IN THE SUPREME COURT FOR THE STATE OF ALASKA

LAW PROJECT FOR PSYCHIATRIC RIGHTS, Inc., an Alaskan non-profit corporation, Appellant, vs. STATE OF ALASKA, et al., Appellees.	Supreme Court No. S-13558 Superior Court No. 3AN 08-10115CI

APPEAL FROM THE SUPERIOR COURT
THIRD JUDICIAL DISTRICT AT ANCHORAGE
THE HONORABLE JACK W. SMITH, PRESIDING

APPELLANT'S EXCERPT OF RECORD
VOLUME 2 OF 3

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The New York Times
nytimes.com

November 25, 2008

Research Center Tied to Drug Company

By GARDINER HARRIS

When a Congressional investigation revealed in June that he had earned far more money from drug makers than he had reported to his university, Dr. Joseph Biederman, a world-renowned child psychiatrist, said that his "interests are solely in the advancement of medical treatment through rigorous and objective study."

But e-mails and internal documents from Johnson & Johnson made public in a court filing reveal that Dr. Biederman pushed the company to fund a research center at Massachusetts General Hospital whose goal was "to move forward the commercial goals of J&J," the documents state. The documents also show that Johnson & Johnson wrote a draft summary of a study that Dr. Biederman, of Harvard University, was said to author.

Dr. Biederman's work helped to fuel a 40-fold increase from 1994 to 2003 in the diagnosis of pediatric bipolar disorder and a rapid rise in the use of powerful, risky and expensive antipsychotic medicines in children. Although many of his studies are small and often financed by drug makers, Dr. Biederman has had a vast influence on the field largely because of his position at one of the most prestigious medical institutions in the world.

Johnson & Johnson manufactures Risperdal, also known as risperidone, a popular antipsychotic medicine. More than a quarter of Risperdal's use is in children and adolescents.

Last week, a panel of federal drug experts said that medicines like Risperdal are being used far too cavalierly in children and that federal drug regulators must do more to warn doctors of their substantial risks. Other popular antipsychotic medicines, also referred to as neuroleptics, are Zyprexa, made by Eli Lilly; Seroquel, made by AstraZeneca; Geodon, made by Pfizer; and Abilify, made by Bristol-Myers Squibb.

Thousands of parents have sued Johnson & Johnson, AstraZeneca and Eli Lilly, claiming that their children were injured after taking the medicines, whose risks the companies minimized, the parents claim. As part of the suits, plaintiffs' attorneys have demanded millions of documents from the companies. Nearly all of those documents have been provided under judicial seals, but a select few that mentioned Dr. Biederman became public after plaintiffs attorneys sought a judge's order to require Dr. Biederman to be interviewed by plaintiff attorneys under oath.

In a motion filed two weeks ago, attorneys for the families argued that they should be allowed to interview Dr. Biederman under oath because his work has been crucial to the widespread acceptance of pediatric uses of antipsychotic medicines. To support this contention, the lawyers included more than two dozen documents, including e-mails from Johnson & Johnson that mentioned Dr. Biederman. That interview request has yet to be ruled upon.

The documents offer an unusual glimpse into the delicate relationship that drug makers have with influential doctors. In one November 1999 e-mail, John Bruins, a Johnson & Johnson marketing executive, begs his supervisors to approve a $3,000 check to Dr. Biederman in payment for a lecture he gave at the University of Connecticut.

“Dr. Biederman is not someone to jerk around,” Mr. Bruins wrote. “He is a very proud national figure in child psych and has a very short fuse.”

Mr. Bruins wrote that Dr. Biederman was furious after Johnson & Johnson rejected a request that Dr. Biederman had made to receive a $280,000 research grant. “I have never seen someone so angry,” Mr. Bruins wrote. “Since that time, our business became non-existant (sic) within his area of control.”

Mr. Bruins concluded that, unless Dr. Biederman received a check soon, “I am truly afraid of the consequences.”

A series of documents described the goals behind establishing the Johnson & Johnson Center for the study of pediatric psychopathology, for which Dr. Biederman still serves as chief.

A 2002 annual report for the center stated that its research must satisfy three criteria: improve psychiatric care for children, have high standards and “move forward the commercial goals of J&J,” according to court documents.

“We strongly believe that the center’s systematic scientific inquiry will enhance the clinical and research foundation of child psychiatry and lead to the safer, more appropriate and more widespread use of medications in children,” the report stated. “Without such data, many clinicians question the wisdom of aggressively treating children with medications, especially those like neuroleptics, which expose children to potentially serious adverse events.”

A February 2002 e-mail from Georges Gharabawi, a Johnson & Johnson executive, stated that Dr. Biederman approached the company “multiple times to propose the creation” of the center. “The rationale of this center is to generate and disseminate data supporting the use of risperidone in” children and adolescents, the e-mail stated.

Johnson & Johnson gave the center $700,000 in 2002 alone, documents show.

A June 2002 e-mail from Dr. Gahan Pandina, a Johnson & Johnson executive, to Dr. Biederman included a brief abstract of a study of Risperdal in children suffering disruptive behavior disorder. The study was intended to be presented at the 2002 annual meeting of the American Academy of Child & Adolescent Psychiatry, the e-mail stated.

“We have generated a review abstract, but I must review this longer abstract before passing this along,” Dr. Pandina wrote. One problem with the study, Dr. Pandina wrote, is that the children given placebos and those given Risperdal both improved significantly, “so, if you could, please give some thought to how to handle this issue if it occurs.”

The draft abstract that Dr. Pandina included in the e-mail, however, stated that only the children given Risperdal improved, while those given placebos did not. Dr. Pandina asked Dr. Biederman to sign a form listing himself as author so the company could present the study to the conference, according to the e-mail.

"I will review this morning," Dr. Biederman responded, according to the documents. "I will be happy to sign the forms if you could kindly send them to me." The documents do not make clear whether Dr. Biederman approved the final summary of the brief abstract in similar form or asked to read the longer report on the study.

Drug makers have long hired professional writers to compose scientific papers and then recruited well-known doctors to list themselves as authors. The practice, known as ghostwriting, has come under intense criticism recently, and medical societies, schools and journals have condemned it.

In June, a Congressional investigation revealed that Dr. Biederman had failed to report to Harvard at least $1.4 million in outside income from Johnson & Johnson and other makers of antipsychotic medicines.

In one example, Dr. Biederman reported no income from Johnson & Johnson for 2001 in a disclosure report filed with the university. When asked by Senator Charles E. Grassley, a Republican of Iowa, to check again, Dr. Biederman said he received $3,500. But Johnson & Johnson told Mr. Grassley that it paid Dr. Biederman $58,169 in 2001.

On Monday, David J. Cameron, a Harvard spokesman, said the university was still reviewing Mr. Grassley's allegations against Dr. Biederman. He added that they had not seen the drug company documents in question and that the university is not directly involved in the child psychiatry center at Massachusetts General Hospital.

Calls to Dr. Biederman were not returned. Johnson & Johnson did not immediately comment or make executives available for comment.

From: Cote, Christine [JANUS]
Sent: Tuesday, February 05, 2002 12:55 PM
To: Gharabawi, Georges [JANUS]; Vergis, Janet [JANUS]; Parish, Irene [JANUS]
Cc: Mahmoud, Ramy [JANUS]; Pandina, Gahan [JANUS]; Kovacs, Clare [JANUS]; Deloria, Carmen [JANUS]; Kalmeijer, Ronald [JANUS]
Subject: RE: Janssen-MGH Child and Adolescent Bipolar Center - Dr Joe Biederman

I am able to do the 14th March and will block out the day ,,I am leaving for a big trip on the 28th so unless it was early am and local I would not be able to do 28th

Dr. Christine Cote
V.P. Medical Affairs
Janssen Pharmaceutica, Inc.
Tel: 609-730-3677
Fax: 609-730-3406

-----Original Message-----
From: Gharabawi, Georges [JANUS]
Sent: Tuesday, February 05, 2002 7:42 AM
To: Vergis, Janet [JANUS]; Cote, Christine [JANUS]
Cc: Mahmoud, Ramy [JANUS]; Pandina, Gahan [JANUS]; Kovacs, Clare [JANUS]; Deloria, Carmen [JANUS]; Kalmeijer, Ronald [JANUS]
Subject: Janssen-MGH Child and Adolescent Bipolar Center - Dr Joe Biederman

Subject
Invitation to a meeting with Prof Biederman and his team at Janssen on March 14 or March 28, 2002 (date pending your approval) to agree on the main deliverables from the Janssen/MGH Center for Child and Adolescent Bipolar Disorders and prioritize the different activities - Your attendance of the 1st hour is needed.

Background
Dr Biederman is the pioneer in the area of C&A Bipolar Disorders. He approached Janssen multiple times to propose the creation of a Janssen-MGH center for C&A Bipolar disorders. The rationale of this center is to generate and disseminate data supporting the use of risperidone in this patient population. I met with Dr Biederman in August 2001 and discussed with him the feasibility of this center and agreed that, should Janssen decide to support it, the main focus will be on 2 topics: 1) Diagnostics, including the creation of a screening/diagnostic tool to train clinicians (Pediatricians and General Psychiatrists) on how to diagnose C&A BPD, use of genetics and Neuro-imaging techniques to recognize C&A BPD and the different variants of the disorders and 2) Therapeutics, including short and long-term outcomes of the management of C&A BPD with risperidone including the long-term prophylactic effect on drug abuse. Following a number of internal discussions within the Brand team and with Janet, it was decided to 1) explore the feasibility of involving other J&J companies that would be interested in participating in the center and share the financial support and 2) fund the center pending the submission of a 5-year plan of deliverables including retrospective analyses and prospective exploratory research.

Current status
* In a number of meetings with McNeil and OMP, it was agreed that there was a need for all J&J companies to act as partners and share this research, data generation and dissemination opportunity. Further, it was agreed that the 3 teams should meet and elaborate a plan that would ultimately include research initiatives on combination therapies.
* A Risperdal Reanalyses, Research and Publication grid was produced by Dr biederman's team. The grid includes proposed deliverables over the upcoming 5 years starting from 2002. It is planned to produce similar grids for the J&J sister companies over the next 3-6 months.
* The Risperdal Brand team agreed to fund the center for the year 2002. 500KUS$ were paid and assigned to the

year 2002.

Next Steps
We recently organized a meeting with Dr Biederman including the marketing group from McNeil in order to discuss the next steps. We invited Dr Biederman and his group to an HOV at Janssen Titusville. This meeting will involve, in addition to Dr Biederman's research team, the Risperdal, REDACTED teams with the objective of elaborating a full research plan for the years 2002-2007 including a reanalyses and publications plan.

Proposed agenda
- Opening address (J&J)
- Background on Child and Adolescent Bipolar Disorders- A clinical and research perspective (Dr Joe Biederman)
- Breakout session:
- Epidemiology and genetics of C&S BPD
- Diagnosis: Reanalyses, validation and publication of screening tools
- Neuro-imaging plans, publication plan
- Reanalyses of the existing Risperdal data, publication plan
- Prospective short and long-term studies

Christine and Janet, Your presence, at least at the first part of the meeting is highly desirable and would allow us to continue positioning Janssen as a major partner in the area of C & A psychopharmacology. Further, following your approval of the proposed date, we will extend the invitation to S. Spielberg but will eet with him first.

Sincerely

Georges

Georges Gharabawi M.D.
Janssen Pharmaceutica Inc.
Tel (609) 730 3277
e-mail: ggharaba@janus.jnj.com

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SUPERIOR COURT OF NEW JERSEY
LAW DIVISION - MIDDLESEX COUNTY

In re: Risperdal/Seroquel/Zyprexa Litigation Case Code 274

Alma Avila, as next friend of Amber N. Avila, an individual case

v.

Johnson & Johnson Company, Janssen Pharmaceutica Products, L.P., a/k/a Janssen, L.P., et al.

Civil Action
Docket Number
L-6661-06

Video Deposition of Joseph Biederman, M.D.
Friday, February 27, 2009
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Also Present:
George Döbrentey, Videographer
on behalf of Hogan & Hartson

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Q. Are these the side effects associated with Risperdal?
A. Yes.

Q. The next point -- And, by the way, the use of Risperdal in the pediatric population was off-label at this time, wasn't it?
A. Yes.
Q And what does that mean?
A. Off-label means that the medicine is used by physicians that is not specifically approved by the FDA for that use.
Q So it means a drug is being used for something that the FDA hasn't approved it for. Right?
A. Yes.
Q. Okay. And so you were proposing to do research on off-label uses of Risperdal Right?
A. I was proposing to do research on the efficacy and safety of risperidone relative to other

medicines.
Q. In an off-label population. Right?
A. The use in children at that time was off-label and two years ago has been approved.
MR. TRAMMELL: Objection, nonresponsive.

Q. One of the things you wanted to study was the efficacy of Risperdal in preschoolers. Right?
A. Yes.
Q. And how old are preschool kids?
A. Could you repeat the question?
Q. How old are preschool kids?
A. Four to six.
Q. And what age range was Risperdal approved for at that time?

A. It was approved, to my recollection, for individuals older than 18.

Q. So what you're saying is there's evidence that is accumulating that kids or that pediatric bipolar disorder onsets in these preschool kids, who I assume are three and four years old?
A Usually four to six.
Q Okay. So pediatric bipolar disorder onsets in four- to six-year-old kids coupled with the fact that the drugs are widely used, despite that, there's not a lot of data on efficacy. Right?
MR. PECK: Object to form. It's a compound question.
A. On efficacy and safety, yes.
Q. And so basically what you mean is, what you're trying to say is that we have kids suffering

from this disease or it's possible that they're suffering from this disease in the preschool years, the drug is used a lot in these kids, we ought to have some data to instruct doctors about whether it's safe and effective to be doing this?
A. Yes.

Q Who makes Wellbutrin?
A. Bupropion was initially made by Glaxo or Wellcome, Burroughs Wellcome, and then when they merged I don't know who owns Wellbutrin. I think GlaxoSmithKline, I think.

Q. Did Janssen fund any studies that you did to study other companies' drugs?

Q. And the purpose of the scientific process is what?
A. You are in a study, you are testing, you are addressing a question, you are testing a hypothesis. You subject the data to statistical analysis to examine whether the findings are chance or not likely to be chance, and you draw conclusions based on your findings.
Q. It is a search for the greatest truth that can be obtained. Correct?
A. It is a method to investigate.
Q. And the method to investigate that you use requires that you be very precise. Correct?
A. As precise as the field allows.
Q. And you are a very precise individual, are you not?
A. I am.
Q. You are a very deliberate individual, are you not?
A. I am not sure what you mean by that.
Q. Well, what you do is a result of your intentional conduct?
A. Well, what I do is I ask questions that I have about how to improve the life of the people under my care. So all my research is based on

trying to understand the diseases that the children that are under my care are afflicted and how to better approach them therapeutically, with medicines and with psychosocial treatments.
Q. Now, you've already told us that you consider yourself a world-renowned scientist. Correct?
A. It is not what I consider myself. It is what others consider myself.
Q So you're familiar with your reputation across the world. Correct?
A. I am familiar with my reputation.
Q. And your reputation is that you are a specialist in the field of bipolar disease in children?
A. I am a specialist in pediatric psychopharmacology.
Q. Which includes bipolar mania?
A. It is one of many conditions that afflict children.
Q. Well, I thought you indicated to me yesterday -- and correct me if I'm wrong -- that your two subspecialties within the field of psychopathology are bipolar mania and ADHD.
A. I indicated that that's the predominance

of my scientific work, not the only work that I do or the only type of research that I do.
Q. When the Grassley committee hearing or the Grassley investigation was initiated, you were the subject of newspaper comments, were you not?
A. I was.
Q. And I have today a copy of a page from The New York Times, November 25, 2008. Was that approximately when this issue came to the public's eye? Approximately.
A. November 2008, I think The New York Times published e-mails that you released to the press from some attempt to quash the subpoena. This is what I think happened in the paper in 2008. There was an article, there are articles before that, but the 2008 I believe is related to e-mails that you released to the press.
Q. You think I released something to the press?
A. Obviously somebody released.
Q. Well, you said "you" and you looked at me. Do you think I released it?
A. I am using the "you" generically.
Q. Okay. So the "you" could be anybody in the world. Right?

A. No, could be somebody related to this case.
Q. Well, who?
A. I don't know. It's not -- I have no access to that information.
Q. Well, the purpose for this is that in this document, and I only have one copy but I will represent to you that I'm going to read it accurately, it says "Dr. Joseph Biederman, a world-renowned child psychiatrist." And that's how people see you, do they not?
A. Yes.
Q. Would you consider yourself the leading psychiatrist in the world for the treatment of bipolar mania or bipolar disease in children?
A. One of the leaders.
Q. One of the leaders?
A. (Witness nodded.)
Q. Are you a football fan?
A. Fair-weather.
Q. Fair-weather. We had a football coach in Texas named Bum Phillips. You ever hear of Bum Phillips?
A. No.
Q. His son Wade Phillips is actually the

opposite." That research is not forthcoming.
So the people, the mostly vocal critics are people that have not done any critical body of research disputing the findings. They're only saying I don't like it, which in science is not the same. You're not having the same interlocutors by saying I don't like that. You can say it about a hamburger or a hotdog but not in science. In science in order for you to say that this is not true, you need to show equal amount of work that shows the opposite result, and that's the dispute. Today pediatric bipolar illness is accepted by the practicing community.
MR. FIBICH: Object to that as being nonresponsive.
BY MR. FIBICH:
Q. Do you disagree with this statement: The diagnosis of pediatric bipolar disease is controversial?
A. I disagree. The controversy is about how to best define, what are the best ingredients. That's the controversy, not that a group of children that are very sick with high levels of morbidity and disability exist. That controversy is over. The controversy today is about how to best define it.

That's the controversy.
MR. FIBICH: Mark this as the next exhibit. And we're skipping one but I'll come back to it.
MR. BURNEY: So I'm sorry. The number on this is 19 or 20? You said the next exhibit but we're skipping one.
MR. FIBICH: Hold on.
THE WITNESS: This is 18.
MR. FIBICH: This is going to be 20.
MR. BURNEY: This is going to be 20? Okay.
(Biederman Deposition Exhibit 20 marked for identification.)
BY MR. FIBICH:
Q. Let me show you what I've marked as Exhibit 20, Dr. Biederman.
A. Mm-hmm.
Q. And this is an article out of The Washington Post, February 2005. Do you see that?
A. Mm-hmm.
Q. And if you would turn to page 3 and under the heading Very Disturbed Children, read the comments that are attributed to you, sir.
A. Mm-hmm.

Q. Did you talk to The Washington Post?
A. I don't remember who I talked to, but apparently I talked to this person.
Q. The comments that are contained in the first two paragraphs are comments of yours and you were quoted accurately. Correct?
A. This is not a quote, this is an interpretation of what I said.
Q. Is it a correct interpretation of what you said?
A. I said the same as I said to you. I did not compare myself to Galileo. I said that Earth was once flat. The reporter is not quoting me here. It is her interpretation. She could have said that I am comparing myself to God. This is her interpretation of what I said. I said that Earth was once flat. This is what I said.
Q. Well, why didn't you compare yourself to God?
A. Because I am not God. I am saying that the interpretation of my statement is her interpretation.
Q. Is her interpretation of your statement an accurate statement?
A. I said that Earth was once flat. I did

not compare myself to Galileo.
Q. Sir, I'm asking you, what she says is "Joseph Biederman, a professor of psychiatry at Harvard and one of the most forceful advocates of the aggressive treatment of preschoolers, thinks bipolar disorder has been severely underdiagnosed in children." Is that a correct statement?
A. That is correct. That's a quote.
Q. Okay, that's a quote. And the next statement is "He likens the criticism he has encountered to the outrage that greeted Galileo's challenge to the notion that the Earth was flat." Is her interpretation of what you said accurate? Yes or no.
A. Yes, it was accurate.
Q. And do you agree that you are one of the most forceful advocates of the aggressive treatment of preschoolers?
A. It is her statement about me.
Q. I didn't ask you if it was her statement about you. I'm asking you if you agree that you are one of the most forceful advocates of the aggressive treatment of preschoolers.
A. I am.
Q. Doctor, what is the purpose of publishing

that you do not consider the research you do to be what is termed clinical research?
A. No, it is clinical research.
Q. You what?
A. It is clinical research.
Q. Okay. There seemed to be some misunderstanding about that.
Now, before we go any further, I'd asked you if you generally understood what was in the label for Risperdal.
A. Yes.
Q. And are you aware that the label contains a statement that the mechanism of action for Risperdal is unknown?
A. Correct.
Q. And what does that mean?
A. It means that the exact way that the risperidone and other medications work in the brain is not fully elucidated.
Q. Well, I'm not interested in other medications. I'm just interested in Risperdal with respect to that question. Okay?
A. Yes, yes.
Q. What it means is we don't know really how it works. Right?

A. Fully. We have some ideas. For example, the prolactin problem that we talked yesterday is due to the effect of risperidone on a particular type of receptors in the dopamine system that are called dopamine 2 receptors. So other mechanisms are not fully known.
Q. Well, basically we know that Risperdal affects the chemistry in the brain. Correct?
A. The hypothesis, the reason that risperidone, Clozaril and others are called atypical neuroleptics is because they exert influences at least in two brain systems. One is dopamine and the other one is serotonin.
Q. And do children's brains develop over time?
A. Children's brain and adults' brain develop over time.
Q. And are there any studies on the long-term effect of giving children Risperdal for any period of time, the safety of that?
A. There are studies today of a few years, not more than a few years' follow-up. When a drug is, say, brought to market there is a requirement that there is at least one or two years of follow-up, so I believe that risperidone has some

type of follow-up data.
Q. You believe so? You don't know so?
A. I do not know for sure. As I told you, I did not participate in the study so I do not know. But that's a standard requirement of the FDA.
Q. And of course if the drug is being used off-label, then the FDA would not have required that type of study. Correct?
A. Physicians use all the time medicines available to them to help their patients off-label. It's a legal activity; it's done all the time; and many of the discoveries in medicine, in psychiatry and other fields occurred through using medications off-label. So off-label is not a bad practice necessarily. Only means that the pharmaceutical company has not yet conducted the clinical study. In the case of risperidone, as you know, the pivotal studies were conducted.
MR. FIBICH: Object to that as being nonresponsive.
BY MR. FIBICH:
Q. What I was asking you was, were there any long-term studies of the effect of Risperdal on children? And you said --
A. To my knowledge we, in our research, we

followed the children that responded to risperidone, our small sample, for a year. So we had some small data on long-term effects.
Q. You have anecdotal evidence from your practice. Correct?
A. No, it's -- Yes, I have anecdotal evidence, but we followed in the studies of risperidone that we conducted, we followed those children that responded and were willing to be followed, we followed them for a year and we collected data.
Q. And my question is the long-term effect. Are you aware of any published data that established the safety of Risperdal on children for a long period of time?
A. The risperidone -- I am not aware, but there is no data on adults either, on long-term effects.
Q. I didn't understand what you said.
A. There is not only absence of long-term data in pediatrics, but there is neither long-term data in adults.
Q. So this is a drug that we don't know how it works and you propose giving it to certain children under the age of six. Correct?

