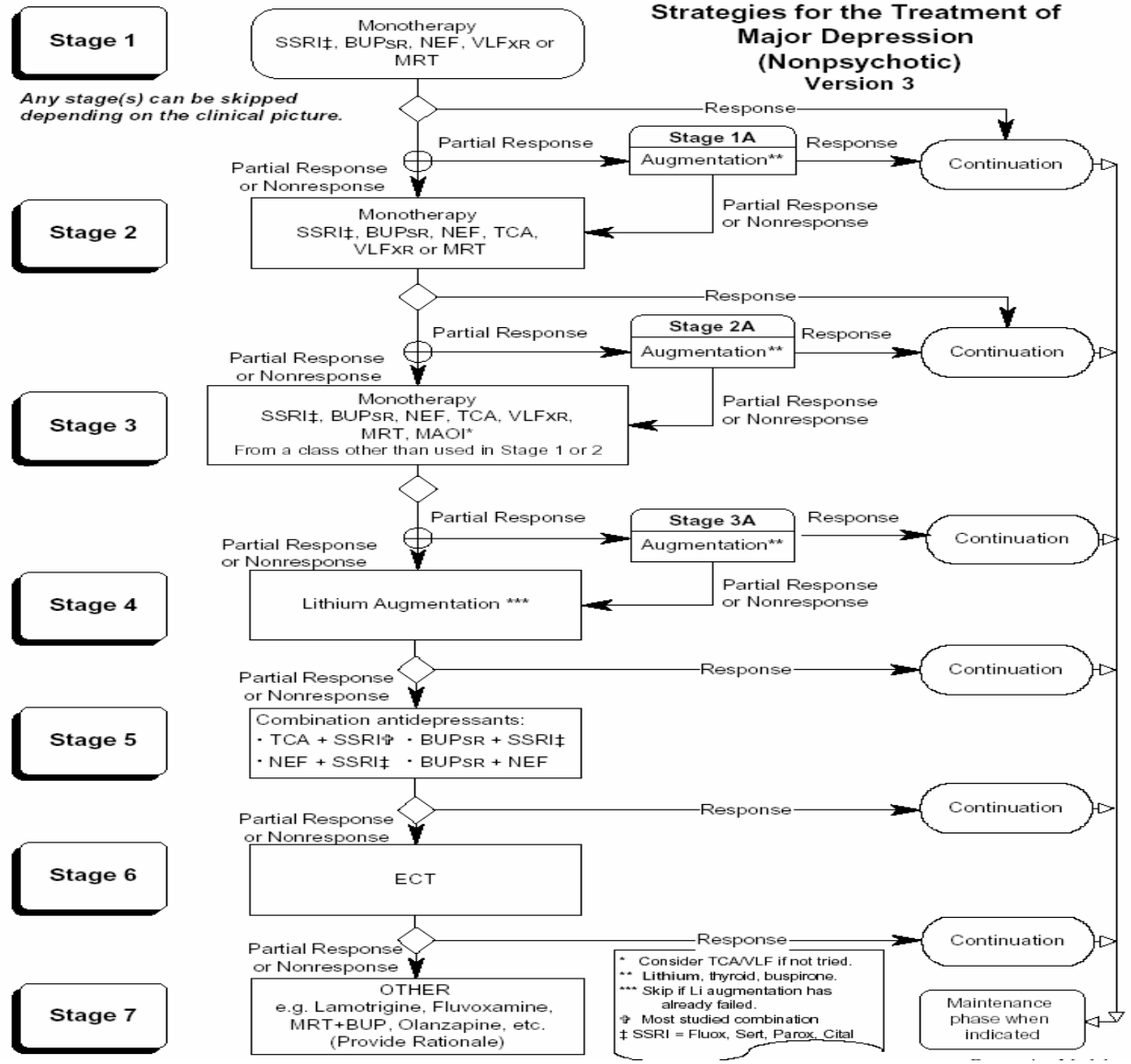
[lvi] Zyprexa (olanzapine) was approved by the U.S. Food and Drug Administration, on March 19, 2000 for "the short-term treatment of acute manic episodes associated with bipolar disorder."

[lvii] See Krishnamoorthy, J. and King, B. H. 1998. Open-label olanzapine treatment in five preadolescent children. Journal of Child and Adolescent Psychopharmacology. 8:107-13.

[lviii] Temple, RT and Himmel, MH "Safety of Newly Approved Drugs Implications for Prescribing," JAMA, Editorial, Vol. 287 No. 17, May 1, 2002, p. 2273.