IN THE SUPERIOR COURT FOR THE STATE OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

IN THE MATTER OF:

Plaintiff,

vs.

WB: WILLIAM BIGLEY

Defendant.

Case No. 3AN-08-00493 PR CI

[redacted]

VOLUME II

TRANSCRIPT OF MOTION HEARING

BEFORE THE HONORABLE SHARON GLEASON
Superior Court Judge

Anchorage, Alaska
May 14, 2008
10:17 A.M.

APPEARANCES:

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3AN6308-79
10:17:01
THE COURT: Okay. We are back on record in a case involving Mr. Bigley, who is present here in the courtroom. And we have Mr. Twomey and Mr. Gottstein.
And I received paperwork from you, Mr. Gottstein, yesterday. And in it, it indicated you had not yet received the chart. Has that been remedied, or what is the status there?
MR. GOTTSTEIN: Your Honor, I received -- it was there when I got back from my supreme court oral argument, so yesterday.
THE COURT: All right. And I see a rather lengthy witness list. And I am concerned about the timeframe. So -- and it looks like three are simply to have available for cross examination of the materials you submitted, which I have reviewed; is that correct?
MR. GOTTSTEIN: Yes, Your Honor. I really only have three witnesses I plan to call.
THE COURT: Dr. Jackson, Dr. Hopson, and Camry Altaffer (phonetic)?
MR. GOTTSTEIN: Altaffer.
THE COURT: Altaffer. All right.
Mr. Twomey, are you ready to proceed?

MR. TWOMEY: Yes, Your Honor.
THE COURT: All right. And who would you seek to call first, Mr. Gottstein?
MR. GOTTSTEIN: Dr. Jackson. And her number is area code 910/208-3278.
THE COURT: All right. Thank you.
So did I indicate until noon today we could go, or did I -- is that what I had indicated? Or did I make any indication?
I have to go to an event at noon or there about. So we'll see where we are time-wise. I know it's an important issue for your client, Mr. Gottstein. If we need to find more time in the next couple of days, we can do so. So let's see what progress we can make up until noon.
MR. GOTTSTEIN: You indicated noon.
THE COURT: I did. All right. That was my recollection, but I didn't see it in the log notes. All right.
We are a little late getting started, which was not really my fault, but my reality, anyway.
MR. GOTTSTEIN: Your Honor, I gave the clerk exhibits for this morning.
THE COURT: I have them right here. A through F; is that correct?

MR. GOTTSTEIN: Yes, ma'am. And I gave them to Mr. Twomey.
THE COURT: Mr. Twomey, you have a copy, as well?
MR. TWOMEY: Yes. I received them this morning, Your Honor.
THE COURT: Do I have Grace Jackson on the phone?
THE WITNESS: Yes.
THE COURT: All right. Good morning, Ms. Jackson. My name is Judge Gleason. We have you on a speakerphone here in a courtroom in Anchorage, Alaska.
You have been called as a witness on behalf of the respondent, William Bigley. It is a matter here where I have the lawyer from the state and Mr. Gottstein present.
I am going to be recording your testimony here in just a moment. I will administer an oath to you. But any questions first?
THE WITNESS: No.
THE COURT: All right. If you'd raise your right hand, please.
(Oath administered.)
THE COURT: If you would then please state

and spell your full name.
THE WITNESS: Grace Elizabeth Jackson. That's G-R-A-C-E, Elizabeth, E-L-I-Z-A-B-E-T-H, Jackson, J-A-C-K-S-O-N.
THE COURT: All right. Thank you.
Go ahead, please, Mr. Gottstein.

DR. GRACE JACKSON

called on behalf of the respondent, testified telephonically as follows on:

DIRECT EXAMINATION

BY MR. GOTTSTEIN
Q Thank you, Dr. Jackson. First off, did you send me a copy of your curriculum vitae?
A Yes, I did.
Q And it's 11 pages?
A I believe that is correct, yes.
MR. GOTTSTEIN: I'd move to -- it's Exhibit A. I would move to admit.
THE COURT: Any objection there?
MR. TWOMEY: No, Your Honor.
THE COURT: All right. A will be admitted.
(Exhibit A admitted.)
MR. GOTTSTEIN: Should I give this to the clerk at this point?
THE COURT: That's fine. You can hold on to

it, and we'll get it later, if that's easier for you.
BY MR. GOTTSTEIN
Q Okay. And if I might just take care of the other part of it, too. Did you also send me essentially an analysis of the neuroleptics, neurotoxicity of -- oops, I didn't number it -- 19 pages.
A Yes, that's correct.
Q And is that your work?
A Yes, that is my work.
Q And this analysis is true to the best of your knowledge?
A That's correct.
MR. GOTTSTEIN: I would move to admit that, Your Honor.
THE COURT: That is Exhibit E?
MR. GOTTSTEIN: E.
THE COURT: All right. Any objection to E, Mr. Twomey?
MR. TWOMEY: No, Your Honor.
THE COURT: All right. E will be admitted.
(Exhibit E admitted.)
BY MR. GOTTSTEIN
Q Thank you, Dr. Jackson. Could you briefly describe to the court your experience, training --

training, education and experience?
A Certainly. I attended medical school at the University of Colorado between 1992 and 1996.
Following that, I entered and successfully completed residency in psychiatry, which was performed actually within the U.S. Navy. And that residency was performed -- well, the internship was in 1996 through '97, the residency 1997 through 2000.
Subsequent to completing that residency program, I served as an active duty psychiatrist in the U.S. military. I actually transitioned out of the military in the spring of 2002, and I have been actually in self-employed status since 2002 working at a variety of different positions in order to have some flexibility for research, lecturing, writing, and clinical work, and also forensic consultation.
Q Could you describe -- so have you published papers?
A Yes. I have published papers in peer-review journals. I have contributed chapters to other books which have been edited by other mental health professionals, both in this country and overseas.
And I am also the author of my own book, which I published in the year 2005.
Q And what was the name of that book?

A That book is called Rethinking Psychiatric Drugs, a Guide for Informed Consent.
Q And have you testified as an expert -- testified or consulted as an expert in psychopharmacology cases?
A Yes. I have served as a consultant in a number of cases involving psychiatric rights similar to this case.
Also involving disputes over the use of medications versus alternative treatments in regards to child treatments. I've served as a consultant to families or their doctors in other states in order to assist in the preparation of different treatment plans.
And I've also been involved as an expert witness in consulting on product liability cases.
Q Were you qualified as an expert in psychiatric and psychopharmacology in what's known as the Myers case in Alaska here in 2003?
A Yes, I was.
Q And did Dr. Moser testify I think something like that you -- that you knew more about the actions of these drugs on the brain than any clinician he knew in the United States?
MR. TWOMEY: Objection, hearsay, Your Honor.

THE WITNESS: I'm sorry. I'm getting a lot of beeps on my phone. Can you hear me all right?
THE COURT: Yes.
But, Mr. Gottstein, your response to the hearsay objection?
MR. GOTTSTEIN: It's actually in the testimony that was filed, I believe.
THE COURT: Well, then the testimony speaks for itself.
MR. GOTTSTEIN: Okay.
THE COURT: So you can go forward.
MR. GOTTSTEIN: I would move Dr. Jackson as an expert in psychiatry and psychopharmacology.
THE COURT: Any objection there, Mr. Twomey, or voir dire?
MR. TWOMEY: No, Your Honor.
THE COURT: All right. Then I will find the doctor so qualified in those two fields.
Go ahead, please, Mr. Gottstein.
BY MR. GOTTSTEIN
Q Dr. Jackson, in preparation for this case, have you reviewed the -- what's known as the -- well, the affidavit of Robert Whitaker?
A Yes, I have.
Q And what is your opinion on that affidavit?

A I believed it was very truthful. I thought it was a very accurate presentation of the history of this specific class of medications which we are discussing in this case, the antipsychotic medications.

And also a very succinct but accurate description of some of the problems that have emerged, not only in the conduct of the research, but also in terms of the actual lived experience of patients. So I felt it was a very accurate and very clear presentation of the information as I understand it myself.

Q Now, would it be fair to say that this information is not generally shared by most clinicians in the United States?

A Oh, I think that would be a very fair -- very fair statement.

Q And why would you say that is?

A Well, I think we have a short time here. It's really a broad subject. But quite succinctly what has happened is that the educational process throughout medicine, not just psychiatry, and also the continuing medical education process, even when physicians have completed the first steps of their training, have actually presented a very biased

depiction of the history, or actually omitting the history of many medications.

So a lot of this is a reflection of the educational process, both in the first stages of medical school and residency, and then what is occurring in the medical literature even now.

Q Let me stop you right there just for a minute. So were you trained in this way?

A Yeah. I was -- absolutely. I was trained in the traditional sense that basically serious -- especially severe -- quote, severe mental illness or mental illnesses are diseases of the brain which require chemical treatments, i.e., medication treatments, and that in most cases, these medications must be used on a very chronic or even permanent basis.

Q And did something happen to cause you to change your mind or question that information?

A Lots of things happened. Probably one of the most important things is that I was fortunate enough to be trained -- or be training in a location that exposed me to some additional information.

In other words, some of the history, and also some of the alternative work which could be done that might be effective. So that was one part, is I did

begin to have an exposure to a different perspective.

But the most -- probably the most important thing for me was the lived reality of my patients, just opening my eyes and really paying attention to see whether or not people were improving.

Q I'm sorry; I missed that a little bit. Could you go into that a little bit further, what you found?

A Sure. Well, what really happened is that internship -- I should probably just back up and say that I regard -- in retrospect, I look at the educational process as really an indoctrination.

And I think it's rather unique or heroic when people can begin to examine things more critically. And I was just lucky enough to have an exposure to some individuals who allowed me to do that.

But more specifically, I began to see that in clinic after clinic, whatever setting I was moving through, I was seeing the patients were in fact not improving, that in most cases, in fact, patients were getting sicker and sicker.

And there are two ways to react to that. One could either blame that on the underlying illness and say that we just don't have treatments yet that are effective, or one could even begin to pay attention and ask a broader question or more pointed question,

gee, is it possible that there's something about the way we are approaching these phenomena that is in fact getting in the way of recovery?

And once I began to ask that question, I basically had a 180-degree turnabout in terms of how I had to practice ethically and according to science.

Q And did that result in a -- I think you kind of testified to this -- in a change in direction more towards researching this issue?

A Oh, absolutely. Well, basically, it resulted in two things. It resulted in a great deal of conflict between myself and most conventional settings. It's why I'm an independent practitioner and not a person enjoying an academic appointment or an appointment in a facility.

So it really made -- I had to make a firm decision, was I going to be truthful to science or was I going to go after a $200,000 a year job with nice perks and the respect of my colleagues?

So it was very clear to me that in order to honor the dictum first do no harm, I had to really stay truthful to the science. And that's really what necessitated my breakaway. So that's why I'm really an independent person who does my own research and tried to just help where -- you know, where the help

is actually needed or asked for.
Q Thank you. And so then, just to kind of fill in then this, it's Exhibit C, your neurotoxicity analysis, that would be some of your, you know, more recent work, is that correct, or current state of your research into this issue?
A Yeah. Fairly current.
I am trying to finish a second book this year. And what has really happened over the past two years is that I try to do clinical work to keep myself current with that.
But I also step aside. And probably every single day, I am working on the most current research in the field in order to, you know, lecture and to also write this second book.
What really happened about four years ago is I began to appreciate the fact that most physicians -- and this isn't just a criticism of psychiatry, by any means. But most of us ignore something which is called target organ toxicity. We don't pay attention to how the treatments we're using might actually be adversely affecting the very target we are trying to fix or help improve or repair.
So in my case, about two years ago, I started to just begin focusing on the most current research

that looked at the brain-damaging effects of different kinds of interventions. And that is really what I've been focusing on.
So the document that you have there is a reflection of some of that research. I should say that it's not completely up to date, because some of the research I've been doing more recently even demonstrates that these drugs are more toxic than what I have written in this report.
Q Okay. Thank you. I want to get to that -- get to that also a little bit more. But I'm also -- are there other reasons why clinicians are not really understanding this -- this state of affairs?
A Sure. Well, I think there are so many things that happened.
I'll just take my example. I went to medical school in 1992, graduated in '96, and did my residency until 2000. This was a very pivotal time in what was occurring within the mental health field and also within the United States culturally. And if I just picked, like, maybe four key things.
One is the government decided to name this decade the decade of the brain. In doing so, it sort of attached a governmental license or the (indiscernible) of sanctioning regarding these

phenomena as brain diseases.
The second thing that happened was the birth of something called evidence-based medicine. This was -- actually sort of became official through the Journal of the American Medical Association and other major journals to really elevate an importance, not the actual day-to-day observations that a doctor would be making and not the actual science of what causes illness, but clinical trials that are aimed at just improving or changing symptoms.
The third thing that happened was something that is called direct consumer advertising in 1997, which again was trying to market these drugs and make them more popular or appealing to the public.
And the fourth big thing that has really changed is something called the preemption doctrine. And also, the Daubert litigation.
Daubert was a supreme court decision in 1993 that has really made it quite difficult for toxic tort litigation to occur, so that the implications of that for doctors -- and they don't realize this. It's very much behind the scenes -- is that the pharmaceutical industry began publishing as many papers that they could as fast as possible in the journals in order to meet the Daubert standard of something called weight

of evidence or preponderance of the evidence.
So essentially what happened in the 1990s is that the journals, more than ever before in history, became a tool of marketing, a marketing arm for the drug companies. And drug companies shifted in terms of previous research in the United States.
Most of the research had previously been funded by the government and conducted in academic centers. In the 1990s, that was pretty much over, and most of the funding is now coming from the pharmaceutical industry. So that's really in a nutshell what happened in the 1990s when I was training.
Now, where are we now? What that means is that the journals that most doctors are relying upon for their continuing information continued to be dominated by pharmaceutical industry funded studies and by papers which are being written, if not entirely by the drug companies, then by authors who have part of their finances paid for by the drug companies.
And while I don't believe that it's necessarily going to buy us the information in an article, I think trials have to be funded by someone. Unfortunately what has happened is that there have been too many episodes of the suppressed information,

so that doctors cannot get the whole truth.
Q Well, I want to follow up on that. What do you mean by suppressed information?
A Well, one of the things that has happened repeatedly, and again, most doctors don't realize this, is that the pharmaceutical industry has not been forthcoming in terms of surrendering all of the information to the Food and Drug Administration that they were by law I believe, or at least under ethics, required to do.

For instance, in January of this year, the New England Journal of Medicine published a very important article that had been done. Actually, one of the key authors was a former reviewer at the Food and Drug Administration, who is now back in private practice, or somewhere.

And he and his co-authors had actually had access and reviewed the clinical trial database on the antidepressant medications. And they found that 31 percent of the trials were never published. So 31 percent of that information was never reported in the journals so that doctors could see it.

Okay. Well, you might say who cares. The point of it is that within that 31 percent, had they been published, the overall risk benefit understanding

of this category of medications would have been changed. Instead of favoring these drug treatments, it would have altered the whole face of the journals, and potentially the use of these medications would have become more limited.

Because that 31 percent of the information was showing that the medications were, A, not terribly effective or not more effective than placebo at all, and, B, it really began to reveal the full scope of the hazard. So by not publishing all this information, there is a false view of efficacy and safety.

I should say the same thing has happened with Vioxx. The same thing has happened with the cholesterol-lowering drugs. This is an epidemic right now, which is a real crisis in the integrity of medicine. It's not just psychiatry.

Q Does the same thing happen with respect to the neuroleptics?
A Absolutely, the same thing has happened with respect to the neuroleptics. I think you're a perfect example of someone who has tried to work to bring some of this hidden material to the forefront, because I still think there are concerns among professionals, and I hope among the public, that the Food and Drug

Administration still may not have seen all of the actual data that has been generated in the actual trials. So it is a continuing problem and a continuing concern.

And yes, I believe that most people -- I'll give you an example. When I was working in the VA clinic a couple summers ago in Oregon, I attended a dinner lecture where a speaker for a specific antipsychotic medication slipped out some information that I thought was extremely important. He said that the FDA and the public still has not seen information on Abilify, Aripiprazole, another antipsychotic.

And he alluded to the fact that there was a severe problem with cardiac toxicity, but he would not go any further. He was speaking on behalf of another company. But he said that it would be possible to contact him and perhaps he could share that information.

Well, my point is, why are the rest of the doctors not getting this information that Abilify is eight times more toxic to the heart than the other antipsychotics? I sort of filed that away in the background of my head and said, boy, you know, I'd like to have this information.

But the point is, doctors are not getting the

information. And that's a real problem both for them and it's a problem for their patients.
Q Is it fair to say that you've really devoted your life to -- or your work at this point to ferreting out this sort of information and making it available?
A Right. As best I can. And you know, it's -- it's really sort of a Catch 22. I would love to have the respect of my peers. I would love to be at Harvard teaching. You know, I would love to be an academic able to teach medical students.

But unfortunately, the system is so skewed still in the direction of the pharmaceutical companies and their products that I can't, you know, even get a foot in the door.

So yes, I am full-time researcher trying to do my best to understand this material accurately, and fairly, and objectively, and then to actually act responsibly in response to that knowledge.
Q So in reviewing this information, is it important to carefully look at the data and analyze what's actually presented?
A It's extremely important to look at the methodology. I don't think -- unless a person is actually working at the Food and Drug Administration

or one of the actual clinical trial researchers, you know, actually producing the data that you would actually -- that a person like myself would have access to the raw data.

But what I can analyze and ask questions about is to go to people who have either performed these studies, or when I read the published studies, which is usually what I have access to, to really use good critical thinking in terms of analyzing the methods that have been used.

And you might -- I'm not sure if we're going to have time to discuss methodology, but this is one of the key things that any physician really has to pay attention to.

It's not just the fact that there might be 10 or 20 studies that say a particular medication is either good, bad, or indifferent. It's actually important to -- you know, before even looking at that conclusion, to address how the study was performed so that one can make a well-informed and an appropriate judgment as to whether or not the conclusion should even be considered.

Q And so without going too much into it, could you describe a couple of methodological concerns that you have with respect to the second generation of

neuroleptic studies of which Risperdal is a member?

A Certainly. One of the things that has happened is that the database or the research (indiscernible), which is actually used to approve medications in this country, psychiatric medications, and then used to continue to argue in their favor, especially in product liability litigation or in a lot of cases. That data set is very limited in terms of generalizability.

What most people don't realize is that when a drug is being approved, the people performing the research want to pick the healthiest or the least sick or the least damaged patients, so that they can try and produce good outcomes. So that is one of the main concerns that all of us doctors have about clinical trials is that we recognize the fact that the generalizability is limited.

What do I mean by that? Well, they usually want to pick people who don't have additional illnesses, such as diabetes, heart disease, lung problems, liver disease.

Well, that's going to rule out a large number of people who are actually existing in the real world, because once they've been on many of these medications, they are guaranteed to have some of these

problems.

Number two is they eliminate the use of additional drugs, meaning additional medication. Well, that eliminates another huge portion of the United States population, because most of the people who are being seen in mental health settings are actually receiving more than one, and in some cases, you know, as many as 10 or even 20 medications for various conditions.

So it makes it very difficult to extrapolate to the real-world setting the information that they get or they find in a clinical trial.

Another problem is the length of a clinical trial. A clinical trial usually is cut off at six weeks. That's it. And the drug companies understand and actually choose the six-week cut off for a very good reason. They know that generally speaking, they can't continue to produce favorable results after six weeks.

And then another big problem with these methodologies is the fact that they really are enrolling people who have previously been receiving medications.

So what does that mean and why does that alter or bias the results? Well, one of the problems

in the antipsychotic medication literature, as in the antidepressant literature, is the fact that patients are brought into the study and they have previously been taking a medication, in some cases right up to the day that they enter the study.

And then the first seven to ten days in most of these trials involve taking the patients off of those previous or pre-existing medications. So seven to ten days, the person is abruptly cut off from their previous drug.

Now the real stage of the trial begins. So that first seven- to ten-day window is something that is called a washout. And sometimes what they'll do is they'll give everybody a sugar pill in those first seven to ten days and call it a placebo washout.

Now, the use of the term washout has two meanings. Washout meaning whatever other drugs the person may have been taking before, those are supposed to wash out of the system. And the second part -- and the second meaning of washout is that if someone begins to improve too much in those seven to ten days, they are removed from the study.

Q So may I interrupt you?

A Sure.

Q Are you saying that when people are withdrawn

from the drugs they were taking previously and they improve when they get taken off the drugs, then they are eliminated from the study?

A That's right. They take them out of the study. Because they only want to have people remaining in the study who are going to continue to look -- you know, either continue to look bad on the placebo if they continue to stay -- if they are randomized to the placebo part of the trial.

Or if they are then switched back on to an active medication, something chemically active instead of a sugar pill, their withdrawal symptoms, having been cut off of a previous drug, will hopefully respond to having another drug that was similar to the previous drug, you know, put back into their system.

So you understand completely, they remove people -- and this is important in terms of this case. Because for instance, in the Zyprexa trials, a full 20 percent of the people improved so much in the first seven to ten days when they were taken off their previous drugs that they kicked all those people out of the trial.

If they had retained them in the trial, they could not have gotten results that made Zyprexa look like it was any better than a sugar pill. It would

have biased the results in favor of the sugar pill.

Q So now, did you -- did you analyze the studies that the FDA used in --

THE COURT: And I am going to cut off here and say what would be helpful to me, Mr. Gottstein, is as I understand it, API is proposing Risperdal here, correct?

MR. GOTTSTEIN: Yes.

THE COURT: And so if we focused exclusively on that, I think given our time constraint and the proposal, I think that would be the most helpful for me.

MR. GOTTSTEIN: Well, Your Honor, one of the problems is that we didn't know until Monday that -- you know, that it was Risperdal.

THE COURT: But now that we do, if we could focus on that, I think that would help.

BY MR. GOTTSTEIN

Q Well, are all these -- are all these things that you mentioned also applicable to the Risperdal studies?

A As far as I know. And I have no reason to believe from what I've read in the literature -- I haven't had time to read the FDA review on Risperidone as I have done with olanzapine. But based on the

trials that I have seen in the regular journals, I have no reason to believe that anything other than this procedure has been used repeatedly.

In other words, the placebo washout and actually switching people or removing people who improve too much, it's sort of a standard protocol that you have a certain score in terms of symptoms. And if people don't meet that cutoff, in other words, they begin to improve too quickly, they don't get to stay in the study.

So I have no reason to believe that Risperidone was any different than Zyprexa in terms of this method of eliminating people who -- and you know, favoring or biasing the result of the study.

Q In the interest of moving forward, is it fair to say there are other methodological problems with these studies?

A Oh, absolutely. What many of these studies will do is to allow certain concomitant treatments. In other words, certain additional medicines during the study so that you can't really be sure that the results they are claiming are the result of the actual interventional drug. For instance, Risperdal instead of a benzodiazepine or an antihistamine.

Another thing is the way that the data

themselves get reported. And one of the things that is frequently done is to use something called LOCF, or last observation carried forward. So what that means is if you were to enter a study for instance, and they started you on Risperdal, and you start to have a severe side effect, let's say Parkinsonian symptoms, and you dropped out of the study at two weeks, but the study is supposed to end at six weeks, they will carry forward your score to the six-week mark.

Now, this will sometimes -- people will actually drop out when they have a higher score and they'll carry that forward, as well. But the use of LOCF statistics, especially when they carry forward people who are dropping out on placebo, those are people who are dropping out because they are in withdrawal. They have been cut off from a previous drug.

And so they carry forward an end result, which is not a reflection of the underlying illness, let's say, but a reflection of this introductory bias, the placebo washout.

So the fact they report all of these LOCF data, meaning the fact that they are just carrying forward the results or the statistics from people who drop out of the study early, biases the results in

favor of the drug, when in fact it's not an accurate reflection of what's really going on in the study.

And that happens quite often, and that certainly happened in the Risperdal/Risperidone literature.

Q So just to kind of finish up this part, would it just generally be fair to say that it would be pretty difficult for a practicing psychiatrist in clinical practice to have this information that you are providing to the court?

A Oh, it would be almost impossible. It's -- it would be something you would really have to devote your study to.

And actually, you know, not only would it be difficult for the ordinary doctor to know this is going on, but he or she would read what is published in the regular journals and see that the results are promising, like 70 to 80 percent response rates, meaning a good response with patient satisfaction, et cetera.

And then he or she would be in the real-world setting, and maybe be lucky see 30 or 40 percent of the patients able to even tolerate the drug. So it not only is something that would be hard for doctors to know, but what they're actually being exposed to is

so far removed from reality that they are very unlikely to understand what is going on in the real world.

Q Okay. So what is going on in the real world? What is the impact of drug -- well, specifically Risperdal on patients?

A Well, the real effects in the real world are -- are really in two categories. And as a doctor, you know, I am sort of thinking in terms of safety first. I sort of think of, boy, what do I really have to look out for here if somebody comes into my office and they are receiving this medication or I am asked to begin it?

So one of the things that, you know, we are really talking about is safety. Are people dying on these drugs? Do people die from taking Risperidone? Yes. People are actually experiencing shorter life spans.

Initially it was felt that the life spans for people on medications like Risperidone were perhaps shortened maybe ten or 15 years. And I think that's even been elevated in the most recent government studies to more like 20- or 25-year shorter life spans. So instead of a male -- and we're usually talking about, you know, males with mental illness,

would probably be living, you know, if they were lucky, 72, 74 years of age for men in the United States these days. And we are really talking about something which drops the lifespan down into the 60s.

So at the worst what is going on is that we are actually contributing to morbidity, actually shortening people's life spans. And that's -- and that is either through an acute event like a stroke or a heart attack or something called a pulmonary embolism, or we are talking about more chronic illnesses that eventually take their tolls, things like diabetes and heart failure.

So at the very worst, what is going on in the United States is an epidemic of early suffering or mortality that was not present before these medications were being used, you know, by such a prevalence -- in such high numbers.

The second thing that is going on is that we are arguably worsening the long-term prognosis of people, and in directions that were not previously seen or talked about. And I think my affidavit speaks to this. And also Mr. Whitaker's affidavit speaks to the history and the actual historical outcomes when individuals were being offered something other than just the medication or the priority on medication.

And so that is the other big thing in terms of what's going on.

What's going on is that people are suffering in great numbers, and that people are dying early, and that people are having what might have previously been a transient, that is a limited episode, converted into a chronic and more disabling form of experience.

Q Is -- are these drugs brain damaging?

A Well, I try and not sound like I am, you know, really off -- off my rocker. Because people probably wouldn't like it if I actually used a term for what's happening.

But I sort of say we have unfortunately contributed to a population of CBI patients, meaning chemically brain injured.

I was in the military, so I am very used to TBI patients, traumatic brain injury from, you know, concussions and explosions and what's going on in Iraq and Afghanistan.

But what is the elephant in the room that people aren't addressing in psychiatry and neurology is this population of CBI, chemically brain injured.

So yes, I actually would say that what we have created, and I think Mr. Bigley is an example of this, is that we are creating dementia on a very large

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

March 20, 2009

Via Electronic Transmission

Dr. Drew Gilpin Faust
President
Harvard University
Massachusetts Hall
Cambridge, MA 02138

Dr. Peter L. Slavin
President
Massachusetts General Hospital (Partners Healthcare)
55 Fruit Street
Boston, MA 02114

Dear Drs. Faust and Slavin:

The United States Senate Committee on Finance (Committee) has jurisdiction over the Medicare and Medicaid programs and, accordingly, a responsibility to the more than 80 million Americans who receive health care coverage under these programs. As Ranking Member of the Committee, I have a duty to protect the health of Medicare and Medicaid beneficiaries and safeguard taxpayer dollars appropriated for these programs. The actions taken by thought leaders, like those at Harvard Medical School, often have a profound impact upon taxpayer funded programs like Medicare and Medicaid and the way that patients are treated and funds expended.

I have also taken an interest in the almost $24 billion annually appropriated to the National Institutes of Health (NIH) to fund grants at various institutions such as yours. As you know, institutions are required to manage a grantee's conflicts of interest.[1] But I continue to learn that this task is sometimes made difficult because physicians do not consistently report all the payments received from drug companies. To encourage transparency, Senator Kohl and I introduced the Physician Payments Sunshine Act (Act). This Act will require drug companies to report publicly any payments that they make to doctors, within certain parameters.

Recently, I was provided a number of documents, including slides, that became available during ongoing litigation.[2] A number of the documents reviewed by my staff relate to, among other matters: Dr. Joseph Biederman of Harvard University (Harvard) and Massachusetts General Hospital (MGH/Partners), (collectively, the Institutions); and to the Johnson & Johnson Center for Pediatric Psychopathology Research (Center). As part of the litigation, Dr. Biederman produced several slide sets, and my staff have pulled several slides from these various presentations. I am not certain if these slides sets were

[1] Responsibility of Applicants for Promoting Objectivity in Research for Which PHS Funding is Sought, 42 C.F.R. 50 (1995).
[2] Alma Avila, as Next Friend of Amber N. Avila, an Individual Case vs. Johnson & Johnson, et al., Docket No.: MID- L-6661-06
(In Re Risperdal/Seroquel/Zyprexa; Superior Court of Middlesex County, New Jersey).

United States Senate
COMMITTEE ON FINANCE
WASHINGTON, DC 20510–6200

created by Dr. Biederman, and I am not certain if he has ever presented these slides publicly. However I do know that they were produced by Dr. Biederman.

The slides raise potential concerns about, among other matters, Dr. Biederman and the Center. My main concern is whether or not the attached slides suggest a predisposition to specific findings and conclusions prior to the studies being commenced. My other concern is whether or not NIH was aware that Dr. Biederman was performing research sponsored by J&J on psychiatric disorders when it awarded him a grant to collaborate with other doctors to study those same psychiatric disorders. I am also wondering if the physicians Dr. Biederman was collaborating with under the NIH grant were notified of Dr. Biederman's corporate sponsored research.

Accordingly, this letter seeks, among other things, your guidance as to whether or not the materials discussed in this letter are in compliance with all applicable rules followed by the Institutions. In addition, I would like to better understand the role played by the Institutions when proposals are drafted by professors, and whether those policies and procedures were followed with regard to the materials attached to this letter.

I. Attachment A

Slides in Attachment A, highlight several "Key Projects for 2005," and state:

- Concerta for the treatment of ADHD NOS in adolescents
  - Extend to adolescents positive findings with Concerta in ADHD NOS in adults

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Please explain:

1) Why do these slides suggest an expectation of positive outcomes for the drugs prior to the commencement of the clinical trials?

II. Attachments B and C

Slides set forth in Attachment B seem to explain what MGH would provide Johnson & Johnson in return for the funding. As part of the "deliverables," the slide reads:

- Research posters at major national and international meetings
- Research publications in peer reviewed journals
- Programs and symposia at major national and international meetings
- Help J&J develop state of the art, data based CME [continuing medical education] programs and educational materials

Several of the deliverables set forth in this slide are typical deliverables when performing scientific research, with the exception of the statement that the Center will in some way be helping J&J to create "state of the art, data based" CME programs. Accordingly please explain the following:

1) According to protocols and policies of Harvard/MGH, is it appropriate that a portion of the deliverables include the development of "state of the art data based CME programs and educational materials" for a particular pharmaceutical sponsor, in this case J&J? Please explain.

The slides in Attachment C describe, among other things the "Benefits" of the J&J Center. One slide reads:

- Supports research on the disorders that J&J products treats:
  - Concerta
  - Risperdal
  - Reminyl
  - Topamax

Another slide in Attachment C says the following:

- Provides rationale to treat chronically and aggressively highly morbid child psychiatric disorders

And yet another slide reads:

- Provides ongoing consultation for protocol development of new J&J products or new uses for existing compounds
  - Concerta for adult ADHD NOS
  - Reminyl for ADHD

1) Please explain why the slides set forth above suggest that the study being proposed could find new uses for J&J products?

III. Attachments D and E

The slides in Attachment D highlight several additional issues. The first is entitled "Key Projects for 2004" and says:

- Comparative effectiveness and tolerability of Risperidone vs. competitors in the management of pediatric bipolar disorder: acutely and chronically

  - Will clarify the competitive advantages of risperidone vs. other atypical neuroleptics

Another slide in Attachment D reads, in pertinent part:

- Effectiveness and safety of Risperdone in pre-schoolers

- Will support the safety and effectiveness of risperidone in this age group

The slides in Attachment E titled "Planned Investigator Initiated Studies" seem to complement those in Attachment D and say:

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Accordingly, please respond to the questions below regarding Attachments D and E.

1) Please explain how these slides could suggest that a study, which had not yet commenced "will support the safety and effectiveness of…." any particular drug and "complement" other efforts?

2) Is it possible that the study proposed in Attachment D would not support the safety and effectiveness of risperidone in pre-schoolers and if this is the case, why would the slide not so state?

Again, Dr. Faust and Dr. Slavin, I am having difficulty putting the Attachments to this letter in proper context. Indeed, I reached out to a physician researcher for an independent review of the slides attached to this letter. In response to my inquiry, the physician researcher said that it appeared that the slides discussed in this letter were nothing more than marketing tools, as opposed to discussions of independent scientific research.

IV. The Janssen Study

We also learned that these slides did result in funds being paid to Dr. Biederman and that he eventually published a Janssen supported study that found a 30% reduction in ADHD symptoms in 29% of study subjects when taking risperidone. This study was published in 2008 and its finding seem to correlate with the slides that were apparently produced years earlier and attached to this letter.[3] More specifically, Dr. Biederman's study concluded, "treatment with risperidone is associated with tangible but generally modest improvement of symptoms of ADHD in children with bipolar disorder." Even more troubling, the published study lists support from Janssen, the Stanley Medical Research Institute, and the NIH. In fact, the NIH funding for this study raises still more concerns in that federal dollars may have been used to support research when the results may have been "predicted" before the study began.

[3] Biederman, Joseph et al "Risperidone treatment for ADHD in children and adolescents with bipolar disorder" *Neuropsychiatr Dis Treat*, Feb 2008, 4(1): pp 203-207. Published online Feb 2008.

V. Attachment F and Possible Conflict of Interest

There is yet another aspect of documents reviewed in this matter that is concerning me. It is my understanding that Dr. Biederman was seminal in the creation of the Center and that he received almost half a million dollars [Attachment F] from the NIH to run the annual Collaborative Pediatric Bipolar Disorder Conference (2003: $95,015, 2004: $96,631; 2005: $99,209; 2006: $101,865; 2007: $101,567). It appears that running the Center on bipolar disorder, while also running a conference for the NIH on bipolar disorder could be perceived as a conflict. Therefore, I would appreciate your views on this. I also want to advise you that the NIH told me that MGH never informed them of this possible conflict.

VI. Attachments G and H

In addition to materials regarding the Center and Dr. Biederman, I also received materials produced for ongoing litigation by J&J. It seems, based upon a review of J&J internal communications, that the collaboration between the Center and J&J was driven more by business and marketing as opposed to pure science and research. For instance, in Attachment G there are J&J slides titled "2003 Business Plan." In one slide J&J notes that it will "leverage" the MGH Center to raise awareness of bipolar disorder in kids because "use of psychotropic medications in [children and adolescents] remains controversial." Another slide identified as Attachment H was presented by a J&J employee and was titled "A New Initiative! J&J Pediatric Research Center at Mass General Hospital." The relevant slide states that the initial discussions with MGH to create the Center involved participation "with marketing." So I ask, is it typical in your experiences to include the marketing division of a sponsor company during discussions of possible collaboration with your institution?

VII. Attachment J

Another document provided to me is entitled, "PHARMA SALARY SUMMARY" is identified as Attachment J. This document appears to be a summary of payments made to Dr. Biederman over a 3 year period. Accordingly, please respond to the following questions:

1) Explain the payments made and the services provided.

2) Address whether or not these payments were reported to you by Dr. Biederman.

3) Address whether or not if these payments were reported by you to me in previous correspondence.

4) Regarding Attachment J, please explain if Dr. Biederman received compensation from these companies as detailed in the attachment. If yes, provide an annual summary from each company.

VIII. Protocol Violations

Based upon a review of still other documents produced, I see that MGH's Institutional Review Board (IRB) found "a serious breach of the protocol and procedures and provisions" in Dr. Biederman's study of risperidone and olanzapine in preschool children. Based upon the materials in my possession [Attachment I], when this issue was brought to Dr. Biederman's attention in 2004, the human research committee at MGH reported that this was the sixth protocol violation for the study. If a study is supported with federal funds, then such violations should have been reported to the Office for Human Research Protection (OHRP) at the Department of Health and Human Services. Additionally, when the study was apparently published in 2005, the article listed support from the Stanley Medical Research Institute and the National Institute of Mental Health.[4] However, OHRP informed me that it was never notified of any protocol violations for this study.

Accordingly, please respond to the following questions and requests for documents. For each response, first repeat the question followed by the appropriate answer.

1) Why did Harvard/MGH not inform the NIH about Dr. Biederman's collaboration with J&J when it applied for the NIH bipolar disorder grant?

2) Several documents that Dr. Biederman supplied to the court make note of a "JB rent fund." What is the "JB rent fund" and to whom did the money go?

3) Why did MGH not inform OHRP about the IRB protocol violations in Dr. Biederman's study?

4) For that particular study, please explain each IRB protocol violation and how those violations were resolved.

5) Did representatives of MGH discuss collaborating on the Center with marketing people from J&J, as Attachment H states?

6) Were the slides detailed in the attachments to this letter created by Dr. Biederman? If not, who created them?

7) Please explain if these slides were ever presented to an audience. If so, who saw these presentations?

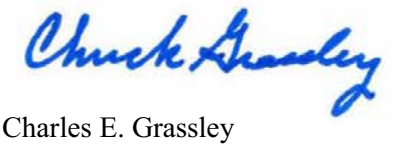
Thank you again for your continued cooperation and assistance in this matter. As you know, in cooperating with the Committee's review, no documents, records, data or information related to these matters shall be destroyed, modified, removed or otherwise made inaccessible to the Committee.

---

[4] Biederman, Joseph, et al "Open-Label, 8-week Trial of Olanzapine and Risperidone for the Treatment of Bipolar Disorder in Preschool-Age Children," *Biol Psychiatry*, 2005, 58: pp 589-594.

I look forward to hearing from you by no later than April 17, 2009. All documents responsive to this request should be sent electronically in PDF format to Brian_Downey@finance-rep.senate.gov. If you have any questions, please do not hesitate to contact Paul Thacker at (202) 224-4515.

Sincerely,



Charles E. Grassley
Ranking Member

cc: Raynard Kington, M.D., PhD.
Acting Director
National Institutes of Health

Attachments

Attachment A

Johnson & Johnson Center for Pediatric Psychopathology Research

Director: Joseph Biederman, M.D.

Co- Director: Steve Faraone, Ph.D.

Data Management Director: Eric Mick, Sc.D

Business Administrator: Kate Balcke, MA

Administrative Coordinator: Megan Aleardi

Massachusetts General Hospital
Harvard Medical School

Key Projects for 2005

Planned IITs

- Concerta for the treatment of ADHD NOS in adolescents
  - Extend to adolescents positive findings with Concerta in ADHD NOS in adults

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Attachment B

Deliverables

Johnson & Johnson Center for Pediatric Psychopathology Research

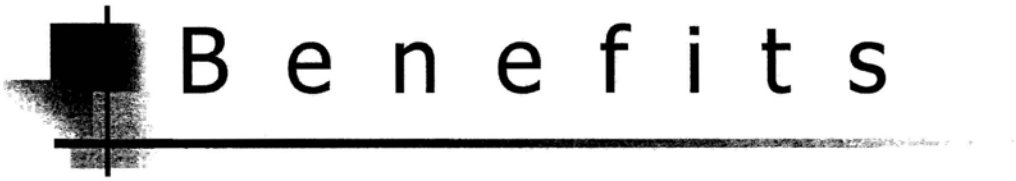
Massachusetts General Hospital

- Research posters at major national and international meetings
- Research publications in peer reviewed journals
- Programs and symposia at major national and international meetings
- Help J&J develop state of the art, data based CME programs and educational material

Deliverables

- Manuscripts
  - ADHD Follow-ups
  - Smoking as Gateway Drug
  - Ris for pediatric bpd
  - Ris for preschoolers
  - Age, gender; anxiety; cohort analyses
  - Driving
  - Lab workplace
  - PET
- Abstracts
  - APA
  - Biol Psych
  - CINP
  - ECNP Stanley
  - Bipolar Conf
  - Special issue

Attachment C


Benefits

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- **Gains access to many millions of dollars in data that have already been collected through NIH and other grants**
- **Gains access to world class experts in a variety of fields**
  - **Pediatric and Adults Psychopathology**
  - **Clinical Trials**
  - **Genetics**
  - **Neuroimaging**
  - **Biostatistics and Epidemiology**
  - **Neuropsychology**
  - **Driving Simulation**

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- **Supports research on the disorders that J&J products treat**
  - Concerta
  - Risperdal
  - Reminyl
  - Topamax

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Documents the morbidity and disability associated with ADHD, pediatric bipolar disorder and related psychiatric and cognitive comorbidities
- Provides rationale to treat chronically and aggressively highly morbid child psychiatric disorders

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Puts J&J at the forefront of pediatric psychiatry research
- Provides ongoing consultation for protocol development of new J&J products or new uses for existing compound
  - Concerta for adult ADHD NOS
  - Reminyl for ADHD
- Facilitates pilot and proof of concept studies

Attachment D

Key Projects for 2004

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Comparative effectiveness and tolerability of Risperidone vs competitors in the management of pediatric bipolar disorder: acutely and chronically
  - Will help clarify the competitive advantages of risperidone vs. other atypical neuroleptics

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Risperidone in the treatment of pediatric ADHD when comorbid with bipolar disorder
  - Will complement prior work on risperidone for DBD

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Effectiveness and safety of Risperidone in pre-schoolers
  - Will support the safety and effectiveness of risperidone in this age group
- Pharmacogenetics of Risperidone
  - Will search for markers of response and adverse effects in pediatric bipolar disorder

Attachment E

Planned Investigator Initiated Studies

Planned IITs

- Concerta for the treatment of ADHD NOS in adolescents
  - Extend to adolescents positive findings with Concerta in ADHD NOS in adults

Planned IITs

- PET studies of Concerta in ADHD
  - Further clarification of Concerta's unique pharmacological and therapeutic profile

Johnson & Johnson Center for Pediatric Psychopathology Research

Massachusetts General Hospital

- Randomized Clinical Trial of Risperidone vs. Placebo in children younger than 10 years of age with bipolar disorder
  - Will complement registration efforts of studies with older youth
  - Will provide Janssen with critical competitive data on safety and efficacy of risperidone in children (80% of referrals)

Attachment F

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

FEB 13 2009

The Honorable Charles E. Grassley
United States Senate
Washington, D.C. 20510

Dear Senator Grassley:

I am writing in response to your letter of December 19, 2008, regarding Drs. Joseph Biederman and Timothy Wilens of Harvard University (Harvard) and Massachusetts General Hospital (MGH). Specifically, you asked if Harvard and/or MGH notified the National Institutes of Health (NIH) about any potential conflicts of interest regarding NIH grant U13 MH 064077, titled *Collaborative Pediatric Bipolar Disorder Conference*.

MGH, the grantee institution responsible for reporting financial conflicts of interest to NIH under the regulation at 42 CFR Part 50, Subpart F, *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought*, has not notified the NIH of any potential conflicts of interest concerning the above-referenced grant for which Dr. Biederman served as Principal Investigator.

Subsequent to your letter, MGH informed the NIH of the results of its financial conflict of interest review for those NIH grants under which Drs. Biederman, Wilens, and/or Spencer had a role in the design, conduct, or reporting of the research. The NIH is in the process of following up with MGH regarding its review, including, specifically, its review of U13 MH 064077.

I hope this information is helpful. If you need any additional information, please contact Marc Smolonsky, NIH Associate Director for Legislative Policy and Analysis, at (301) 496-3471.