Attachment # 3

❖ *The Depression Algorithms*



BUP-buproprion, BUP_{SR}-buproprion SR, NEF-nefazodone, VLF_{XR}-venlafaxine XR, MRT-mirtazapine, SSRI-selective serotonin reuptake inhibitor, TCA-tricyclic antidepressant, MAOI-monoamine oxidase inhibitor, ECT-electroconvulsive therapy.

Attachment #4

Drugs of 4 patients subbed without OK

Switch at Fuller mental health clinic aimed at research

By Ellen Barry, Globe Staff, 11/10/2003

A doctor at a state mental health facility changed patients' medications last year so that they would be eligible for a study of a new psychiatric drug, violating basic guidelines for research on human subjects and causing dangerous side effects in a 43-year-old man with schizophrenia, a state investigation has found.

The Disabled Persons Protection Commission uncovered numerous ethical violations at the Solomon Carter Fuller Mental Health Center by Boston Medical Center physicians contracted to treat patients there.

According to a DPPC report, patients' medications were switched without informed consent and without a clear medical need, the changes were made more than two months before the human-studies review boards approved the research protocol, and the patients involved were clearly not eligible under the criteria for the study, which specified that subjects be outpatients.

One of the four patients whose medication was switched, a man who had been stable for 10 years on the drug Clozaril, became so ill and acutely psychotic that he spent months in and out of hospital wards. He was diagnosed with neuroleptic malignant syndrome, a rare, sometimes lethal side effect of medication changes, according to the commission's report.

When the man's health problems grew serious enough to discuss in a Department of Mental Health case conference, a top state mental health official expressed shock that there was a plan to use patients as human research subjects.

"The incident . . . was an egregious series of events that led to a patient experiencing debilitating psychiatric and medical symptoms," wrote Clifford Robinson, Department of Mental Health area director, in a September memorandum about the investigation. The incident "delineated what can happen when a research project is introduced into a clinical environment that is unprepared for it."

The DPPC is an independent state agency that investigates alleged abuse against any disabled person in the Commonwealth. A year ago, Janssen Pharmaceutica was preparing to introduce Risperdal Consta, a two-week injectible form of Risperdal, its drug to treat schizophrenia.

To troubleshoot its instructions for physicians switching patients from oral Risperdal to Consta injections, Janssen asked a number of researchers -- among them Dr. Domenic Ciraulo, Boston Medical Center's chief of psychiatry -- to test the transition on a total of 60 adult patients who were on oral Risperdal, said Carol Goodrich, a Janssen spokeswoman.

Each site would be paid on completion of the trial, Goodrich said. Janssen declined to reveal the amount.

Ciraulo turned to the Fuller as a site for the study, delegating authority to its medical director, Dr. Douglas Hughes. The prospect of a clinical trial at the Fuller promised to bring prestige to a downtown community health center that, situated among many august research centers, "had not been an attractive place for residents and medical students," Hughes later told investigators. "We saw the Consta study as an opportunity."

But as they looked for eligible subjects, one doctor began asking patients about participating in the trial. Last fall, months before review boards for Boston University and the Department of Mental Health had approved the study, the doctor switched four patients to oral Risperdal so they could be enrolled in the trial, the report said.

By late January, one of the four became so confused and delusional that he was sent to the emergency room and frequently needed to be restrained. Months later, when he returned to the Fuller, he was emotionally drained and sensitive to any antipsychotic medication. Known among the staff as an avid and "very knowledgeable" Red Sox fan, the patient was asked by a state investigator for a favorite player on the current team. He mentioned Carl Yastrzemski, who retired from baseball 20 years ago, and had no response to the names "Nomar," "Manny," or "Pedro," the report said.

The clinical trial at the Fuller was halted in February, and no patients there ever received Consta. The other three patients switched to Risperdal suffered no ill effects.

Changing medications for research without the patients' consent is unethical, and it's especially questionable in a state institution, said Dr. Peter Lurie, a medical researcher with Public Citizen's Health Research Group, which monitors research ethics.

Institutionalized patients, like prisoners, may feel pressure to become subjects, and researchers, as well as their institutions, could benefit financially from recruiting subjects, Lurie said. As soon as medication changes were made, the clinical trial was effectively underway, without oversight to protect subjects' rights -- "a flagrant violation of clinical ethics," he said.

The names of doctors involved were deleted from the commission report, but Department of Mental Health officials and Hughes acknowledged their identities.