Sincerely yours,

Raynard S. Kington, M.D., Ph.D.
Acting Director

			assess how gene variants will predict adult outcome. In our preliminary work, we have begun to address each of the Specific Aims that are the focus of the proposed work. We view the proposed extension of our work as an essential step for several reasons. First, although there have been seven follow-up studies of ADHD children and only two (our included) used DSM-III-R criteria. Moreover, unlike most prior follow-up studies, the proposed work can comprehensively address psychiatric comobidity in ADHD because we did not use comorbid conditions to exclude cases at baseline and we assessed for a wide range of comorbid conditions at each assessment. Only a few prior studies assessed intelligence, achievement and school functioning, none have thoroughly examined attentional-executive neuropsychological functions and only one examined psychosocial and family functioning. In contrast, our study has taken a multidimensional approach to measurement; we have assessed these domains of functioning at baseline and each follow-up assessment. Because the treatment interventions used in our sample are not being controlled, we will be able to document to naturalistic course of treatment use. Also, we are the only long-term study to collect clinical and molecular genetic data on all first degree relatives and to follow the siblings of ADHD and control subjects into adulthood. For these reasons, we expect the proposed work to clarify the course and outcome of ADHD.	
2003	1U13MH064077-01A1	Collaborative Pediatric Bipolar Disorder Conference	DESCRIPTION (provided by applicant): We are proposing a multi-year conference grant which seeks to establish a forum for researchers to pursue collaborative studies of pediatric bipolar disorder. This application was conceived in response to a recent roundtable discussion convened by the NIMH's Director, Dr. Steve Hyman, in collaboration with the Developmental Psychopathology and Prevention Research Branch and the Child and Adolescent Treatment and Preventive Intervention Research Branch. Despite controversy, the notion that pediatric bipolar disorder is exceedingly rare has been challenged by case reports and emerging research findings that suggest that this disorder may not be rare but, rather, that it is difficult to diagnose. It is also quite clear that, despite debate over nosological issues, many clinicians recognize that a sizable number of children suffer from a severe form of psychopathology associated with extreme irritability, violence, and incapacitation that is highly suggestive of bipolar disorder. Since a sizable clinical population currently exists for which relatively little systematic information is available, efforts that increase the pace and utility of research are desperately needed. Thus, an appropriate mechanism designed to facilitate regular communication among investigators and clinicians is needed as a first step to build collaborative research and guide clinical efforts that will foster a more efficient and streamlined approach to the understanding and treatment of this perplexing disorder. The main aim of the proposed conference grant is to overcome the hurdles to collaboration by establishing yearly conferences among investigators studying pediatric bipolar disorder. Subgoals of these conferences are: (1) to define the boundaries of the bipolar spectrum phenotype and determine if children who technically meet criteria for bipolar disorder actually have this disorder or are affected with another condition.; (2) to standardize data collection methods across different centers to facilitate pooling of diagnostic data and validation of the disorder; (3) to facilitate joint submissions of large collaborative projects that will enable the study of a broad spectrum of scientific questions including genetic, imaging and therapeutic protocols; and (4) to create a mechanism for pooling samples so that potential findings from one group may be cross-validated on	$95,015

			pooled data from other groups. Although scientific projects studying pediatric bipolar disorder are likely to be funded in the coming years, these efforts will likely take many years to unfold. This scientific void and ongoing diagnostic and therapeutic uncertainties calls for immediate action to foster contact and dialogue among interested parties in the clinical and scientific community. While the field faces a dearth of information, more and more children and families are being referred to clinics for evaluation and treatment. Thus, steps that increase the identification of children with bipolar spectrum disorder and the development of initial therapeutic approaches to help them is of high clinical, scientific and public health importance. While the proposed conference does not intend to solve all outstanding problems associated with pediatric bipolar disorder, it will provide a forum to begin formulating a solution.	
2004	5R01HD036317-07	Adult Outcome of Attention Deficit Hyperactivity Disorder	same as 2R01HD036317-06	$541,514
2004	5U13MH064077-02	Collaborative Pediatric Bipolar Disorder Conference	same as 1U13MH064077-01A1	$96,631
2005	5R01HD036317-08	Adult Outcome of Attention Deficit Hyperactivity Disorde	same as 2R01HD036317-06	$559,193
2005	5U13MH064077-03	Collaborative Pediatric Bipolar Disorder Conference	same as 1U13MH064077-01A1	$99,209
2006	5R01HD036317-09	Adult Outcome of Attention Deficit Hyperactivity Disorde	same as 2R01HD036317-06	$566,125
2006	5U13MH064077-04	Collaborative Pediatric Bipolar Disorder Conference	same as 1U13MH064077-01A1	$101,865.
2007	1R03MH079954-01	Course of psychopathology in female youth: Analysis with extant longitudinal data	DESCRIPTION (provided by applicant): Although attention-deficit/hyperactivity disorder (ADHD) is more prevalent in boys than girls, little doubt exists that ADHD is also an important cause of psychiatric disability in girls. Despite this, the scientific literature on females with ADHD is scarce, and mostly cross-sectional. Thus, large-scale studies examining the course and outcome of psychopathology in ADHD in girls are sorely needed. Such information can inform patients, families, teachers and clinicians and facilitate prevention and intervention efforts for females with ADHD, an understudied population. We propose a data analysis project that utilizes an existing longitudinal database to address these questions. The overall goal of this application is to use longitudinal measurements, a multigenerational perspective and an extensive assessment of multiple domains of functioning to investigate the developmental course and outcome of psychopathology in female youth with and without ADHD. Our specific aims are to: 1) examine the risk for psychopathology associated with ADHD across development; 2) describe the clinical characteristics of psychopathology in a sample of ADHD girls; 3) estimate the effect of antecedent risk factors on psychopathology in a sample of ADHD girls; and 4) to estimate the effect of psychopathology on subsequent functional outcomes in a sample of ADHD girls. The psychopathological conditions to be examined	$87,500

Attachment G

Child and Adolescent & Other New Business

2003 Business Plan

July 29, 2002

Strategic Initiatives

Use of psychotropic medications in C&A remains controversial	*Limited education and awareness of appropriate use of APSs*	*Physician misperception of RIS safety profile*	*Lack of indication*
Raise awareness regarding prevalence, economic and emotional burden	***Develop educational platform***	***Establish Risperdal as having a favorable risk-benefit ratio***	***Partner with JJPRD to facilitate development plans***
• Partner with advocacy to drive caregiver education • Generate and disseminate data supporting clinical rationale and utility of APS in C&A • Leverage CAPRI initiative with NIMH • Leverage J&J-MGH Pediatric Psychopathology Center to drive awareness	• Partner with McNeil to drive and leverage educational program • Targeted medical education to pediatricians and neurologists • Leverage J&J-MGH Pediatric Psychopathology Center to drive educational needs	• Neutralize safety and tolerability concerns • Leverage current datasets • Develop EMRP plan addressing datagaps: ADHD, bipolar disorder, autism, acute agitation, Tourette's • Maximize RUPP autism publication	• Work to expedite enrollment in ongoing Schizophrenia trial • Assist in development of adolescent bipolar trial • Expedite transfer and analysis of RUPP database • Work with JJPRD and Pediatric Development Group to expedite receipt of written request

Use of psychotropic medications in children is controversial

- Raise awareness regarding prevalence, economic, and emotional burden of untreated C&A mental illnesses and the long-term implications

Key Tactic: C&A Mental Health Summit

Description

One day national summit which addresses current issues in mental illnesses in children and adolescents

Audience

Advocacy, KOLs, AACAP, NIMH

Subject to legal and regulatory review

2003 Business PLan

Limited education and awareness of appropriate use of APS

- Develop educational platform to establish the role of APSs in the treatment of C&A mental illness

Key Tactic#1: "Branded" educational initiative

Description

Multi- medium, comprehensive branded educational campaign on the role of APS in the treatment of C&A mental health: Centers of excellence, Regional CME symposia, monographs

Audience

National and regional key opinion leaders, community based physicians

Key Tactic#2: Academic collaboration (MGH and CAPRI)

Lack of indication

- Partner with JJPRD and J&J Pediatric Institute to facilitate current development plans
  - RUPP (autism)
  - Schizophrenia
  - Bipolar Disorder
  - Exclusivity

Subject to legal and regulatory review

Risperdal C&A 2003 PME's

Description	2002 PME ($K)	Proposed 2003 PME ($K)	2003 PME (%)
Medical Marketing/Education	**3,890**	**3,300**	**51.6%**
CME Branded Initiative		1,800	
PsychLink/Teletopics		450	
Symposia (2)		350	
Publications		500	
National Ad Board		200	
Advisory Boards (RAB/HOV)	**1,800**	**1,900**	**29.7%**
Public Relations	**325**	**500**	**7.8%**
C&A Summit		400	
Other		100	
Grants	**160**	**300**	**4.6%**
Other	**225**	**400**	**6.3%**
Total PME	**$6,400**	**$6,400**	**100%**

Subject to legal and regulatory review

2003 Business PLan

Attachment H

J&J Pediatric Research Ctr. at MGH

Background *(continued)*

- With marketing, held initial discussions with MGH to discuss collaboration re: specific extramural research with risperidone
- Discussed the concept of a J&J center at MGH, reviewing specific scientific questions related to key business areas
- Discussed partnerships with J&J sister companies (OMP, McNeil) to coordinate support of MGH collaboration
- Designed a model methodology for collaboration, with specific scientific deliverables and timelines for delivery

Attachment I

INVESTIGATOR REPORT OF MAJOR PROTOCOL VIOLATION

This form is to be used to report **major** protocol violations. Protocol violations are deviations from the IRB-approved protocol that are not approved by the IRB prior to initiation or implementation. A **major protocol violation** is a violation that may impact subject safety, affect the integrity of the study data, and/or affect the willingness of the subject to participate in the study. Refer to PHRC guidance document Protocol Violations, Deviations, and Exceptions for more information and for examples of major and minor violations, see http://healthcare.partners.org/phsirb/prodevex.htm.

1. PROTOCOL INFORMATION

Protocol #:	**2001-P-000422**
Principal Investigator:	**Joseph Biederman, MD**
Title of Study:	**Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder**

2. SUBJECT INFORMATION

Subject(s) ID #	Subject Initials	Date of Violation	Date of Discovery
3601102	**MATMCD**	**03/07/02**	**03/12/04**

3. DESCRIPTION OF THE VIOLATION

Briefly describe the protocol violation.

Subject MATMCD missed visits 4 through 6 during the acute phase of the study and subsequently all the necessary tasks (ie questionnaires, vitals) were not completed. Additionally, six weeks instead of the usual four lapsed between the week 3 and week 7 visits. At week 8, the subjects olanazpine dose was increased beyond the protocol specifications. For the purpose of stabilizing the subject, the dose was increased to 10 mg/QD when the maximum dose per protocol is 7.5 mg/QD. At month 1 of extension, the dose was again increased to 12.5 mg/QD. Each increase was well tolerated and was initiated for the purpose of stabilizing the subject.

4. CORRECTIVE ACTION

For guidance on appropriate corrective action, see http://www.partners.org/phsqi/ Contact the Quality Improvement/Human Subject Protection Program if additional guidance is needed.

☐	None to date
☒	Note-to-file was prepared
☐	Subject was consented/re-consented
☐	Other, describe below

NOTE: Major violations should be reported to the sponsor in accordance with the reporting requirements in the sponsor's protocol.

5. PREVENTIVE MEASURES

Describe below preventive measures developed/implemented to prevent similar violations from occurring in the future.

In no way was the subject's safety jeopardized as the treating clinician was in constant contact with the family and made adjustments to the dosing regimen based on reports from the subject's primary reporter. Study coordinators have been asked to stress the

importance of subjects' coming into the office for each weekly appointment. Furthermore, study coordinators will contact subjects before each visit in order to remind them of their appointments. The treating clinician and study staff will be instructed to follow the protocol strictly.

6. CHANGES TO THE PROTOCOL DOCUMENTS AND/OR CONSENT FORM

☒ No	☐ Yes	If Yes, submit amendment form and revised documents, as applicable

7. SIGNATURE OF PRINCIPAL INVESTIGATOR (required)

Signature of Principal Investigator	Date

MASSACHUSETTS GENERAL HOSPITAL

HARVARD MEDICAL SCHOOL

15 Parkman Street, WACC 725
Mail Zone WAC 725
Boston, Massachusetts 02114-3139
Tel: 617 726-1731, Fax: 617 724-1540
E-mail: jbiederman@partners.org

Joseph Biederman, M.D.
Chief, Clinical and Research
Program in Pediatric Psychopharmacology
and Adult ADHD
Massachusetts General Hospital
Professor of Psychiatry
Harvard Medical School

DATE: April 9, 2004
TO: Human Research Committee

RE: Response to IRB review of Violation: "Open-Label Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 years of age with Bipolar Spectrum Disorder"

Dear Committee Members:

Enclosed please find a response to your review of a violation that will be brought to a full committee.

Sincerely,

Joseph Biederman, MD

INVESTIGATOR RESPONSE TO IRB QUESTIONS/CONCERNS

PROTOCOL#: 2001-P-000422

1. PRINCIPAL/OVERALL INVESTIGATOR:

(cannot be resident or research fellow-except for bem/onc studies)

Name: **Joseph Biederman, MD**
First Name, Middle Initial, Last Name, Degree(s)

Institution: ☐ BWH ☐ DFCI ☒ MGH Employee ID#: 231-03-91

Dept/Service: **Psychiatry** Div/Unit: **Pediatric Psychopharmacology Unit**

Address: **185 Alewife Brook Parkway, Suite 2000, Cambridge MA 02138**

Telephone: **617-503-1063** Beeper: **35417** FAX: **617-503-1092**

E-Mail/Internet Address: **jbiederman@partners.org**

2. STUDY TITLE

Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder

3. IRB Review Date: Please indicate date of IRB Review

4/1/04

4. Submission Reviewed: Indicate what was reviewed; e.g., 8/8/96 Amendment

Major Violation

5. RESPOND POINT BY POINT TO IRB QUESTIONS/CONCERNS:

I am fully aware that this breach will be brought to the attention of the full Partners Healthcare Human Research Committee as it represents a major violation. While this serious violation should never have occurred and is not justified, the HRC should be aware of the circumstances in which the violation occurred.

The main points are:
1) The clinician raised the dose above the protocol limit in an attempt to stabilize a very sick child who was experiencing severe psychopathology.
2) The dose used was above that approved in the protocol but within the range of what is used clinically. The correct procedure would have been to terminate the child and continue treatment at the higher clinically indicated dose.
3) The child experienced no adverse outcome.

To avoid the recurrence of this unfortunate and unacceptable event, the following steps were taken:
1) A stern notification was sent to all research clinicians in my program via email alerting them of this violation and stating the utmost seriousness of the event and the absolute need to fully comply with all aspects of an IRB approved research protocol and its dosing

requirements.
2) A formal meeting was held on 4-6-04, with the clinical staff of our research program to review this critical issue and formalize procedural changes moving forward.
3) Research staff was informed that in the case that an urgent or otherwise compelling clinical situation were to arise that appeared to warrant an exception to the approved protocol, the clinician will contact the PI immediately to review the situation and if the clinical circumstances are judged to warrant a potential protocol deviation, the PI will contact Harry Demonaco, Dr. Jonathan Alpert, or Dr. Elizabeth Hohmann at the IRB to review the situation and seek appropriate authorization to move forward with a protocol exception per PHRC guidelines . Without such authorization, no changes will occur.
4) If changes are still deemed necessary and the proposed exception is not authorized, the subject will be dropped from the protocol and treated clinically.

I hope that these procedures will avoid future inappropriate violation as the one that occurred. Please feel free to contact me with additional suggestions and recommendations if you feel that these procedures are inadequate and I will be happy to implement them immediately.

Principal/Overall Investigator Signature (required)

4/8/04
Date

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

Violation/Deviation: Notification of IRB REVIEW
Protocol #: 2001-P-000422/40; MGH

Date: 04/05/2004

To: Joseph Biederman, MD
Psychiatry
Warren 705

From: Ronda Cox Goldman
MGH Research Management
LRH 3

Title of Protocol:	Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder
IRB V/D #:	6
IRB Review Type:	Expedited
IRB Review Date:	04/01/2004
IRB Review Action:	Requires Modification

This Violation/Deviation has been reviewed by the MGH IRB, Assurance # FWA00003136. During the review of this Violation/Deviation, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please read this memo carefully and respond in a point-by-point manner to the issues raised below within 60 days of the review date.

This is a serious breach of the Protocol procedures and provisions. The maximum dose of olanzepine allowed during the study participation is 7.5mg. The dose escalation to 12.5mg in the context of non-compliance on the part of the parents to study procedures seems inappropriate based on study requirements. Although the distinction between clinical care and clinical research is blurred in this subject popualtion, the absolute requirements of the Protocol should have required subject discontinuation from the study and clinical management. Continued participation in this subject is a serious violation of study procedures.

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

This breach will be brought to the attentionof the full Partners Healthcare Research Committee as it represents a major violation. Any additional information concerning this subjects' participation should be forwarded as soon as possible. This is the sixth violation of Protocol procedures noted in the study file. One other violation involved the addition of prohibited concomitant medications. The investigator is asked to provide additional details concerning procedural changes that will ensure that clinicians follow mandated study procedures. This subject should be considered discontinued from further study participation and managed clinically as deemed appropriate by caregivers.

Direct any questions, correspondence and forms to Ronda Cox Goldman, (617) 724-2130.

c: Stephanie Dunkel, BA

FAX COVER SHEET

To: Joseph Birnbaum MD / Stephanie Dankel From: Ronda Cox Goldman

Fax #: 617 583-1060 Tele #: 617-724-2130

Fax #: 617-724-1919

Date: 4-5-04

Message:

Number of Pages: 3

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

Violation/Deviation: Notification of IRB Approval/Activation

Protocol #: 2001-P-000422/41; MGH

Date: 05/10/2004

To: Joseph Biederman, MD
Psychiatry
Warren 705

From: Ronda Cox Goldman
MGH Research Management
LRH 3

Title of Protocol:	Open-Label Comparative Study of Risperidone Versus Olanzapine for Mania in Preschool Children 4 to 6 Years of Age with Bipolar Spectrum Disorder
Sponsor:	Private Grant
IRB Review Type:	Full
IRB Approval Date:	04/27/2004
Approval Effective Date:	05/10/2004
IRB Expiration Date:	01/06/2005

This Violation/Deviation has been reviewed and approved by the MGH IRB, Assurance # FWA00003136. During the review of this Violation/Deviation, the IRB specifically considered (i) the risks and anticipated benefits, if any, to subjects; (ii) the selection of subjects; (iii) the procedures for securing and documenting informed consent; (iv) the safety of subjects; and (v) the privacy of subjects and confidentiality of the data.

Please note that if an IRB member had a conflict of interest with regard to the review of this project, that member left the room during the discussion and the vote on this project.

NOTES: Subject MATMCD missed visits 4 through 6 during the acute phase of the study and none of the study procedures were completed. In addition, the time between weeks 3 and 7 visits was six weeks rather than four weeks. At week 8 the subject's dose was increased to 10 mg/QD and the protocol states the maximum is 7.5 mg/QD. At month one of the extension phase of the study the dose was increased to 12.5 mg/QD. Each increase was well tolerated.

The investigator responded to HRC concerns and the full HRC reviewed the violation.

As Principal Investigator you are responsible for the following:

1. Submission in writing of any and all changes to this project (e.g., protocol, recruitment materials, consent form, etc.) to the IRB for review and approval prior to initiation of the change(s), except where necessary to eliminate apparent immediate hazards to the subject(s). Changes made to eliminate apparent immediate hazards to subjects must be reported to the IRB within 24 hours.

Human Research Committee
Massachusetts General Hospital
Lawrence House
10 North Grove Street
Boston, MA 02114
(617) 726-3494

2. Submission in writing of any and all adverse event(s) that occur during the course of this project that are both serious and unexpected within 10 working/14 calendar days of notification of event.
3. Submission in writing of any and all unanticipated problems involving risks to subjects or others.
4. Use of only IRB approved copies of the consent form(s), questionnaire(s), letter(s), advertisement(s), etc. in your research. Do not use expired consent forms.
5. Informing all physicians listed on the project of changes, adverse events, and unanticipated problems.

The IRB can and will terminate projects that are not in compliance with these requirements. Direct questions, correspondence and forms (e.g., continuing reviews, amendments, adverse events, safety reports) to Ronda Cox Goldman, (617) 724-2130.

c: Stephanie Dunkel, BA, Psychiatry, 185 Alewife

Attachment J

PHARMA SALARY SUMMARY

	2005	2006	2007
JB concerta (MCNEIL)	$ 14,888	$ 16,411	$ -
Lillt Ctr (ELI LILLY)	$ 30,034	$ 27,697	$ 13,143
J&J Ctr	$ 7,919	$ 7,266	$ 3,976

DETAILS

	Biederman, Joseph Oct-06	$	1,490.49
	Biederman, Joseph Sep-06	$	1,490.43
	Biederman, Joseph Aug-06	$	1,473.11
	Biederman, Joseph Jul-06	$	1,490.58
	Biederman, Joseph Jun-06	$	1,490.58
	Biederman, Joseph May-06	$	1,490.58
	Biederman, Joseph Apr-06	$	1,490.58
	Biederman, Joseph Mar-06	$	1,490.58
	Biederman, Joseph Feb-06	$	1,490.58
	Biederman, Joseph Jan-06	$	1,490.58
JB CONCERTA 2006		$	14,888.09
	Biederman, Joseph Dec-05	$	1,490.58
	Biederman, Joseph Nov-05	$	1,490.58
	Biederman, Joseph Sep-05	$	1,490.58

	Biederman, Joseph Aug-05	$	1,490.58
	Biederman, Joseph Jul-05	$	1,490.58
	Biederman, Joseph Jun-05	$	1,490.58
	Biederman, Joseph May-05	$	1,490.58
	Biederman, Joseph Apr-05	$	1,490.58
	Biederman, Joseph Mar-05	$	1,490.58
	Biederman, Joseph Feb-05	$	1,490.55
	Biederman, Joseph Jan-05	$	1,505.34
JB CONCERTA 2005		$	16,411.11
	Biederman, Joseph Jun-07	$	2,070.77
	Biederman, Joseph May-07	$	2,070.77
	Biederman, Joseph Apr-07	$	2,070.77
	Biederman, Joseph Mar-07	$	2,310.40
	Biederman, Joseph Feb-07	$	2,310.40
	Biederman, Joseph Jan-07	$	2,310.40
Lilly crtr 2007		$	13,143.51
	[redacted]		

	2005	2006
JB concerta (MCNEIL)	$ 14,888	$ 16,411
Lillt Ctr (ELI LILLY)	$ 30,034	$ 27,697
J&J Ctr	$ 7,919	$ 7,266

	Biederman, Joseph Dec-06	$ 2,310.40
	Biederman, Joseph Nov-06	$ 2,310.40
	Biederman, Joseph Oct-06	$ 2,310.40
	Biederman, Joseph Sep-06	$ 2,310.23
	Biederman, Joseph Aug-06	$ 2,283.49
	Biederman, Joseph Jul-06	$ 2,310.36
	Biederman, Joseph Jun-06	$ 2,310.36
	Biederman, Joseph May-06	$ 2,310.36
	Biederman, Joseph Apr-06	$ 2,310.36
	Biederman, Joseph Mar-06	$ 2,310.36
	Biederman, Joseph Feb-06	$ 2,310.36
	Biederman, Joseph Jan-06	$ 2,310.36
Lilly crtr 2006		$ 27,697.44
	Biederman, Joseph Dec-05	$ 2,310.36
	Biederman, Joseph Nov-05	$ 2,310.36
	Biederman, Joseph Oct-05	$ 2,310.36

	[redacted]	$	2,310.36
	Biederman, Joseph Aug-05	$	2,310.36
	[redacted]	$	2,310.36
	Biederman, Joseph Jun-05	$	2,310.36
	[redacted]	$	2,310.36
	Biederman, Joseph Apr-05	$	2,310.36
	[redacted]	$	2,310.36
	Biederman, Joseph Feb-05	$	4,620.71
	[redacted]	$	2,310.36
Lilly crtr 2005 J&J		$	30,034.67
	Biederman, Joseph Jun-07	$	661.18
	[redacted]	$	661.18
	Biederman, Joseph Apr-07	$	661.18
	[redacted]	$	661.18
	Biederman, Joseph Feb-07	$	661.18
	[redacted]	$	661.18

J&J crtr 2007		$	3,967.08
	[redacted]		
	Biederman, Joseph Dec-06	$	661.18
	[redacted]	$	661.18
	Biederman, Joseph Oct-06	$	661.18
	[redacted]	$	661.29
	Biederman, Joseph Aug-06	$	653.57
	[redacted]	$	661.39
	Biederman, Joseph Jun-06	$	661.39
	[redacted]	$	-
	Biederman, Joseph Apr-06	$	661.39
	[redacted]	$	661.39
	Biederman, Joseph Feb-06	$	661.39
	[redacted]	$	661.39
J&J crtr 2006		$	7,266.74
	[redacted]		
	Biederman, Joseph Dec-05	$	661.39
	[redacted]	$	661.39

	Biederman, Joseph Oct-05	$	661.39
	Biederman, Joseph Sep-05	$	661.39
	Biederman, Joseph Aug-05	$	661.39
	Biederman, Joseph Jul-05	$	661.39
	Biederman, Joseph Jun-05	$	661.39
	Biederman, Joseph May-05	$	661.39
	Biederman, Joseph Apr-05	$	661.39
	Biederman, Joseph Mar-05	$	661.39
	Biederman, Joseph Feb-05	$	661.14
	Biederman, Joseph Jan-05	$	644.92
J&J crtr 2005		$	7,919.96

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-639 S-048

AstraZeneca Pharmaceuticals LP
Attention: Kathryn Bradley
Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Ms. Bradley:

We acknowledge receipt of your supplemental new drug application dated and received December 4, 2008, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seroquel (quetiapine fumarate) tablets.