On Sept. 29, Hughes resigned his position as medical director of the Fuller, explaining in a letter to center director Dr. Mary Louise White that he believed he "share[d] responsibility"

for the change of medication, which he ascribed to a "failure of communication between the principal investigator and the physicians . . . at the SCFMHC."

Hughes, who was listed as one of Boston magazine's "Best Doctors" in 2000, is now associate director of training and medical director of outpatient services at BMC's department of psychiatry. He is a paid speaker for Janssen Pharmaceuticals, and earned more than $30,000 in speaking fees last year, he said.

The attending physician who switched the four patients, Dr. Valentina Jalynytchev, is still working at the Fuller, said Lester Blumberg, chief of staff at the Department of Mental Health.

Jalynytchev did not respond to requests to be interviewed for this article, but told investigators that she believed preparing the patient to receive Consta -- the first injectible form of a newer-generation antipsychotic -- was a "good treatment option," made with "nothing but his best interest in mind."

Both doctors plan to appeal the report's findings, said Ellen Berlin, a Boston Medical Center spokeswoman. Berlin would not say whether either doctor had been disciplined.

The doctors could also be disciplined through the Massachusetts Board of Registration in Medicine, which reviews complaints of misconduct and regulates doctors' licenses to practice medicine. No public information is available about action in this case, said Nancy Achin Audesse, the board's executive director.

In an interview, Hughes said Ciraulo had given him authority over the study at the Fuller, but he had received no training in working with human subjects. The physicians at the Fuller, he said, believed that it was permissible to switch patients' medications so they could be eligible for the study. When staff members complained that the switch was unethical, Hughes said, he asked Ciraulo informally whether informed consent was necessary.

"I said, `Is this OK? Is this a problem? Can we not switch people's medications from one approved atypical [antipsychotic medication] to another?' " Hughes recalled in a telephone interview last week. Ciraulo, he said, told him doctors were free to do that.

Through Berlin, Ciraulo declined requests to be interviewed for this article. But in the state report, Ciraulo was quoted as saying that he had "no clinical responsibility" over Fuller psychiatrists.

His attorney told the Disabled Persons Protection Commission that the Fuller "does not allow [Ciraulo] . . . the authority necessary to deal with situations that may be regarded as his responsibility" as the leader of the study.

Ciraulo, a well-published researcher, has received research grant funding from Janssen Pharmaceutica, served as a Janssen consultant, and received support from Janssen for the department of psychiatry, a Boston University faculty disclosure report said.

Top officials of the Department of Mental Health first learned of the study in February, during a medical staff conference to discuss patients. After the meeting, the area medical director, Dr. David Hoffman, wrote of his shock to discover that a trial was underway: "I was never cc'd on any of this, and I didn't know anything about a drug study at the Fuller involving our patients as human subjects. At that point, I began to realize how problematic this was. The medication switch from Clozaril to Risperdal was a violation of the drug study's protocols."

Within weeks, investigations were underway at the commission, the Department of Mental Health, and Boston Medical Center. The Consta study was terminated by the DMH's Research Review Committee on Feb. 21.

In its review, the Department of Mental Health determined that neither Jalynytchev nor Hughes, her supervisor, intentionally jeopardized patients.

"This was a physician who was poorly informed and poorly supervised about conducting research," said Blumberg, the chief of staff. "Her direct supervisor should have known, if he didn't know."

Instead, Robinson, the Department of Mental Health area director, wrote a blistering memorandum pointing to a "major systems failure" in Boston Medical Center's patient safeguards.

Robinson also criticized the hospital's internal review, which "failed to identify, in any material way, what went wrong, how broad the breakdown was and what could be learned from it." The review did not address the fact that Jalynytchev had switched the medication of four patients, not just the one who was injured, he wrote.

"The absence of a sense of remorse in any document reviewed is another noteworthy commentary on the failure of this process to attend to the harm that resulted," Robinson noted.

Berlin, the BMC spokeswoman, did not respond to the criticism of the internal review.

Boston Medical Center "immediately implemented" a corrective action plan to improve aspects of patient care at the Fuller, according to a press release from the hospital. The two institutions are discussing a range of changes to prevent a recurrence, from appointing a liaison to oversee joint activities to eliminating all research, the release said.

Researchers at the hospital are also being asked to undergo recertification in the ethics of human research. An e-mail widely circulated last week among medical center psychiatrists and psychologists announced that they will have to take monthly quizzes on such issues as federal regulations, internal review-board policies, and conflict of interest. The e-mail was provided to the Globe.

The quizzes, which will be graded, may be a "bureaucratic hurdle," the letter explains, but the Office of Clinical Research sees it as "a necessary step to keep our researchers current on

clinical research information and to provide appropriate protection for the subjects who volunteer for our studies."

Mental health officials could prohibit Boston Medical Center from undertaking clinical trials at state facilities, Blumberg said.

The episode has not jeopardized the mental health agency's contract with the medical center, he said. "It's been a long and positive relationship," he said. "Part of what is so troubling about this is that it's an anomaly in our relationship with them."

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Attachment # 5

http://www.ahrp.org Alliance for Human Research Protection. Extensive files of relevant, well researched material with links to other pertanint sites.

http://www.ama-assn.org/ama/pub/category/4263.html AMA Gift Guidelines

http://www.fda.gov/cder/warn/index.htm FDA warning letters

http://www.followthemoney.org/index.phtml Money in state politics including Pharma

http://bmj.com/cgi/content/full/325/7358/243?view=full&pmid=12153919 Atypicals/Diabetes

http://www.nofreelunch.org Watchdog Group

http://www.opensecrets.org/ Money in Federal Politics

http://www.publicintegrity.org/dtaweb/home.asp The Center for Public Integrity

http://www.adrugrecall.com A side-effects law firm.

http://aspe.dhhs.gov/health/reports/?plain General medical reports

http://www.findarticles.com/cf_0/PI/subject.jhtml?topic=health excellent Health issue search engine

http://oig.hhs.gov/fraud/complianceguidance.html HHS OIG Guidelines

http://www.bio-itworld.com/news/111202_report1519.html FDA Mark McClellan

http://www.cspinet.org/integrity/index.html Excellent site ties Pharma money to groups/individuals

http://www.nytimes.com/2003/07/22/politics/22DRUG.html?th=&pagewanted=print&position drug reimportation article

http://www.fda.gov/cder/warn/index.htm FDA warnings to drug companies

http://www.namiscc.org/Research/2002/AntipsychoticSuicideRisk.htm report on suicide and anti-psychotic drugs

http://www.fda.gov/cber/guidelines.htm FDA Guidance documents

http://www.fda.gov/medwatch/index.html FDA medication safety/adverse reaction site

http://www.citizen.org/hrg Public Citizen medical watchdog group

http://www.namiscc.org/Research/2002/AntipsychoticSuicideRisk.htm report on suicide and anti-psychotic drugs

http://www.researchprotection.org/infomail/0503/10.html Paxil Suicides

www.drugawareness.org

http://www.thejournalnews.com/rtc/27part1.htm psycholeptic drugs and kids

http://www.tribnet.com/news/v-printer/story/1943204p-2053843c.html Pharma money in research

http://education.guardian.co.uk/print/0,3858,4417163-48826,00.html Healy follow-up

http://www.pharmapolitics.com CBC on Healy affair

http://moshersoteria.com Dr Loren Mosher

http://www.socialaudit.org.uk/58092-DH.htm#SSRIs%20&%20WITHDRAWAL Antidepressant withdrawal Healy

http://www.socialaudit.org.uk/58090-DH.htm#ANTIDEPRESSANTS%20AND%20SUICIDE Antidepressant suicide Healy

http://www.socialaudit.org.uk/58000-00.htm#Correspondence Antidepressant debate Healy

http://www.mhmr.state.tx.us/centraloffice/medicaldirector/TMAPover.html TMAP History

http://www.bhicares.org/guidelines.shtml Colorado version of TMAP

http://www.capitol.state.tx.us/tlo/76R/billtext/HB02952I.HTM Texas TMAP legislation

TEXAS LEGISLATION

http://www.capitol.state.tx.us/cgi-bin/tlo/textframe.cmd?LEG=77&SESS=R&CHAMBER=S&BILLTYPE=B&BILLSUFFIX=00644&VERSION=5&TYPE=B

http://www.capitol.state.tx.us/cgi-bin/tlo/textframe.cmd?LEG=77&SESS=R&CHAMBER=H&BILLTYPE=B&BILLSUFFIX=00772&VERSION=5&TYPE=B

http://www.capitol.state.tx.us/cgi-bin/tlo/textframe.cmd?LEG=77&SESS=R&CHAMBER=H&BILLTYPE=B&BILLSUFFIX=01314&VERSION=5&TYPE=B