This "Changes Being Effected" supplemental new drug application provides for revised labeling to include new safety information for both adult and pediatric patients.

We have no objection to your submission of the new safety information pertaining to the clinical trials as a CBE supplement. However, the Division is requesting that you reformat the information for better integration in the overall label prior to your intended implementation on January 4, 2009. Specifically:

1. Place the pediatric safety information in the relevant sections of labeling with the adult data rather than separately in sections 5.19 and 8.4. For example, the proposed pediatric data in the section 8.4 subtitled "Changes in Thyroid Function Tests" should be placed at the end of section 5.10 (Warnings and Precautions: Hypothyroidism). The same principle applies to other pediatric safety information that already has adult data included prominently.
2. The weight gain signal is significant for both adult and pediatric populations and should be elevated to the Warnings and Precautions section rather than the vital signs section (the latter section could refer back to the information in Warnings and Precautions section) with inclusion of data for both populations. In fact, the data for weight change, glucose changes, and lipid changes from the clinical trials, both adult and pediatric, need to be elevated to the Warnings/Precautions section of labeling. Please see the format used in the currently distributed label for another antipsychotic drug, i.e., Zyprexa, for the correct format for this information.
3. The safety data for Increases in Blood Pressure is an unexpected signal and there is currently no similar adverse event signal for the adult population. Because of this unexpected and clinically significant signal that may be specific to the pediatric population, this safety data should be included in a separate section in Warnings and Precautions. Please offer your rationale for this unusual finding.

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4. For each section describing pediatric safety signals, the following statement should be included "Safety and effectiveness of SEROQUEL have not been established in pediatric patients and SEROQUEL is not approved for patients under the age of 18 years".
5. Please replace your proposed Hyperprolactinemia statement with the standard language now used for more recently approved atypical antipsychotic agents, e.g., Invega. Any actual clinical trials data regarding prolactin elevation should, of course, be data for quetiapine, including the pediatric data.
6. All pediatric safety data and the other changes we are requesting for Seroquel should be included in revised labeling for Seroquel XR as well.

The above requested changes should be implemented immediately, and they should be submitted as an amendment to your pending supplemental application to the Seroquel NDA and as an original supplemental application to the Seroquel XR NDA, 22-047, within 30 days from the date of this letter, or notify FDA that you do not believe these changes are warranted, and submit a statement detailing the reasons. If you wish to have our prior comment on your alternative proposal in response to these requests, we would be happy to provide such comment.

Please note that your proposed labeling language in the above referenced CBE is under continuing review by the Agency. Please also note that the Division is currently reviewing your metabolic data submission and the pediatric efficacy supplements submitted under this NDA (S-045 and S-046). We will be providing further labeling comments, if any, and will take final action on these submissions when reviews are completed.

If you have any questions, call Kimberly Updegraff, M.S., Regulatory Project Manager, at 301-796-2201.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CONFIDENTIAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Laughren
12/18/2008 04:06:08 PM

CONFIDENTIAL

AstraZeneca

Clinical Overview

Drug Name Quetiapine fumarate

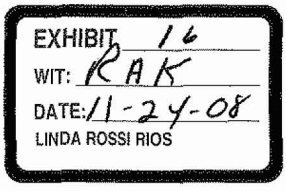
Date July 2008

SEROQUEL™ (quetiapine fumarate)
Clinical Overview on Weight Gain in pediatric patients

Authors:

Leigh Jefferies M.D.
Global Safety Physician
Patient Safety, Wilmington, DE

Eva S.K. Alam, M.S., Pharm.D., RPh
Safety Surveillance Team Leader
Patient Safety, Wilmington, DE



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LIST OF TABLES

1. PRODUCT DEVELOPMENT RATIONALE

1.1 Introduction

The Core Data Sheets for SEROQUEL is to be amended following an internal safety evaluation and review meeting on 09 July 2008. The purpose of this document is to summarize the key information on which the decision to amend the CDS was based, to document the Core Data Sheet amendment and to support changes to local Prescribing Information.

1.1.1 SEROQUEL and SEROQUEL XR

SEROQUEL and SEROQUEL XR are atypical antipsychotic agents, presented as tablets containing quetiapine fumarate, which exhibits affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. In addition, SEROQUEL/SEROQUEL XR also have high affinity at histaminergic and adrenergic α1 receptors, with a lower affinity at adrenergic α2 receptors, but no appreciable affinity at cholinergic, muscarinic or benzodiazepine receptors.

SEROQUEL was first approved for marketing in the United Kingdom (UK) on 31 July 1997 and was first launched in the UK on 22 September 1997. By 31 March 2008, SEROQUEL has been approved in 89 countries for schizophrenia, 86 countries for bipolar mania, (with Mexico being the first country to approve bipolar mania on 29 May 2003), 26 countries for bipolar depression, (with Czech Republic being the first country to approve bipolar depression on 27 September 2006), and in one country for bipolar maintenance (USA being the first country to approve bipolar maintenance on 14 May 2008). SEROQUEL is presented as tablets delivering a dose of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL is not approved for children or adolescents below 18 years of age.

SEROQUEL XR was first approved for marketing in the United States (US) for acute schizophrenia on 18 May 2007 and for maintenance of schizophrenia on 15 November 2007. By 31 March 2008, SEROQUEL XR has been approved in 30 countries for schizophrenia (including 14 countries in the Mutual Recognition Procedure), 7 countries for bipolar mania (with Slovakia being the first country to approve bipolar mania on 28 June 2007), and in one country for bipolar depression (Mexico being the first country to approve bipolar depression in October 2007). SEROQUEL XR is presented as tablets delivering a dose of 50 mg, 200 mg, 300 mg, or 400 mg of quetiapine free-base. SEROQUEL XR is not approved for children or adolescents below 18 years of age.

1.2 Proposed label change

The following text will be added to Section 4.8 *Undesirable effects* of the SEROQUEL CDS under a subheading of *Children and adolescents.*

Children and adolescents

The same ADRs described above for adults apply to children and adolescents. The following table summarizes ADRs that occur in a higher frequency category in children and adolescents patients (10-17 years of age) than in the adult population or ADRs that have not been identified in the adult population.

Weight gain in children and adolescents

In one 6-week, placebo-controlled trial in adolescent patients (13-17 years of age) with schizophrenia, the mean increase in body weight, was 2.0 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty one percent of quetiapine-treated patients and 7% of placebo-treated patients gained ≥ 7 % of their body weight.

In one 3-week, placebo-controlled trial in children and adolescent patients (10-17 years of age) with bipolar mania, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine-treated patients and 0% of placebo-treated patients gained ≥ 7 % of their body weight.

In the open-label study that enrolled patients from the above two trials, 63% of patients (241/380) completed 26 weeks of therapy with quetiapine. After 26 weeks of treatment, the mean increase in body weight was 4.4 kg. Forty five percent of the patients gained ≥ 7% of their body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

Since clinical trials in pediatric patients have been conducted with SEROQUEL and not SEROQUEL XR this change applies only to the SEROQUEL CDS.

2. OVERVIEW OF BIOPHARMACEUTICS

This section is not relevant to this document.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not relevant to this document.

4. OVERVIEW OF EFFICACY

This section is not relevant to this document.

5. OVERVIEW OF SAFETY

5.1 Data summary and discussion

5.1.1 Pediatric clinical trial data

The data presented below is taken from two acute placebo-controlled studies with SEROQUEL in pediatric patients with schizophrenia or bipolar mania and one longer-term open-label study with SEROQUEL. The patients in the longer-term trial were originally enrolled in one of the two acute placebo-controlled trials. The following is a brief description of these three trials.

- D1441C00112: a 6-week, International, Multicenter, Randomized, Double-blind, Parallel group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 800 mg Compared with Placebo in the Treatment of Adolescents with Schizophrenia

- D1441C00149: a 3-week, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Phase IIIb Study of the Efficacy and Safety of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg and 600 mg Compared with Placebo in the Treatment of Children and Adolescents with Bipolar I Mania

- D1441C00150: a 26-week, International, Multicenter, Open-label Phase IIIb Study of the Safety and Tolerability of Quetiapine Fumarate (SEROQUEL™) Immediate-release Tablets in Daily Doses of 400 mg to 800 mg in Children and Adolescents with Bipolar I Disorder and Adolescents with Schizophrenia

5.1.2 Acute placebo-controlled data

5.1.2.1 D144C00112

Mean increase in body weight

In study D144C00112, mean weights were similar at baseline for the three treatment groups. Mean changes in weight from baseline were higher for quetiapine-treated patients at each time point compared to placebo. At Day 42, the mean changes from baseline were 2.2 kg in the 400 mg/day quetiapine group, 1.8 kg in the 800 mg/day quetiapine group, and –0.4 kg in the placebo group (see Table 1).

Table 1 D144C00112: Mean increase in weight from baseline

Change from Baseline	QTP 400 mg	QTP 800 mg	PLACEBO
Day 42	2.2 kg	1.8 kg	-0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (23.21% in the 400 mg/day and 18.18% in the 800 mg/day) had ≥7% weight gain at Day 42 compared to the placebo-treated patients (6.82%) (see Table 2).

Table 2 D144C00112: Patients with ≥ 7% weight gain (Summary safety population)

Visit	QTP 400 mg N=56 n (%)	QTP 800 mg N = 55 n (%)	PLA N = 44 n (%)
Day 42	13 (23.2)	10 (18.2)	3 (6.8)

5.1.2.2 D144C00149

Mean increase in weight

Mean increases in weight from baseline to Day 21 were higher for quetiapine-treated patients at each time point compared to placebo. These increases from baseline were 1.7 kg in the 400 mg quetiapine-treated group, 1.7 kg in the 600 mg quetiapine-treated group and 0.4 kg in the placebo group. Quetiapine-treated patients experienced higher mean increases in weight compared to placebo at Day 21 (see Table 3).

Table 3 D144C00149: Mean increase in weight from baseline

Change from baseline	QTP 400 mg	QTP 600 mg	PLA
Day 21	1.7 kg	1.7 kg	0.4 kg

Patients with ≥7% weight gain

A higher percentage of quetiapine-treated patients (14.47% in the 400 mg/day and 9.88% in the 600 mg/day) had ≥7% weight gain at Day 21 compared to placebo-treated patients (0%) (see Table 4).

Table 4 D144C00149: Patients with ≥7% weight gain (Summary safety population)

Visit	QTP 400 mg N = 76 n (%)	QTP 600 mg N = 81 n (%)	PLACEBO N = 68 n (%)
Day 21	11 (14.5)	8 (9.9)	0 (0)

5.1.3 Longer-term open-label pediatric data

5.1.3.1 D1441C00150

Study D1441C00150 was an open-label extension study designed to assess the safety and tolerability of quetiapine (flexibly dosed at 400 mg/day to 800 mg/day) in adolescents with schizophrenia (continuing from Study D144C00112) and in children and adolescents with bipolar I disorder (continuing from Study D144C00149). There were a total of 380 patients in the safety analysis set, including 175 with schizophrenia and 205 with mania. Sixty-three percent of patients (241) completed 26 weeks of therapy with quetiapine.

All patients treated with quetiapine 50 mg/day on Day 1 then escalated to 400 mg on Day 5. From Day 5, the target dose of 400 mg/day was maintained or increased by no more than 100 mg/day, up to 800 mg/day or adjusted down to 200 mg/day. Patients were treated for up to 26 weeks.

Mean increase in weight

The mean change in weight for schizophrenia and bipolar I patients (who enrolled) from OL baseline as well as DB baseline to final visit are provided in Table 5.

Table 5 **Study D1441C00150: mean changes from baseline to the final visit (safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline									
Final visit (150 OL BSLN)	62	67.4	16.3	113	64.8	19.2	175	65.7	18.2
Change from 112 DB BSLN	62	4.1	8.5	113	4.8	10.8	175	4.6	10.0
Change from 150 OL Baseline	62	4.3	6.9	113	2.8	10.1	175	3.3	9.1
149 DB Baseline									
Final visit (150 OL BSLN)	64	68.3	21.9	136	64.5	18.4	200	65.8	19.6
Change from 149 DB BSLN	64	5.8	6.4	136	5.1	5.7	200	5.3	5.9
Change from 150 OL Baseline	64	5.5	5.8	135	3.2	4.8	199	4.0	5.2
Total 149 and 112 pooled DB Baseline									
Final visit (150 OL BSLN)	126	67.9	19.3	249	64.7	18.7	375	65.7	19.0
Change from DB BSLN	126	5.0	7.50	249	5.0	8.3	375	5.0	8.1
Change from 150 OL Baseline	126	4.9	6.4	248	3.0	7.6	374	3.7	7.3

In patients who completed 26 weeks of therapy with quetiapine (n=241) in Trial D1441C00150, the mean change in weight from OL baseline was 4.4 kg.

Patients with ≥7% weight gain

In the safety population, 134 patients (35.6%) experienced ≥7% weight gain from OL baseline to final visit (see Table 6).

Table 6 **Study D1441C00150: Patients with ≥ 7% weight gain (Summary safety population)**

	Acute feeder study treatment								
	Prior Placebo (N=129)			Prior All QTP (N=251)			Total (N=380)		
	N	n	(%)	N	n	(%)	N	n	(%)
Pooled data 149 and 112									
From DB Baseline	127	58	45.7	249	119	47.8	376	177	47.1
From 150 OL Baseline	127	50	39.4	249	84	33.7	376	134	35.6
Study 112 (schizophrenia)									
From DB Baseline	62	24	38.7	113	43	38.1	175	67	38.3
From 150 OL Baseline	62	19	30.6	113	32	28.3	175	51	29.1
Study 149 (BP I)									
From DB Baseline	65	34	52.3	136	76	55.9	201	110	54.7
From 150 OL Baseline	65	31	47.7	136	52	38.2	201	83	41.3

Of the patients who completed 26 weeks of treatment with quetiapine, 44.8% (108/241) had a ≥7% increase in weight from OL baseline.

5.1.4 Additional analysis of Pediatric data

5.1.4.1 Z-scores

Since body weight and height should increase in children, data showing an increase in weight with time sometimes may not indicate a problem. One convenient way to express body weight is in terms of body mass index (BMI), since with BMI, the weight is adjusted for height (Correll et al 2006).

A better measure of weight change in children and adolescents is to convert the mean weight and BMI to a Z-score taking into consideration the age and gender of the subject. Z-scores are able to show how different a child's weight or BMI is from the average children of the same height (Reyes et al 2006).

One of the criteria proposed to show significant weight gain in children and adolescents is a greater than or equal to an increase in BMI Z-score of 0.5 over any duration of time (Correll et al 2006). This increase represents a change of 0.5 standard deviation from baseline.

BMI Z-scores

The mean BMI Z-scores (for patients who enrolled in study D1441C00150) from the DB baseline for schizophrenia to the final visit and end of treatment are higher for the prior placebo group compared to the prior quetiapine group (see Table 7).

Table 7 Study D1441C00150: Mean values of BMI Z score at baseline, end of treatment and final visit (safety population)

	Acute feeder study treatment								
	Prior Placebo (N=129)			All prior QTP (N=251)			Total (N=380)		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
112 DB Baseline	62	**0.3**	1.2	113	**-0.1**	1.4	175	**0.0**	1.3
Week 26	41	0.4	1.1	86	0.1	1.22	127	0.2	1.2
Final Visit	62	**0.5**	1.0	113	**0.2**	1.3	175	**0.3**	1.2
149 DB Baseline	67	**1.0**[a]	1.0	138	**0.9**[a]	1.1	205	**0.9**[a]	1.0
Week 26	37	1.2	1.0	77	1.2	1.0	114	1.2	1.0
Final Visit	63	**1.2**	1.0	135	**1.0**	1.0	198	**1.1**	1.0
DB Total Baseline	129	**0.6**	1.2	251	**0.4**	1.3	380	**0.5**	1.3
Week 26	78	0.8	1.1	163	0.6	1.2	241	0.7	1.2
Final Visit	125	**0.9**	1.0	248	**0.7**	1.2	373	**0.7**	1.2

[a] The mean BMI Z score at baseline is much higher for the 149 population

Table 8 below shows patients who had a ≥ 0.5 shift in BMI Z-score during trial D1441C00150 from both DB baseline and OL baseline and by indication. Of all patients who completed 26 weeks of treatment with quetiapine, 18.3% (44/241) had a shift of ≥ 0.5 BMI Z-score.

Table 8 **Patients with ≥ 0.5 shift in BMI Z score in Study D1441C00150 by indication**

Occurrence	Schizophrenia to OL 150		BP to OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	N/N (%)
End of Treatment/DB	24/113 (21.2)[a]	17/62 (27.4)[a]	29/135 (21.5)[c]	12/63 (19)[c]	82/373 (22)
End of Treatment/OL	16/113 (14.2)[b]	15/62 (24)[b]	11/133 (8.3)[b]	12/63 (19)[b]	54/371 (14.6)[b]

[a] From double blind baseline of study 112 to end of study 150; [b] From OL baseline of study 150 to end of study 150; [c] From double blind baseline of study 149 to end of study 150

Patients with ≥0.5 shift in standardized BMI Z-score in Study D1441C00150 by age group

A similar percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (28% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (25% at EOT) from the DB baseline (see Table 9).

A higher percentage of patients ≤12 years of age (who enrolled in study D1441C00150) treated with prior placebo (24% at EOT) had ≥0.5 shift in standardized BMI Z-score compared with prior quetiapine-treated patients (8.6% at EOT) from the OL baseline (see Table 9).

A similar percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (22% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (20.1% at EOT) from the DB baseline (see Table 9).

A higher percentage of pediatric patients 13-18 years of age (who enrolled in study D1441C00150) treated with prior placebo (21% at EOT) had ≥0.5 shift in standardized BMI Z-score compared to prior quetiapine-treated patients (11.7% at EOT) from the OL baseline (see Table 9).

Table 9 **Patients with ≥0.5 shift in BMI Z score in Study D1441C00150 by age group***

Occurrence	≤ 12 years OL 150		13 to 17 years OL 150		OL 150
Time/baseline	DB All Quetiapine	DB Placebo	DB All Quetiapine	DB Placebo	OL All - Quetiapine
	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
End of Treatment/DB	15/59 (25)	7/25 (28)	38/189 (20.1)	22/100 (22)	82/373 (22)
End of Treatment/OL	5/58 (8.6)	6/25 (24)	22/188 (11.7)	21/100 (21)	54/371 (14.6)

* Study 112 was a six week placebo controlled trial in adolescent patients (13-17 years) and study 149 was a three week trial in children and adolescent patients (10-17 years)

5.1.4.2 Overall summary of pediatric clinical trial data

In trial D1441C00112, the mean increase in body weight was 2 kg in the quetiapine group and -0.4 kg in the placebo group. Twenty-one percent of quetiapine patients and 7% of placebo patients had gained ≥7% of their body weight.

In trial D144C00149, the mean increase in body weight was 1.7 kg in the quetiapine group and 0.4 kg in the placebo group. Twelve percent of quetiapine patients and 0% of placebo patients had gained ≥7% of their body weight.

In trial D1441C00150, where 63% of patients (241/380) completed 26 weeks of therapy with quetiapine, the mean increase in body weight was 4.4 kg. Forty-five percent of the patients had ≥7% increase in body weight, not adjusted for normal growth. In order to adjust for normal growth over 26 weeks, an increase of at least 0.5 standard deviation from baseline in BMI was used as a measure of a clinically significant change; 18.3% of patients on quetiapine met this criterion after 26 weeks of treatment.

6. BENEFITS AND RISKS CONCLUSIONS

The purpose of this application is to update the SEROQUEL Core Data Sheet and local Prescribing information with current findings in relation to weight gain in patients treated with quetiapine. AstraZeneca believes that these data do not alter the overall safety and tolerability profile of SEROQUEL and SEROQUEL XR and that the benefit/risk profile of SEROQUEL and SEROQUEL XR remains positive.

7. REFERENCES

Correll et al 2006
Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J. Am. Acad. Child. Adolesc. Psychiatry. 2006; 45 (7):771-791.

Reyes et al 2006
Reyes M, Croonenberghs J, Augustyns I, Eerdekens M. Long-term use of risperidone in children with disruptive behavior disorders and subaverage intelligence: efficacy, safety and tolerability. J. Child. Adolescent. Psychopharmacol. 2006; 16(3): 260-272.

According to his/her respective qualification the undersigned expert declares hereby to have performed the duties set out in the Article 12 and in accordance with Annex I Part I 1.4 of Directive 2001/83/EC, as amended

CLINICAL:

Name of the expert: Leigh Jefferies, MD
Global Safety Physician
Patient Safety

Signature:

Address:
1800 Concord Pike
Wilmington, DE 19850

Date:

According to the Annex I of Directive 2001/83/EC as amended, brief information (curriculum vitae) on the educational, training and occupational experience of the expert is attached.

Unknown

From: Gavin Jim JP
Sent: Wednesday, December 08, 1999 12:32 PM
To: De Vriese Geert
Cc: Holdsworth Debbie D;Tumas John JA;Tugend Georgia GL;Czupryna Michael MJ;Gorman Andrew AP;Wilkie Alison AM;Litherland Steve S;Murray Michael MF;Rak Ihor IW;Owens Judith J;O'Brien Shawn SP;Denerley Paul PM;Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Attachments: jamapubs.pdf

Thanks for this Geert. If I could add my own thoughts in advance of the GPT tomorrow...Certainly any progress on the (selective) use of data from COSTAR would be particularly appreciated, as I'm currently getting mixed messages on whether we use the EPS data from this trial.

I was interested to hear that we are discussiing the recent JAMA article on the reporting of clinical trials (link attached). This article concerns me as it highlights what appears to be an increasing scepticism among journal editors with regards to certain aspects of company-sponsored publications. Janssen have had their fingers burned in the past in this regard, and are consequently cited every time such an editorial appears, something that presumably irritates the hell out of them. Quite apart from any ethical considerations, if they thought we were publishing positive data vs risperidone from QUEST while results from a second trial were being buried, they'd be onto it in a flash. Selectively using (for example) the EPS data from COSTAR is pushing it too far in my opinion, and might prove extremely damaging in the long run (and you can bet Janssen would push it), and would destroy our current high standing in the publishing community.

jamapubs.pdf (112 KB)

Regards
Jim

From: Owens Judith J
Sent: 08 December 1999 09:24
To: Gavin Jim JP
Subject: FW: 2 EPS Abstracts for APA

FYI

From: De Vriese Geert
Sent: 08 December 1999 08:42
To: Baker Kendra; Tumas John JA
Cc: Scanlon Rose Ann RA; Denerley Paul PM; Owens Judith J
Subject: RE: 2 EPS Abstracts for APA

Kendra,
John,

REDACTED

From: Baker Kendra
Sent: 07 December 1999 22:49
To: Owens Judith J; De Vriese Geert
Cc: Tumas John JA; Scanlon Rose Ann RA; Denerley Paul PM
Subject: FW: 2 EPS Abstracts for APA

PRIVILEGED AND CONFIDENTIAL

EXHIBIT 42
WIT: RAK
DATE: 11-25-08
LINDA ROSSI RIOS

REDACTED

Best regards,
Kendra Baker
Attorney
Legal Department
AstraZeneca
Tel. (302) 886-4233 Fax: (302) 886-8221
Kendra.Baker@astrazeneca.com

From: Scanlon Rose Ann RA
Sent: Tuesday, December 07, 1999 2:33 PM
To: Baker, Kendra
Subject: FW: 2 EPS Abstracts for APA

REDACTED

Rose Ann Scanlon
Assistant General Counsel
AstraZeneca
Telephone: 302 886 4009
Fax: 302 886 8221

From: Denerley Paul PM
Sent: December 07, 1999 10:24 AM
To: Scanlon Rose Ann RA
Subject: FW: 2 EPS Abstracts for APA

From: Tumas John JA
Sent: Monday, December 06, 1999 11:45 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S; Gavin Jim JP
Cc: Holdsworth Debbie D; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Please allow me to join the fray.

There has been a precedent set regarding "cherry picking" of data. This would be the recent Velligan presentations of cognitive function data from Trial 15 (one of the buried trials). Thus far, I am not aware of any repercussions regarding interest in the unreported data.

That does not mean that we should continue to advocate this practice. There is growing pressure from outside the industry to provide access to all data resulting from clinical trials conducted by industry. Thus far, we have buried Trials 15, 31, 56, and are now considering COSTAR.

The larger issue is how do we face the outside world when they begin to criticize us for suppressing data. One

could say that our competitors indulge in this practice. However, until now, I believe we have been looked upon by the outside world favorably with regard to ethical behavior. We must decide if we wish to continue to enjoy this distinction.

The reporting of the COSTAR results will not be easy. We must find a way to diminish the negative findings. But, in my opinion, we cannot hide them.

Best regards,

John

From: Gavin Jim JP
Sent: Monday, December 06, 1999 1:59 PM
To: Owens Judith J; Jones Martin AM - PHMS; Litherland Steve S
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert; Shadwell Pamela PG
Subject: RE: 2 EPS Abstracts for APA

Steve's comments are pertinent, as the EPS abstracts (for the APA) and the Scourge of EPS review both emanate from the ECNP symposium, and as such represent a potential transition of COSTAR data from a "closed" mtg to a public forum. Coming in late to the debate, the only directive I have on QUEST/COSTAR (contained in a document compiled by Ihor & Martin in August) suggested using them "as clinically appropriate", but independently.

I believe the newly-formed Commercial Support Team will be considering looking at potential ways of using COSTAR. With regards to the present outputs however, a short-term solution (given the impending APA deadline) is to avoid reference to COSTAR in the proposed APA abstract. Whether or not we discuss it in either the poster or the review subsequently will need to decided by the team, with reference to how we would then need to approach the efficacy story.

Regards
Jim

From: Litherland Steve S
Sent: 06 December 1999 11:51
To: Owens Judith J; Jones Martin AM - PHMS
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM; Woods Paul PB; Holdsworth Debbie D; De Vriese Geert
Subject: RE: 2 EPS Abstracts for APA

Martin has drawn our attention to an enduring problem which requires resolution as soon as possible.

- should we publish COSTAR? The disadvantages are obvious, not least that we provide the opposition with potentially damaging data when they calculate p values re the primary efficacy endpoint
- if not, can we extract some information and use this to support our messages? The following is scheduled to appear in Clear Vision (proceedings of the ECNP EPS meeting):

A second study comparing flexible dosing of risperidone (6-10 mg daily) and quetiapine (300-600 mg daily) reported that over 10 weeks significantly more risperidone patients (31.4%) than quetiapine patients (14.1%)In my draft 30.4 and 13.1% ; need to check experienced EPS or akathisia (30.4% and 16.6 15.4 in MR doc%, respectively) ($p<0.001$ for both comparisons) (Data on file).

This was sanctioned for the meeting but when it appears in Clear Vision it will be in the public domain. We can be accused of "cherry picking" and this may fuel demands to see the entire study (Cochrane would be most interested, for example).

- Are we using QUEST promotionally? If so, we could be accused of not telling the complete story

I am concerned that by doing nothing re COSTAR, except to allow details to emerge in dribs and drabs we are not taking control of the situation. An initial step may perhaps be to canvass expert opinion

outside the Company (I know that we have had some feedback but I understand this was conflicting and uncoordinated).

Steve

From: Jones Martin AM - PHMS
Sent: 06 December 1999 10:55
To: Owens Judith J
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP; Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Subject: RE: 2 EPS Abstracts for APA

Judith

I have no real comments on the Juncos abstract, but am concerned about Tandon's.

In Tandon's results section, he refers to a randomised comparative study. This study is COSTAR. I think that we are still not comfortable about communicating the overall results of this study. Whilst this data may have been presented orally in London, I think this abstract would be the first time we have put anything 'down on paper'. Are we sure that this we can present the EPS data in isolation given the nature of the other results ? Will we not create a desire for further information about the study ? Can we not refer to published (non-comparative) data for risperidone, as we must be doing this for olanzapine ? Should we be looking at the ziprasidone data too ? They seem to have dose-response effect as well.

Martin

From: Owens Judith J
Sent: 02 December 1999 17:14
To: Wilkie Alison AM; Gavin Jim JP; Litherland Steve S; Murray Michael MF; Rak Ihor IW; Jones Martin AM - PHMS; O'Brien Shawn SP; Denerley Paul PM; Goldstein Jeffrey JM
Cc: Holdsworth Debbie D; Tumas John JA; Tugend Georgia GL; Czupryna Michael MJ; Gorman Andrew AP
Subject: 2 EPS Abstracts for APA
Importance: High

Dear All
Please find attached, for your review, 2 EPS abstracts that are intended for submission to APA. The abstracts are based on presentations at the AstraZeneca symposium 'CLEAR VISION - A fresh look at EPS' held during this year's ECNP.
Please return any comments you may have by midday (UK time) **Monday 6 December**.
Kind regards
Judith
<<File: Juncos abstract.doc>><<File: Tandon abstract.doc>>

Judith Owens
Ext: 24164
11F34 Mereside

The Washington Post

A Silenced Drug Study Creates An Uproar

By Shankar Vedantam
Washington Post Staff Writer
Wednesday, March 18, 2009; A01

The study would come to be called "cursed," but it started out just as Study 15.

It was a long-term trial of the antipsychotic drug Seroquel. The common wisdom in psychiatric circles was that newer drugs were far better than older drugs, but Study 15's results suggested otherwise.

As a result, newly unearthed documents show, Study 15 suffered the same fate as many industry-sponsored trials that yield data drugmakers don't like: It got buried. It took eight years before a taxpayer-funded study rediscovered what Study 15 had found -- and raised serious concerns about an entire new class of expensive drugs.

Study 15 was silenced in 1997, the same year Seroquel was approved by the Food and Drug Administration to treat schizophrenia. The drug went on to be prescribed to hundreds of thousands of patients around the world and has earned billions for London-based AstraZeneca International -- including nearly $12 billion in the past three years.

The results of Study 15 were never published or shared with doctors, even as less rigorous studies that came up with positive results for Seroquel were published and used in marketing campaigns aimed at physicians and in television ads aimed at consumers. The results of Study 15 were provided only to the Food and Drug Administration -- and the agency has strenuously maintained that it does not have the authority to place such studies in the public domain.

AstraZeneca spokesman Tony Jewell defended the Seroquel research and said the company had disclosed the drug's risks. Since 1997, the drug's labeling has noted that weight gain and diabetes were seen in study patients, although the company says the data are not definitive. The label states that the metabolic disorders may be related to patients' underlying diseases.

The FDA, Jewell added, had access to Study 15 when it declared Seroquel safe and effective. The trial, which compared patients taking Seroquel and an older drug called Haldol, "did not identify any safety concerns," AstraZeneca said in an e-mail. Jewell added, "A large proportion of patients dropped out in both groups, which the company felt made the results difficult to interpret."

The saga of Study 15 has become a case study in how drug companies can control the publicly available research about their products, along with other practices that recently have prompted hand-wringing at universities and scientific journals, remonstrations by medical groups about conflicts of interest, and threats of exposure by trial lawyers and congressional watchdogs.

Even if most doctors are ethical, corporate grants, gifts and underwriting have compromised psychiatry, said an editorial this month in the American Journal of Psychiatry, the flagship journal of the American Psychiatric

Association.

"The public and private resources available for the care of our patients depend upon the public perception of the integrity of our profession as a whole," wrote Robert Freedman, the editor in chief, and others. "The subsidy that each of us has been receiving is part of what has fueled the excesses that are currently under investigation."

Details of Study 15 have emerged through lawsuits now playing out in courtrooms nationwide alleging that Seroquel caused weight gain, hyperglycemia and diabetes in thousands of patients. The Houston-based law firm Blizzard, McCarthy & Nabers, one of several that have filed about 9,210 lawsuits over Seroquel, publicized the documents, which show that the patients taking Seroquel in Study 15 gained an average of 11 pounds in a year -- alarming company scientists and marketing executives. A Washington Post analysis found that about four out of five patients quit taking the drug in less than a year, raising pointed doubts about its effectiveness.

An FDA report in 1997, moreover, said Study 15 did offer useful safety data. Mentioning few details, the FDA said the study showed that patients taking higher doses of the drug gained more weight.

In approving Seroquel, the agency said 23 percent of patients taking the drug in all studies available up to that point experienced significant weight increases, compared with 6 percent of control-group patients taking sugar pills. In 2006, FDA warned AstraZeneca against minimizing metabolic problems in its sales pitches.

In the years since, taxpayer-funded research has found that newer antipsychotic drugs such as Seroquel, which are 10 times as expensive, offer little advantage over older ones. The older drugs cause involuntary muscle movements known as tardive dyskinesia, and the newer ones have been linked to metabolic problems.

Far from dismissing Study 15, internal documents show that company officials were worried because 45 percent of the Seroquel patients had experienced what AstraZeneca physician Lisa Arvanitis termed "clinically significant" weight gain.

In an e-mail dated Aug. 13, 1997, Arvanitis reported that across all patient groups and treatment regimens, regardless of how numbers were crunched, patients taking Seroquel gained weight: "I'm not sure there is yet any type of competitive opportunity no matter how weak."

In a separate note, company strategist Richard Lawrence praised AstraZeneca's efforts to put a "positive spin" on "this cursed study" and said of Arvanitis: "Lisa has done a great 'smoke and mirrors' job!"

Two years after those exchanges, in 1999, the documents show that the company presented different data at an American Psychiatric Association conference and at a European meeting. The conclusion: Seroquel helped psychotic patients lose weight.

The claim was based on a company-sponsored study by a Chicago psychiatrist, who reviewed the records of 65 patients who switched their medication to Seroquel. It found that patients lost an average of nine pounds over 10 months.

Within the company, meanwhile, officials explicitly discussed misleading physicians. The chief of a team charged with getting articles published, John Tumas, defended "cherry-picking" data.

"That does not mean we should continue to advocate" selective use of data, he wrote on Dec. 6, 1999, referring to a trial, called COSTAR, that also produced unfavorable results. But he added, "Thus far, we have buried Trials 15, 31, 56 and are now considering COSTAR."

Although the company pushed the favorable study to physicians, the documents show that AstraZeneca held

the psychiatrist in light regard and had concerns that he had modified study protocols and failed to get informed consent from patients. Company officials wrote that they did not trust the doctor with anything more complicated than chart reviews -- the basis of the 1999 study showing Seroquel helped patients lose weight.

For practicing psychiatrists, Study 15 could have said a lot not just about safety but also effectiveness. Like all antipsychotics, Seroquel does not cure the diseases it has been approved to treat -- schizophrenia and bipolar disorder -- but controls symptoms such as agitation, hallucinations and delusions. When government scientists later decided to test the effectiveness of the class of drugs to which Seroquel belongs, they focused on a simple measure -- how long patients stayed on the drugs. Discontinuation rates, they decided, were the best measure of effectiveness.

Study 15 had three groups of about 90 patients each taking different Seroquel doses, according to an FDA document. Approximately 31 patients were on Haldol. The study showed that Seroquel failed to outperform Haldol in preventing psychotic relapses.

In disputing Study 15's weight-gain data, company officials said they were not reliable because only about 50 patients completed the year-long trial. But even without precise numbers, this suggests a high discontinuation rate among patients taking Seroquel. Even if every single patient taking Haldol dropped out, it appears that at a minimum about 220 patients -- or about 82 percent of patients on Seroquel -- dropped out.

Eight years after Study 15 was buried, an expensive taxpayer-funded study pitted Seroquel and other new drugs against another older antipsychotic drug. The study found that most patients getting the new and supposedly safer drugs stopped taking them because of intolerable side effects. The study also found that the new drugs had few advantages. As with older drugs, the new medications had very high discontinuation rates. The results caused consternation among doctors, who had been kept in the dark about trials such as Study 15.

The federal study also reported the number of Seroquel patients who discontinued the drug within 18 months: 82 percent.

Jeffrey Lieberman, a Columbia University psychiatrist who led the federal study, said doctors missed clues in evaluating antipsychotics such as Seroquel. If a doctor had known about Study 15, he added, "it would raise your eyebrows."

Subject: Prospective Subpoena in PsychRights v. Alaska
From: Jim Gottstein <jim.gottstein@psychrights.org>
Date: Thu, 19 Feb 2009 09:53:52 -0900
To: cbailey@bpblaw.com
CC: ccoutroulis@carltonfields.com, jisani@hunton.com, mcfisk@bloomberg.net, Jim Gottstein <jim.gottstein@psychrights.org>, Kris Hundley <krishundley@gmail.com>, VERACARE <veracare@ahrp.org>, Lisa Demer <LDemer@adn.com>, "Toomey, Sheila" <SToomey@adn.com>

Dear Mr. Bailey,

In *Law Project for Psychiatric Rights v. State of Alaska, et al.*, Case No. 3AN 08-10115 CI, we are seeking declaratory and injunctive relief that Alaskan children and youth have the right not to be administered psychotropic drugs unless and until:

(i) evidence-based psychosocial interventions have been exhausted,
(ii) rationally anticipated benefits of psychotropic drug treatment outweigh the risks,
(iii) the person or entity authorizing administration of the drug(s) is fully informed, and
(iv) close monitoring of, and appropriate means of responding to, treatment emergent effects are in place,

and that all children and youth currently receiving such drugs be evaluated and brought into compliance with the above.

We understand you are lead attorney in the *Seroquel Products Liability Litigation* in the US District Court for the Middle District of Florida, MDL No. 1769, and that there is a hearing on February 26th before Magistrate Judge Baker regarding Astra-Zeneca's desire to keep under seal certain information of vital public importance.

It is clear this same information is very relevant in *PsychRights v. Alaska*, because as I am sure you know Seroquel is often prescribed to children and youth in state custody and through Medicaid. Thus, we are very interested in the documents and anticipate having a deposition subpoena issued to you for at least the documents set forth on the (hopefully) attached list if they are not unsealed in the near future. Because *PsychRights v. Alaska* is not limited to the problem of Seroquel causing diabetes and other blood sugar/metabolic problems, we are also interested in other negative effects of Seroquel, unpublished studies, including those involving children and youth, and the promotion of Seroquel for pediatric use.

In accordance with our practice, rather than just serve you with a subpoena without warning, if the documents are going to remain sealed for any length of time, we would like to arrange for a mutually satisfactory date/time/location for the deposition, service of the subpoena, delivery of the documents, etc. We are also open to suggestions of a different person(s) to subpoena. I have reviewed the September 19, 2007, Protective Order, including ¶14, and understand it to be the operative document. If I am mistaken in this, please so advise me and provide the operative document. We anticipate Astra-Zeneca, whose attorney is copied on this, will (unlike Lilly) timely invoke ¶14 of the Protective Order and we will be litigating in *PsychRights v. Alaska* our entitlement to the documents and under what conditions, if any, they will be produced.

One question I have is if Magistrate Judge Baker decides at the February 26th hearing that the documents should be unsealed, is that likely to be subjected to further proceedings before the documents are actually unsealed and available to the public?

Please call at your convenience to discuss this matter, remembering that Alaska is three hours behind Houston (one hour behind the West Coast).

--

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PsychRights®
Law Project for Psychiatric Rights

The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging. We are further dedicated to exposing the truth about these drugs and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Extensive information about this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.

090121ListOfAZDocuments.pdf	**Content-Type:** application/pdf **Content-Encoding:** base64

EXHIBIT A -- DOCUMENTS CHALLENGED BY PLAINTIFFS

DOCUMENTS TO RETAIN CONFIDENTIALITY STATUS UNTIL TRIAL

#	PLAINTIFFS 11/24/08 MOTION & SEALED EXHIBIT #	DESCRIPTION
1	Genl Cause - Generic and Case-Specific Ex. 16	June 26, 2008 NDA 20-639 Submission (1,156 pages)
2	Genl Cause - Generic and Case-Specific Ex. 21; Omnibus MSJ Ex. 42	06/25/2008 letter (3-pages) from FDA to AZ
3	Genl Cause - Generic and Case-Specific Ex. 26	Internal email chain including from L Boornazian to M Deyr dated 04/26/2007
4	Genl Cause - Generic and Case-Specific Ex. 27; Omnibus MSJ Ex. 10	Internal email from Lisa Arvanitis dated 8/13/1997
5	Genl Cause - Generic and Case-Specific Ex. 41	Internal email chain including from Richard Owen to Matthew Lowe dated 3/18/05
6	Genl Cause - Generic and Case-Specific Ex. 51	Internal email chain including from David Duff to Kim Gilchrist, et al re Gianfrancesco work dated 5/23/03
7	Genl Cause - Generic and Case-Specific Ex. 52	A Comprehensive Retrospective Study of Associations Between Diabetes and Treatment with Risperidone, Olanzapine, Quetiapine, and Conventional Antipsychotics by HECON Associates, Inc.
8	Genl Cause - Generic and Case-Specific Ex. 58	08/18/00 email from Geller including attached Safety Position Paper
9	Genl Cause - Generic and Case-Specific Ex. 59	Portions of Dep of Wayne Geller (pp. 426-431) re: submission to Dutch health authority
10	Genl Cause - Generic and Case-Specific Ex. 60	Email from Dorothee Wientjens to Wayne Geller
11	Genl Cause - Generic and Case-Specific Ex. 64	Email from Connie Ou to Ronald Leong re Re-Challenge of Seroquel dated 2/4/03
12	Omnibus MSJ Ex. 1	Feb 2005 letter from French afssaps
13	Omnibus MSJ Ex. 2	03/09/2000 Seroquel Commercial Support Team - Technical Document (TD004)
14	Omnibus MSJ Ex. 3	03/06/2000 Seroquel Commercial Support Team - Technical Document (TD 005)
15	Omnibus MSJ Ex. 4	Internal email chain including M. Murray, M. Jones, J.Tumas, J.Goldstein dated 03/23/00
16	Omnibus MSJ Ex. 5	Excerpts of Kevin Birkett dep transcript 4/24/08
17	Omnibus MSJ Ex. 6	Sales Story Flow document
18	Omnibus MSJ Ex. 7	Wayne Macfadden dep transcript excerpts
19	Omnibus MSJ Ex. 8	Draft of article by Joyce Small re: Quetiapine
20	Omnibus MSJ Ex. 11	Martin Brecher dep transcript excerpts
21	Omnibus MSJ Ex. 12	Barry Arnold dep transcript excerpts
22	Omnibus MSJ Ex. 13	Internal memo from Richard Lawrence re: Study 15
23	Omnibus MSJ Exs. 14 (multiple documents)	Various internal emails which include: Internal email from Nick Hough re Small Review dated 5/10/99; 5/11/99 email from John Tumas to Michael Murray, et al; emails including Jim Gavin, John Tumas re: EPS data
24	Omnibus MSJ Ex. 17	Internal email from Don Beamish re: Reinstein
25	Omnibus MSJ Ex. 18	Discussion Document dated 6/22/00

#	PLAINTIFFS 11/24/08 MOTION & SEALED EXHIBIT #	DESCRIPTION
26	Omnibus MSJ Ex. 19	Wayne Geller dep transcript excerpts
27	Omnibus MSJ Ex. 20	Discussion Document
28	Omnibus MSJ Ex. 21	Safety Position Paper
29	Omnibus MSJ Ex. 22	09/18/2000 email thread from Geller re: glucose metabolism disorders and attaching Safety Position Paper
30	Omnibus MSJ Ex. 23	10/03/2000 email thread from D. Wientjens to Geller re Quetiapine and glucose metabolism disorders
31	Omnibus MSJ Ex. 24	Vikram Dev dep transcript excerpts
32	Omnibus MSJ Ex. 25	CBG Medicines Evaluation Board re: 1/2001response to MEB request to amend the SmPC
33	Omnibus MSJ Ex. 26	08/00 Response to FDA request
34	Omnibus MSJ Ex. 27	Internal email chain including Wayne Geller and Melissa Partridge re Metabolic issues dated 12/05/01
35	Omnibus MSJ Ex. 30	Objection Handler on Atypical antipsychotics and glucose dysregulation
36	Omnibus MSJ Ex. 32	Internal voicemail re: Weight and Diabetes Sell Sheet dated 08/15/05
37	Omnibus MSJ Ex. 37	10/15/2003 AZ letter to FDA re NDA 20-639, response to FDA request for labeling change
38	Omnibus MSJ Ex. 39	SERM Minutes 06/08/07
39	Omnibus MSJ Ex. 40	06/22/2007 AZ letter to FDA re NDA 20-639 and NDA 22-047, Supplement-Changes Being Effectuated
40	Haller SJ Motion Ex. 9-10	Speaker/Attendance Info
41	McA SJ Motion Ex. 14	Accounts Payable Info
42	Unger SJ Motion Ex. 15	Accounts Payable Info
43	Burns SJ Motion Ex. 17	Excerpts of Pharmaceutical Sales Specialist Deposition
44	Curley SJ Motion Ex. 12	Excerpts of Pharmaceutical Sales Specialist Deposition
45	Supp. Mem. on General Cause re: Rak	Rak Dep Transcript (includes numerous company documents as dep exhibits and testimony regarding same)
46	From Various Motion Responses	Various Expert Declarations, Expert Reports, and Expert Dep Excerpts, as well as Prescriber Dep Excerpts, which discuss confidential documents that were attached as exhibits to plaintiffs' responses
TRADE SECRET AND CONFIDENTIAL DOCUMENTS TO RETAIN CONFIDENTIALITY STATUS THROUGH TRIAL		
1	Genl Cause - Generic and Case-Specific Ex. 19	04/01/2008 CSR for study 144 (1,922 pages)
2	Genl Cause - Generic and Case-Specific Ex. 15	06/12/2006 CSR for study 125 (4,582 pages)
3	Genl Cause - Generic and Case-Specific Ex. 28	03/08/1996 IND for Seroquel (5,224 pages)
4	Genl Cause - Generic and Case-Specific Ex. 29	11/30/2006 CSR for study 165 (1,800 pages)
5	Genl Cause - Generic and Case-Specific Ex. 32	06/19/2007 CSR for study 127 (6,434 pages)
6	Genl Cause - Generic and Case-Specific Ex. 57	Draft Manuscript for Study 125 by Newcomer, J, et al.
7	Haller SJ Motion Ex. 9-10	Call Notes
8	McA SJ Motion Ex. 10-13	Call Notes
9	Unger SJ Motion Ex. 12-14	Call Notes
10	Whittington SJ Motion Ex. 5-7	Call Notes

#	PLAINTIFFS 11/24/08 MOTION & SEALED EXHIBIT #	DESCRIPTION
11	Guinn SJ Motion Ex. 10, 12, 13	Call Notes
12	Burns SJ Motion Ex. 16	Call Notes
13	Curley SJ Motion Ex. 9-11	Call Notes

Annual Report 2002: The Johnson and Johnson Center for Pediatric Psychopathology at the Massachusetts General Hospital

Director: Joseph Biederman, MD
Co-Director: Stephen V. Faraone, PhD

Executive Summary

Overview

The mission of the Center is to create a common ground for a strategic collaboration between Johnson & Johnson (J&J) and the Pediatric Psychopharmacology Research Program an at the Massachusetts General Hospital (MGH). The Center provides an infrastructure for MGH researchers to collaborate with J&J researchers on comprehensive studies of pediatric psychopathology, including diagnostic, therapeutic, and neurobiologic studies. The formation of the Center has created a forum for multidisciplinary collaborative research in a number of key areas, with an initial focus on pediatric mood and disruptive behavior disorders.