http://www.capitol.state.tx.us/cgi-bin/tlo/textframe.cmd?LEG=77&SESS=R&CHAMBER=S&BILLTYPE=B&BILLSUFFIX=00347&VERSION=5&TYPE=B

http://www.capitol.state.tx.us/cgi-bin/tlo/textframe.cmd?LEG=77&SESS=R&CHAMBER=H&BILLTYPE=B&BILLSUFFIX=01094&VERSION=5&TYPE=B

http://www.capitol.state.tx.us/cgi-bin/tlo/textframe.cmd?LEG=77&SESS=R&CHAMBER=H&BILLTYPE=B&BILLSUFFIX=01887&VERSION=5&TYPE=B

http://www.swmed.edu/home_pages/news/algorith.htm

http://www.mcmanweb.com/article-184.htm

http://www.nasmhpd.org/meddir2.htm 1977 TMAP site with references

http://www.washingtonmonthly.com/search.html

http://www.psychiatrictimes.com/p970664.html 1997 journal article with references

http://www.mentalhealth.ucla.edu/webcasting/speakerbios/trivedi.htmlv ties Trivedi & Rush to 1990 AHCPR depression guideline panel

http://www.icmpe.org/test1/journal/issues/v2i3/v2i3abs04.html check out the funding sources that sponsored this TMAP report

Jason Foster FDA advisory urges caution in children's use of antidepressants The Herald October 28, 2003

Gardiner Harris F.D.A. Intensely Reviews Depression Drugs The New York Times October 28, 2003

Marc Kaufman FDA Cautions on Antidepressants and Youth The Washington Post Oct 27, 2003

FDA Issues Public Health Advisory Entitled: Reports Of Suicidality in Pediatric Patients Being Treated with Antidepressant Medications for Major Depressive Disorder (MDD) October 27, 2003

Jeffrey Kluger Medicating Young Minds: Drugs have become increasingly popular for treating kids with mood and behavior problems. But how will that affect them in the long run? The Times Online Oct. 26, 2003

David Davis Losing the Mind: David Oaks and Others in the 'Mad Pride' Movement Believe Drugs Are Being Overused in Treating Mental Illness, and They Want the Abuse to Stop. Los Angeles Times October 26, 2003

Keith Hoeller No proof mental illness rooted in biology Seattle Post-Intellingencer August 29, 2003

Benedict Carey Psychiatry and preschoolers: More young children are being diagnosed with mental ailments and treated with drugs even as doctors grapple with a lack of research. Los Angeles Times June 30, 2003

Gardiner Harris Britain Says Use of Paxil by Children Is Dangerous The New York Times June 11, 2003

SEROXAT Must Not Be Used For Treatment Of Children With Depression Department of Health (UK) Tuesday 10th June 2003

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Sarah Boseley health editor Seroxat warning over risk to young Suicidal feelings may be side effect for under-18s The Guardian Tuesday June 10, 2003

BBC News Children 'should not take Seroxat' June 6th 2003

Sarah Boseley Prozac made librarian kill herself, says psychiatrist The Guardian June 5, 2003

Mary Duenwald Study Says Drug Group Can't Help Alzheimer's The New York Times June 4, 2003

James Tozer Man slashed wrists after two weeks on anxiety pill: Coroner calls for leading anti-depressant to be withdrawn femail.co.uk 2nd June 2003

Tony Harney Prozac Killed My Wife Leeds Today 02 June 2003

Erica Goode Leading Drugs for Psychosis Come Under New Scrutiny The New York Times May 20, 2003

By Eamon Quinn Drugs giant to face Irish Seroxat lawsuits May 26, 2003 The Sunday Business Post

Pfizer Launches 'Zoloft For Everything' Ad Campaign (Parody) The Onion May 14, 2003

Marjorie Wallace Schizophrenia drug claims questioned BBC News May 9, 2003

Sarah Boseley Seroxat maker abandons 'no addiction' claim: Firm agrees to alter leaflet to patients after complaints The Guardian May 3, 2003

Randy Dotinga Mental Illness Strikes Babies, Too HealthScoutNews April 16, 2003

Geeta Anand and Thomas M. Burto Drug Debate: New Antipsychotics Pose a Quandary For FDA, Doctors Wall Street Journal April 11, 2003

Reuters Drug argument embroils psychiatrists, pharm cos: Critics question whether medication trumps other treatments March 24, 2003

Vera Hassner Sharav 18 Deaths Linked to drug - Serzone Removed from European market, not US. ALLIANCE FOR HUMAN RESEARCH PROTECTION (AHRP) Jan 17, 2003