An essential feature of the Center is its ability to conduct research satisfying three criteria: a) it will lead to findings that improve the psychiatric care of children; b) it will meet high levels of scientific quality and c) it will move forward the commercial goals of J&J. We strongly believe that the Center's systematic scientific inquiry will enhance the clinical and research foundation of child psychiatry and lead to the safer, more appropriate and more widespread use of medications in children. Considering that nearly all psychiatric medication use in children is off label, studies of safety and efficacy in children are essential for clinicians, parents and patients to feel comfortable using these medications in children. The Center is poised to test the effectiveness and safety of RISPERDAL, REDACTED and new products as the emerge from the pipeline.

Equally important to effective use of medications is the demonstration of the validity of disorders. Because parents, patients and clinicians are exposed to a media that frequently questions the validity of childhood disorders, genetic and brain imaging studies are needed to show the validity of these disorders as brain disorders that respond to medication. Epidemiologic studies are needed to show that childhood disorders are frequently chronic and severely debilitating. Without such data, many clinicians question the wisdom of aggressively treating children with medications, especially those like neuroleptics, which expose children to potentially serious adverse events. Epidemiologic studies also show the continuity of childhood and adult disorders. This provides an additional measure of validation for the childhood disorder and in some cases validates the disorder as a disorder of adulthood as we have seen for adult attention deficit hyperactivity disorder (ADHD).

Through the funding provided by J&J, we are creating a team of investigators focusing on the following issues.

Assessing the Efficacy and Safety of Medications for Child Psychopathology

We will generate and publish data on the efficacy and safety of medications for improving currently available treatment options for child psychopathology. This work is an essential precursor to the safe, appropriate and widespread use of medications given that most must be used off-label. Specific goals of this area of work include:

- Assessing the full range of symptoms treated by RISPERDAL by analyzing data from Janssen's study of RISPERDAL among conduct disordered/mentally retarded youth. This will allow us to extend Janssen's prior findings indicating efficacy for conduct disorder to mania, anxiety and other classes of psychopathology.
- Using MGH open-label studies to assess the differential effectiveness and safety of RISPERDAL and ZYPREXA in the treatment of pediatric bipolar disorder (BPD). For example, we have already shown that ZYPREXA leads to twice the weight gain as RISPERDAL.

- Using MGH open-label studies to demonstrate how combination pharmacotherapy can be used to treat complex cases. Examples include using RISPERDAL and CONCERTA to treat ADHD with BPD, REDACTED
- REDACTED
- [redacted]
- [redacted]
- [redacted]

Resolving Complex and Controversial Diagnostic Issues

Many children with psychopathology never receive medical treatment due to controversies in the media and debates among professionals about the validity of psychiatric diagnoses in children. Additional under-treatment occurs due to lack of mental health screening in primary care clinics The Center seeks to address complex and controversial diagnostic issues through empirical research. This domain of work includes validating diagnostic methods, validating tools for screening and treatment monitoring and, if needed, creating new measures which will allow physicians to confidently screen for and diagnoses child psychopathology. Center investigators are now examining diagnostic and measurement issues for three disorders that have been particularly controversial: pediatric BPD, adult ADHD and pediatric psychosis. Specific goals of this area of work include:

- Analyzing databases at MGH to characterize pediatric BPD, adult ADHD and pediatric psychosis. This will help clinicians understand the nature of these disorders, which will facilitate their ability to diagnoses them in their practices.
- Developing and assessing the validity of screening tests for complex disorders such as comorbid ADHD, psychosis and pediatric BPD. Once appropriately validated, the use of these screening tests will alert physicians about disorders that exist which RISPERDAL and CONCERTA might treat. Currently, many children with psychosis and BPD and many ADHD adults are not identified as such so are not treated outside of specialty academic centers.
- Implementing training programs for screening tools in continuing medical education programs targeting pediatricians and general psychiatrists.
- Analyzing baseline data from Janssen funded studies to validate affective disorder sub-type in the conduct disorder subpopulation. Further validation of this group will alert physicians to the existence of a large group of children who might benefit from treatment with RISPERDAL.
- Analyzing data bases at MGH to clarify the continuity between childhood and adult disorders. Showing how pediatric mania evolves into what some have called mixed or atypical mania in adulthood, will provide further support for the chronic use of

RISPERDAL from childhood through adulthood. Such data will teach clinicians about how to identify these symptoms in adults.

- Using the classic criteria of Robins and Guze (1970) to validate diagnostic criteria for pediatric BPD, childhood psychosis and adult ADHD using studies of course, outcome, genetics, cognition and neuroimaging as described in the following sections.
- Using neuropsychological measures to accurately identify executive brain dysfunction and differentiate it from ADHD. Because executive brain dysfunction is seen in many ADHD children, there is some debate about whether it is a separate syndrome or another manifestation of ADHD. By clarifying this issue, we will demonstrate the need for clinicians to assess for executive brain dysfunction and consider potential medical treatments for this condition in their ADHD patients.
- REDACTED

Assessing the Severity and Chronicity of Child Psychopathology

We will study the natural course of pediatric psychopathology, the long-term incidence of the various dysfunctions and the long-term effects of pharmacologic and other interventions. This work validates childhood disorders by demonstrating how it evolves in adult manifestations of the same disorders. It shows clinicians that aggressive treatment is warranted because these disorders lead to substantial disability. By clarifying the chronicity of disorders, it further documents the necessity for the chronic treatment of some disorders by debunking myths which present childhood psychopathology as a normal phase of development. For example, in the past, ADHD was viewed as a remitting disorder and treatment was usually stopped during adolescence. Today, due to longitudinal studies the American Academy of Pediatrics now recommends treating ADHD as a chronic illness. Specific goals of this area of work include:

- Assessing the severity and chronicity of pediatric BPD using the same methods we have used for longitudinal studies of ADHD (Biederman et al., 1998b; Biederman et al., 2000).
- Characterizing the chronic, debilitating course of BPD to help people understand need for aggressive treatments such as RISPERDAL.
- Evaluating the effectiveness of medical and psychosocial treatments on long term outcomes in pediatric BPD using a naturalistic design.
- Evaluating the effect of RISPERDAL treatment on functioning in pediatric BPD in database studies and prospective short and long term studies.
- Assessing the disability associated with adult ADHD to help us understand the future of child ADHD and the need for chronic treatment. We are addressing this through a large longitudinal family study of ADHD and are also developing a day-long laboratory protocol to quantify the "real world" impairments associated with ADHD such as impaired driving skills and difficulty concentrating on work requiring sustained attention.

Clarifying the Biological Basis of Childhood Psychopathology

One of the main obstacles to the medical treatment of childhood disorders is the myth that they simply reflect problems of family and culture rather than dysfunctions of the brain. We will help dispel these myths using genetic and neuroimaging studies. These studies further validate childhood disorders as medical conditions and thereby give physicians more confidence in the use of medical treatments. By clarifying the causes of childhood disorders, these studies also lay

the ground work for the development of more efficacious treatments or the use of current treatments in a more effective manner. Specific goals of this area of work include:

Genetics

- Identifying genes that increase the susceptibility to child psychopathology with an initial emphasis on ADHD and BPD.
- Validating diagnostic criteria and assessing the validity of comorbidity using designs from genetic epidemiology.
- Creating a platform for collaboration between MGH and the J&J pharmacogenetics department by working with J&J to collect, DNA, safety data and efficacy data. The goal of this work is to discover genes which predict therapeutic response or adverse events during treatment with J&J medications.
- Collecting pharmacogenetic data in MGH studies of RISPERDAL, REDACTED REDACTED
- Studying children having a bipolar parent to develop rules for identifying pre-clinical cases. By accurately identifying children at risk for psychopathology, we will be able to develop early intervention and prevention treatment programs.

Neuroimaging

- Using magnetic resonance imaging to identify structural and functional patterns in the brain that characterize psychopathological subgroups, particularly controversial diagnoses such as pediatric BPD and adult ADHD.
- Initiating a prospective study of the efficacy and safety of RISPERDAL in pediatric BPD, including neuroimaging on a subset of patients.
- Using magnetic resonance spectroscopy to examine changes in NAA/CA, Choline, and other brain metabolites in response to RISPERDAL treatment.
- Using structural and functional magnetic resonance imaging in medication naïve patients to demonstrate that brain changes are associated with childhood disorders, not their treatment.

Disseminating Research Results and Educating Clinicians

To have an impact on clinical practice, research results from the Center must be disseminated through scientific publications, presentations and national and international meetings and continuing education programs. Our program of dissemination is as follows:

- Presenting findings and national meetings of the American Psychiatric Association, the American Academy of Pediatrics, the American Academy of Child and Adolescent Psychiatry, the American Psychological Association, Biological Psychiatry, NCDEU and the American College of Neuropsychopharmacology.
- Presenting findings at international meetings of the World Psychiatric Association, the World Congress of Psychiatric Genetics, the European College of Neuropsychopharmacology (ECNP) and the Collegium Internationale Neuro-Psychopharmacologicum (CINP).
- Developing and implementing a BPD continuing education program to teach pediatricians and psychiatrists how to screen for, diagnose and treat BPD

- Present continuing medical education programs at national and international professional meetings:
- Convening a yearly international conference for investigators studying pediatric BPD (this is possible through funding from Janssen and a grant from the National Institute of Mental Health to Dr. Biederman).
- Convening a yearly international conference for investigators studying the genetics of ADHD (this is possible through funding from the National Institute of Mental Health to Dr. Faraone).
- Preparing manuscripts for publication in psychiatric, pediatric and psychological journals.

Details of Center Activities in 2002

In 2002, we made progress in the following areas:

- At MGH, we identified a multidisciplinary team of psychiatrists, psychologists, psychiatric clinical nurse specialists, epidemiologists, and behavioral geneticists to participate in the Center
- We initiated several research projects
- We initiated data analyses of archival J&J and MGH data sets.
- We disseminated the results of our work and national and international meetings.
- We prepared initial manuscripts for publication.
- We supported junior faculty efforts to develop expertise in pediatric BPD.
- We developed and maintained a schedule of regular communication with J&J staff to facilitate collaborative efforts.
- We Initiated Yearly Meetings of Experts in Bipolar Disorder.

Creation of a Multidisciplinary Team

Table 1 lists the MGH investigators participating in the Center. These participants are each faculty members in the Harvard Medical School Department of Psychiatry at MGH. As Table 1 shows, they have experience using a wide range of methods and measurement tools. A comprehensive description of all the prior work in these areas of measurement is beyond the scope of this report, but an examination of the biographical sketches of the investigators (see Appendix A) shows the extent of their prior empirical work, most of which has used the methods and assessment measures to be used in the proposed Center.

Table 1: MGH Participants in Center Research

EXPERTISE	INVESTIGATOR
Psychosocial Treatment Outcome Designs	Stephen Faraone, PhD Ross Green, Ph.D Dina Hirschfeld, Ph.D.
Psychopharmacological Treatment Outcome Designs	Joseph Biederman, MD Tom Spencer, MD Tim Wilens, MD
Epidemiological Designs	Stephen Faraone PhD Eric Mick, Sc.D.
Molecular and Statistical Genetics	Stephen Faraone, PhD James Gusella, PhD Paul Van Eerdewegh, PhD
Psychiatric Assessment, Diagnosis and Treatment-Outcome	Joseph Biederman, MD Tom Spencer, MD Tim Wilens, MD Janet Wozniak, MD
Psychological and Psychosocial Assessment	Stephen Faraone, Ph.D. Ross Green, Ph.D Dina Hirschfeld, Ph.D.
Neuropsychological Assessment	Larry Seidman, PhD Alysa Doyle, Ph.D
Neuroimaging	Larry Seidman, PhD
Statistical Analysis Analysis	Stephen Faraone PhD Eric Mick, Sc.D.
Data Base Programming; Computer Hardware; Networking; Data Quality and Security	Eric Mick, Sc.D.
Biostatistics	Stephen Faraone PhD Eric Mick, Sc.D.

Through this multidisciplinary faculty, the Center has access to the systematic assessments needed for screening, study recruitment and study implementation. Table 2 shows the domains of assessment expertise available to the Center. Most studies need structured interviews for psychiatric diagnostic assessments. Treatment protocols also require measurement in domains of functioning at baseline that might be predictive of subsequent treatment response as well as measures of psychopathology and functioning that will be sensitive to the clinically meaningful changes that will occur with treatment. The Center maintain assessment tools that allow for the assessment of functioning in multiple domains: psychiatric, psychosocial, neuropsychological, quality of life, and the utilization of health services.

Table 2: Measurement Domains Available to the Center

	Type of Study		
	Diagnostic Studies	Treatment Studies	Etiology Studies
Psychiatric Symptoms			✓
Structured Diagnostic Psychiatric Interview	✓	✓	✓
Substance Use Assessments		✓	✓
Clinical Rating Scales	✓	✓	✓
Social Functioning	✓	✓	✓
Family Environment Scale		✓	✓
Expressed Emotion		✓	✓
Family Burden		✓	
Neuropsychological Functioning			
Health Services Utilization	✓	✓	

Because much of the under-treatment of psychiatric disorders in children is due to concerns about the accuracy and validity of diagnostic measures, the ability to validate measures of childhood psychopathology is an essential component of the Center. The availability and use of good measurement technologies leads to improved acceptance of research results by the FDA, physicians, patients, their parents and the general public.

Center investigators have completed many methodological studies that validate the use of these assessment tools in pediatric populations. Examples include:

- Showing that parent-based diagnoses of ADHD are predictive of teacher-based diagnoses (Biederman et al., 1993b; Biederman et al., 1990a). This work has facilitated drug development for ADHD, when teacher reports are lacking. This makes adolescent studies feasible and also provides reassurance to clinicians when they must diagnose children without information from teachers.
- Using clinical trials data to show that parent reports are sufficient for detecting efficacy in studies of long-acting medications for ADHD (Biederman et al., submit). This work provides reassurance to clinicians when they must titrate medications without feedback from teachers
- Demonstrating that structured interview diagnoses of child psychopathology show high reliability and diagnostic efficiency (Faraone et al., 1995). This type of work clarifies the objective nature of diagnosis, which helps clinicians understand the value of applying them in pediatric settings.
- Supporting the validtity of adult ADHD diagnoses by showing that parental ADHD does not bias reports of ADHD in children (Faraone et al., in press), that symptom reports by ADHD adults are not influenced by the presence of ADHD in their children (Faraone et al., 1997) and that adult relatives of ADHD children have high rates of ADHD and that family study methods show adult ADHD to be a valid diagnosis (Faraone et al., 2000a). By demonstrating the validity of adult ADHD diagnoses, this and other work has led to a more widespread acceptance of the diagnosis, including acceptance by the FDA, which previously doubted its validity but has now given Lilly an adult ADHD indication for STRATTERA.
- Creating a method for assessing medication efficacy in a naturalistic setting by applying structured assessments to medical records (Biederman et al., 1999). This provides a simple method for assessing efficacy. As we have shown for the RISPERDAL treatment of bipolar disorder (Biederman et al., 1999), this method provides a quick assessment of whether a currently available medication is worth pursuing in a clinical trial.
- Using multiple definitions of remission to assess course and outcome (Biederman et al., 2000) and creating an assessment and analysis scheme for defining normalized functioning in children (Biederman et al., 1998b) we have been able to quantify the chronicity and severity of disorders and, thus, the need for chronic, aggressive medical treatment.
- Demonstrating the validity of the Social Adjustment Scale for Children and Adolescents (Biederman et al., 1993a) provides a useful tool for assessing the efficacy of medications in this "real world" domain of dysfunction affected by many psychiatric disorders.
- Creating new designs to clarify psychiatric comorbidity using the family study method has validated comorbid conditions and strengthened the rational for treating them (Faraone et al., 1999).

- Showing that exclusive reliance on youth self-reports may identify a mild form of depression associated with limited morbidity and disability compared with that identified by parental reports (Braaten et al., 2001) and showing that the potential distortion of indirect interviews by depressed mothers may be stronger in community than in clinical settings and does not account for the increased risk for MD in referred adolescents with ADHD (Mick et al., 2000) This work will lead to better methods of identifying depression in children.
- Documenting substantial stability of Child Behavior Checklist (CBCL) scales over time for ADHD patients to support the informativeness of the CBCL as a useful measure of longitudinal course in clinical samples of youth with ADHD (Biederman et al., 2001b). This work provides further evidence that the CBCL is a useful tool for screening and monitoring the progression of disorders.
- Developing new methodologic approaches for prevention protocols (Faraone et al., 2002). This work will, in the long-term, lead to psychopharmacologic protocols aimed at the primary prevention of childhood psychiatric disorders

The Center also includes substantial expertise in data management and analysis, which allows it to provide methodological, statistical and data base management assistance to participating investigators. To facilitate study efficiency and data sharing the Center has implemented a common data analytic infrastructure. This infrastructure has enabled the design of shared databases for analytic efforts of data collected across various studies.

Eric Mick, ScD heads the Center's data management efforts. As an epidemiologist, he is highly experienced in the collection, editing and management of large complex data sets from psychiatric studies, including longitudinal and family studies. He and our data base developer, Ellie Remskar, are responsible for setting-up and maintaining the central data management system. To achieve the goals of central data management, he plans for the software and hardware needs of the central system and supervises the day to day work of the central data management staff. He also assures the integrity of data management for each Center project.

Stephen Faraone, Ph.D. heads the Center's data management efforts by coordinating group of two junior faculty and three masters level statisticians well versed in a variety of statistical techniques. This resource is available to participating investigators (i.e., developing and established scientists), clinicians planning to become investigators and students (including graduate students, interns, residents and fellows). The data analysis efforts at the Center also include the development of new methods to deal with new issues that arise in the Center's research program. Prior examples of methods development include:

- The use of analytic mathematics and simulations to choose among methods for analyzing autocorrelated binary data (Faraone and Dorfman, 1987);
- The development of a method to assess inter-observer agreement in the presence of autocorrelation (Faraone and Dorfman, 1988);
- Creation of a method to render radioreceptor assay results comparable between different neuroleptic medications (Young et al., 1989).
- The use of simulations to choose among methods of morbidity risk estimation (Faraone et al., 1994) and to assess the statistical power of linkage studies (Chen et al., 1992).
- The use of multidimensional scaling to clarify diagnostic confusability and reliability (Faraone et al., 1996).
- The use of mathematical genetic considerations to choose phenotypes for genetic analysis (Faraone et al., 2000b).

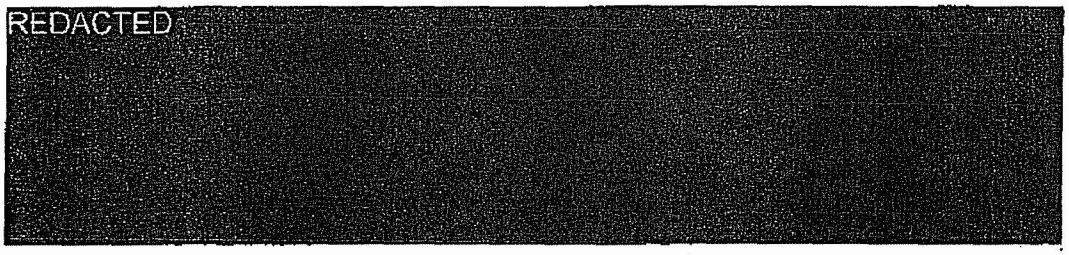
- The use of latent class methods to measure diagnostic accuracy in the absence of a gold standard (Faraone and Tsuang, 1994).
- An analytic demonstration of the effects of fixed-dose, clinical-dose and reduced-dose treatment designs on outcome measures (Faraone et al., 1992).
- The development of a receiver operating characteristic (ROC) based method to optimize the validity of psychiatric diagnoses (Faraone et al., 1993).
- The development of an ROC based method to comprehensively describe differences in efficacy between drug and placebo or between two drugs (Faraone et al., 2000c).
- Comprehensive reviews of ascertainment and statistical methods in psychiatric genetics (Faraone and Santangelo, 1992; Faraone et al., 1999; Faraone and Tsuang, 1995).

Data Collection Efforts Initiated in 2002

Treatment Studies

We will add descriptions of these.

Comparative Effectiveness and Tolerability of RISPERDAL with SEROQUEL, GEODON, ZYPREXIA



RISPERDAL and CONCERTA for ADHD in Children and Adults with Bipolar Disorder

MR spectroscopy study of children before and after RISPERDAL

Development of driving simulator for adults with ADHD

Sleep apnea and ADHD in adults

Treatment of Psychiatric Comorbidity in Bipolar Disorder.

Bipolar youth frequently present with one or more of the following comorbid disorders: ADHD, oppositional defiant disorder, pervasive developmental disorder, anxiety, and major depression. These disorders complicate treatment planning for two reasons. First, little is known about how to sequence the treatments for co-occurring conditions. In addition, the standard treatments for some comorbid conditions (e.g. stimulants for ADHD, SSRIs for depression) may exacerbate mania. Our plan is to develop open label trials targeted at these comorbid conditions to get an early signal regarding the effectiveness of these therapies. Those that look promising will be further developed by pursuing external funding for large scale clinical trials. We have currently initiated the following studies of comorbidity:

- Open-label study of RISPERDAL for pediatric BPD. This study serves as an ascertainment source for cases of BPD with ADHD, which can then be enrolled in a

study assessing the effectiveness of CONCERTA for ADHD in RISPERDAL treated BPD children.

- REDACTED

Pharmacokinetics and Drug-Drug Interactions.

Because many of the medications we are studying have not been used extensively in pediatric populations, it is essential that we collect pharmacokinetic data. Moreover, some of our protocols use more than one compound. Thus, a key component of our program is to evaluate potential drug-drug interactions associated with combined treatments using appropriate pharmacokinetic and pharmacodynamic protocols. Current pharmacokinetic studies are as follows:

- Pharmacokinetics of RISPERDAL in Pediatric ADHD
- REDACTED
- Pharmacokinetics of RISPERDAL and CONCERTA in Children with BPD and ADHD

Olanzapine plus Topiramate.

Topiramate has been used to offset weight gain associated with atypical neuroleptics in clinical practice but has not been systematically evaluated. Thus, the objective of this study is to evaluate the safety and effectiveness of added topiramate to minimize iatrogenic weight gain approaches to the treatment of BPD in children and adolescents.

Initial Treatment Studies of Bipolar Depression.

Since depression is a highly morbid state of bipolar disorder and since antidepressants can exacerbate manic symptoms, the evaluation of safe and efficacious treatments for bipolar depression remains uncertain. To this end, we initiated a clinical trial comparing the effectiveness of buproprion and paroxetine for the treatment of bipolar children with active symptoms of depression. These are potentially useful options to evaluate in this population since they have each been shown to have a low manicogenic risk in adults.

Epidemiologic and Genetic Studies of Pediatric Psychopathology.

Genotyping Efforts and Genetic Databank Development

We have been collecting blood samples from each member of the nuclear family of children with bipolar disorder. This blood is stored so that DNA may be extracted in the future in order to conduct linkage, association or pharmacogenetic analyses.

Phenotypic characterization of velo-cardio-facial (VFC) Syndrome

Since VCF has been associated with bipolar disorder in some studies, we are collecting digital photographs of children with bipolar disorder in order to test the hypothesis that hemizygous deletion of chromosome 22q11 may result in bipolar affective disorder. This finding may eventually lead towards the identification of candidate genes for early onset bipolar disorder.

Studies of Temperamental Risk Factors for Pediatric Bipolar Disorder.

Another major research interest of our group has been the study of temperament as a risk factor for subsequent psychopathology in at-risk children. We currently have a large program which has shown that behavioral inhibition is an early onset precursor of subsequent anxiety disorders

(Biederman et al., 2001a; Biederman et al., 1993c; Biederman et al., 1990b). If the new Center is funded, we plan to create a research program aimed at identifying temperamental risk factors for pediatric bipolar disorder. In particular, we intend to follow-up on some intriguing leads from our pilot studies, which suggest that behavioral disinhibition may be a very early onset risk factor for pediatric bipolar disorder.

Longitudinal Family Study of Pediatric Bipolar Disorder.

Longitudinal studies of pediatric bipolar disorder hold the promise of settling controversies that have plagued the field. If bipolar disorder is a valid diagnosis in children, signs of the disorder should remain evident at follow-up assessments. Equally important will be determining the course of comorbidity in pediatric bipolar disorder to see if they have a course and outcome that parallels that which has been seen for the comorbid disorder when it occurs in the absence of bipolar disorder. Dr. Wozniak collected 110 families ascertained via pediatric bipolar patients through her NIMH Career Development Award. With J&J funding, we have been able to initiate a follow-up study of this sample.

Follow-Up of Preschoolers with Bipolar Disorder.

In light of extensive media attention devoted to a recent pharmacoepidemiological analysis which asserted that large number of preschool children are inappropriately treated with pharmacotherapy and since children with bipolar disorder frequently present to clinics at very young ages with a very severe clinical picture, we are following preschoolers (age<6 years) who meet criteria for bipolar disorder to systematically evaluate the longitudinal course of this disorder in this age group.

Children at High Risk for Bipolar Disorder

We will add descriptions of this.

Neuropsychology and Neuroimaging of Pediatric Psychopathology

Magnetic Resonance Imaging of BPD+ADHD Adults

We will add descriptions of this.

MR Spectroscopy of BPD children before and after treatment with RISPERDAL

Analyses of Archival Data Sets

Data Sets Available Through MGH

Clinic Data

For the past decade we have systematically collected data on consecutive admissions to our pediatric psychopharmacology clinic. As a result, we have extensive clinical data (e.g., structured interviews, rating scales, psychometric tests) on more than 2000 patients not selected for a specific disorder. We also have the capability of completing systematic chart reviews using the methodology developed by Biederman et al. (Biederman et al., 1998a; Biederman et al., 1999). Ongoing analyses of these data are as follows:

- Clinical Features of Pediatric BPD
- Gender and Psychiatric Comorbidity in Adult ADHD
- Clinical Features of Children with Psychosis

Longitudinal Family Study of ADHD

Over the past twenty years, Drs. Biederman and Faraone have, with funding from NIMH, been following families of 140 ADHD boys, 140 ADHD girls and more than 200 gender and age matched control families from childhood to adulthood. Baseline and follow-up studies (which have also included family members) have provided a wealth of data about the course, outcome, clinical correlates and familial aggregation of ADHD. These data sets have allowed for the following analyses:

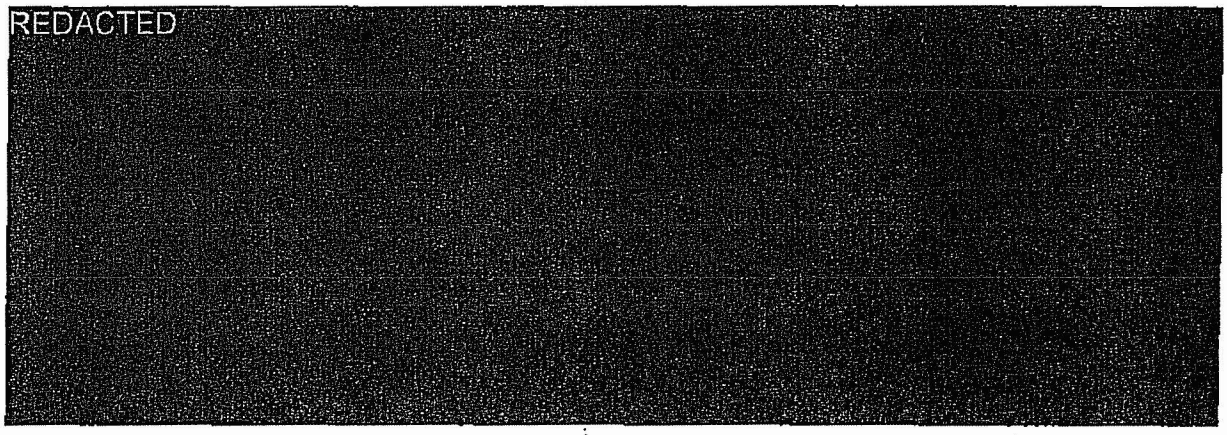
- Comorbid Anxiety Disorders Among Children with BPD
- Exposure to Parental Bipolar Disorder as a Risk Factor.
- Follow-up Study of ADHD children with BPD

Data Sets Available Through J&J

Double-Blind Trial of RISPERDAL in Children with Conduct Disorder and Mental Retardation

This data set contains the results of Janssen's clinical trial of RISPERDAL for conduct disorder and mental retardation. It also includes outcome ratings on a wide variety of symptoms, which makes it useful for assessing the efficacy of RISPERDAL for other conditions in this population and for assessing psychometric features of the measures. Analyses completed to date are:

- Efficacy of RISPERDAL for manic symptoms
- Replication of Factor Analysis of BPD Symptoms



Other Data Sets

Bipolar Genetic Linkage Data.

We have access to the NIMH bipolar disorder genetic linkage data set, which is a public resource available through the NIMH Genetics Initiative Program. We are using this data set for the following:

- Linkage analysis of the age at onset of manic symptoms

- Factor analysis of manic symptoms
- Published Data

We have found meta-analysis to be very useful for clarifying issues in pediatric psychopathology. We have already applied this methodology to studying the DRD4 gene in ADHD (Faraone et al., 2001), the efficacy of ADHD medications (Faraone and Biederman, 2002; Faraone et al., 2002) and to studying the effects of stimulant medications on substance abuse in ADHD (Wilens et al., in press). We are currently using meta-analysis of published data as follows:

- Meta-analysis of multiple studies using CBCL to validate profiles
- Meta-analysis of the DAT gene in ADHD (through collaboration with the ADHD Genetics Network, S. Faraone (PI)).
- Meta-analysis of the DRD5 gene in ADHD (through collaboration with the ADHD Genetics Network, S. Faraone (PI)).

Support of Junior Faculty to Develop Expertise in Pediatric Psychopathology Research

Perhaps the most enduring impact of our Center will be the work of trainees and junior investigators whom we have attracted to the study of pediatric psychopathology. By doing so, we will create a new generation of investigators committed to studying the causes of and treatments for childhood psychopathology.

Table 3 describes the young investigators supported by our research program. The table shows that we have been creating a team of new investigators who have a wide range of expertise including psychopharmacology, psychosocial treatment, substance abuse, neuroimaging and pharmacology. Although each of these new investigators has a specific expertise, our approach to training requires that they study pediatric bipolar disorder within the broader context of childhood psychopathology. For example, we have not set up a bipolar disorder specialty clinic. Instead, clinicians are taught to diagnose bipolar disorder and all comorbid psychopathology. This makes it easier to recognize comorbidity and to devise research protocols aimed at understanding its causes or devising methods for its treatment.

Table 3: Young Investigators Being Trained in the MGH Pediatric Psychopharmacology Research Program

Investigator	Speciality	Projects
Janet Wozniak, MD	Pediatric BPD	Clinical trials and longitudinal family study of BPD.
Ross Greene, PhD	Psychosocial Treatment	Clinical Trials of Psychosocial Therapies for Children with Bipolar Disorder.
Louise Cohen, PharmD	Pharmacokinetics	Developmental Pharmacokinetics of Psychotropic Drugs
Dina Hirshfeld, PhD	Anxiety Disorders	Temperament as a Risk Factor for Psychopathology
REDACTED		
Eric Mick, ScD	Methodology	Methods Development and Applications
Aude Henin, Ph.D.	Children at Risk	Children at Risk for Bipolar Disorder
Alysa Doyle, Ph.D.	Neuropsychology	Cognition and Genetics of ADHD
Dan Geller, MD	Obsessive Compulsive Disorder	Treatment and Epidemiologic Studies of OCD
Eve Valera, Ph.D	Neuroimaging	Structural and Functional MRI of ADHD

Our training program also encourages cross-fertilization among disciplines, a process that is facilitated by the fact that the Center Director, Dr. Biederman, is a psychiatrist, his Co-Director, Dr. Faraone, is a psychologist and the Scientific Coordinator, Dr. Mick, is an epidemiologist. On a practical, training level, cross-fertilization means that junior investigators must learn about

concepts and methods outside their main area of inquiry. Moreover, they must incorporate these into their research protocols.

Communication With J&J Staff to Facilitate Collaborative Efforts
We will add descriptions of this.

Initiation of Yearly Meetings of Experts in Bipolar Disorder

To address the controversy about pediatric bipolar disorder, we initiated a multi-year conference series which seeks to establish a forum for researchers and clinicians to improve dialogue and foster collaborative studies about children who present with extreme temper tantrums and dysregulated mood. Preceding roundtables on pediatric bipolar disorder had stressed the pressing need to advance the scientific knowledge of this severe mental disorder and had recognized the paralyzing effects of the ongoing controversy surrounding pediatric bipolar disorder and bipolar spectrum disorders. This controversy led to a vicious circle of diagnostic skepticism, void of scientific information, and therapeutic nihilism with its detrimental impact on patients and their families.

Fostering dialogue among scientists and clinicians is a key step to better defining the clinical and scientific questions and fostering necessary collaborative research critical to building a scientific foundation for the understanding and treatment of pediatric bipolar disorder. When collaborations are considered, they frequently face hurdles that cannot be easily surmounted. For example, clinical traditions at different centers often clash regarding diagnostic conceptualizations as well as over which clinical and research strategies are best suited to answering important research questions. Thus, the main goal of the conference series on pediatric bipolar disorder is to build consensus through a network of clinicians and investigators who are studying or are planning to study pediatric bipolar disorder. Sub-goals of these conferences are:

- To define the boundaries of the bipolar spectrum phenotype and determine if children who technically meet criteria for bipolar disorder actually have this disorder or are affected with another condition.
- To standardize data collection methods across different centers to facilitate pooling of diagnostic data.
- To facilitate joint submissions of large collaborative projects that will enable the study of a broad spectrum of scientific questions including genetic, imaging and therapeutic protocols.
- To create a mechanism for pooling samples so that potential findings from one group may be cross-validated on pooled data from remaining groups

The first meeting was held in March, 2002, through an unrestricted educational grant by Janssen Pharmaceuticals. The proceedings of the first meeting will be published in Biological Psychiatry (See www.mgh.harvard.edu/depts/pediatricpsych/bipolar_2002.htm to view the slide presentations). A list of the presentations follows:

- Phenotypes of Inpatient Children with Mania: Gabrielle Carlson, MD
- Convergence between Structured Interviews and Clinician Assessments of BPD: Janet Wozniak, M.D.
- High Risk Studies of Children at Risk for BPD: Kiki Chang, PhD.
- Dysphoric Conduct Disorder: The overlap between conduct disorder and BPD: Joseph Biederman, MD
- Proposed Cross Natural Study of Diagnosis of Pediatric Mania: Richard Harrington, MD

- Genetics of Pediatric Bipolar Disorder and Its Comorbidities: Steven Faraone, Ph.D.
- Magnetic Resonance Imaging Studies of Pediatric BPD: Jean Frazier, MD
- Combination Pharmacotherapy in Children and Adolescents with Bipolar Disorders: Robert Kovatch, MD
- Temperament and Mood DisordersóBehavioral Disinhibition: Dina Hirshfeld-Becker, Ph.D.
- Parent Advocacy Perspective: Martha Hellander
- Multifamily Psychoeducation Groups for Pediatric Bipolar Disorder: Mary Fristad, MD
- Defining Clinical Phenotypes of Juvenile Bipolar Disorder: Ellen Leibenluft, MD
- Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD): Andrew Nierenberg, MD
- Children and Adolescents with Bipolar Disorder: Methodological Issues: Boris Birmaher, MD
- Methodological Issues in Pediatric BPD: Eric Mick, Sc.D.
- Retrospective, unblinded chart review of pediatric BPD. Luis Rohde, MD
- BPD Among ADHD Children. Philip Hazell, MD

Plans for the Future

Table 4 presents our original timeline for research at the J&J Center for Psychopathology Research at MGH.

Table 4: Project Timeline for the J&J Center for Psychopathology Research at MGH						
	Yr 0	Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
Treatment Research						
Efficacy of RISPERDAL for Pediatric BPD	X	XP	XP			
Pediatric BPD RISPERDAL PK Study		XP	XP			
Meridia for weight gain in Risp treated patients		XP	XP			
REDACTED						
PK study of stimulants and RISPERDAL		XP	XP			
Efficacy of adding Wellbutrin or Paxil for depression to RISPERDAL treated BPD patients		XP	XP			
PK study of Wellbutrin/Paxil and RISPERDAL		XP	XP			
Cabergolinefor hyperprolactinemia in Risp treated patients		XP	XP			
Efficacy of galantamine for executive dysfunction in BPD			XP	XP		
Efficacy of RISPERDAL for BPD in PDD Children				XP	XP	
Efficacy of RISPERDAL for BPD in OCD Children				XP	XP	
Efficacy of Multimodal treatment of BPD using risperdone and cognitive behavior therapy				XX	XP	XP
Long term follow-up of Efficacy Studies to assess psychosocial outcome, cognitive outcome, symptomatic outcomes and substance use outcomes				XP	XP	XP
Etiologic Research						
Structural MRI of BPD adults with and without ADHD		XX	XP			
Structural MRI of BPD children with and without ADHD	XX			XX	XP	
Pharmacogenetic studies of BPD trials	XX	XX	XP	XP	XP	
Velo-Cardio Facial Syndrome and BPD			XX	XP		
Candidate gene studies of Pediatric BPD			XX	XP	XP	XP
Longitudinal Research						
Validation of affective-type conduct disorder with family study	XX	XX	XX	XP	XP	XP
Follow-up of BPD Children		XX	XX	XP	XP	XP
Follow-up of children at risk for BPD		XX	XX	XP	XP	XP
Analysis of Existing Data						
Efficacy of RISPERDAL for affective-type conduct disorder in Janssen clinical trial	XP	XP				
Use MGH follow-up and family study data to define and validate antisocial and non-antisocial subtypes of BPD	XP	XP				
Use MGH follow-up data to define risk factors and developmental trajectories of BPD			XP			
Use MGH follow-up and family study data to define CBCL screening rules for pediatricians			XP			
Use MGH follow-up and family study data to define executive dysfunction measure for galantamine study		XP				
Educational Initiatives						
Yearly Pediatric BPD Conference	X	X	X	X	X	X
Development of BPD CME Program	X	XX				
Implementation of BPD CME Program	X		XX	XX	XX	XX
BPD Programs at national and international professional meetings: NCDEU, AACAP, Biological Psychiatry, ACNP, APA, AAP, ECNP, CINP, WPA		XX	XX	XX	XX	XX

Appendix A: Biographical Sketches of MGH Investigators

APPENDIX B: Presentations at National and International Meetings in 2002 By MGH Pediatric Psychopharmacology Research Program

APPENDIX C: Preparation of Manuscripts for Publication in 2002 By MGH Pediatric Psychopharmacology Research Program

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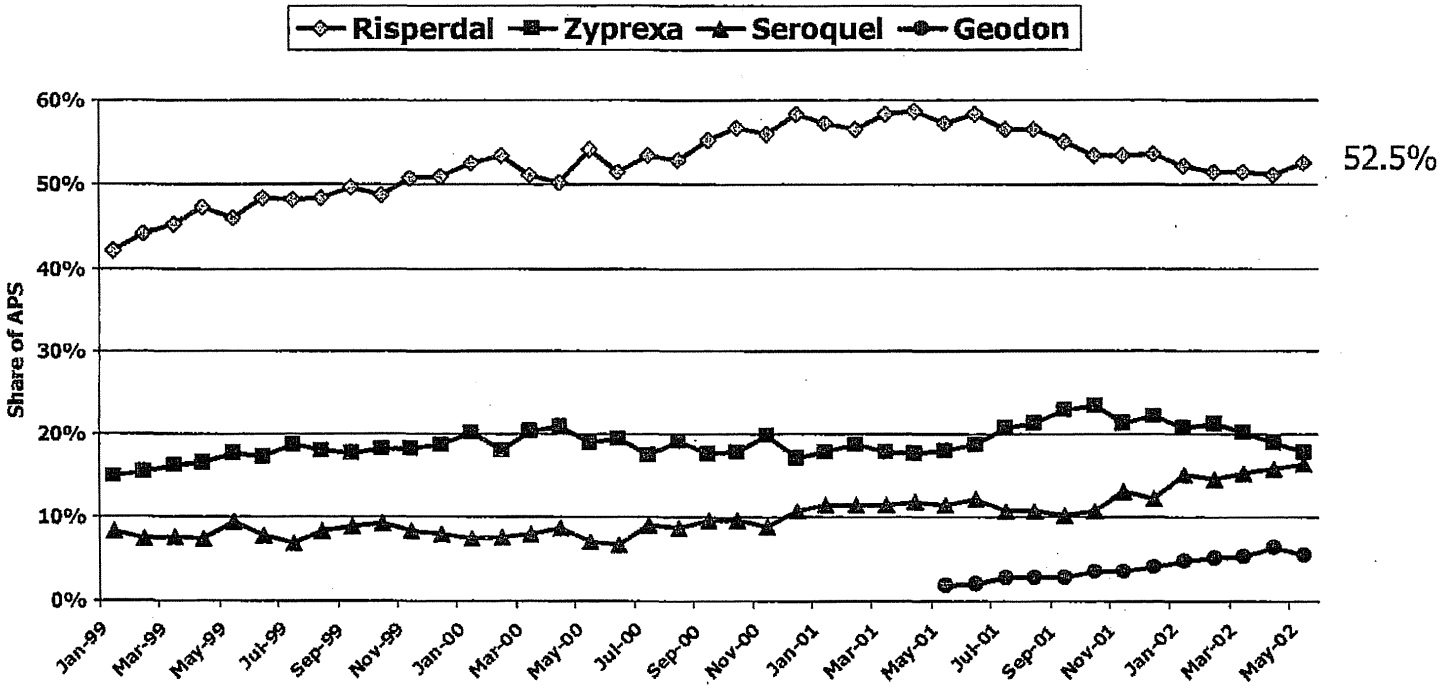
Child and Adolescent & Other New Business

2003 Business Plan

July 29, 2002

Antipsychotic Share in Child & Adolescent Market



Subject to legal and regulatory review

Source: IMS Health, NDTI
Child and adolescent defined as ages 0-17.

2003 Business PLan

Lessons Learned

Lessons Learned

- C&A market is becoming increasingly competitive: increased comfort with newer agents
- Prolactin, EPS, TD and weight gain continue to be important issues (especially long-term implications)
- Competitors are driving negative safety and tolerability perceptions for Risperdal (e.g., prolactin)
- C&A market growth has flattened
- Advocacy is seeking to define a public position regarding C&A use of antipsychotics

Implications

- Generation and dissemination of current and future data is essential
- Dissemination of re-analyses of safety databases is critical
- Stigma and lack of education regarding appropriate use of APS in C&A must be addressed
- Opportunities exist for partnerships with advocacy

Subject to legal and regulatory review

2003 Business PLan

SWOT Analysis

STRENGTHS

- **APS market leader in C & A market**
- **Perceived efficacy advantage:**
  - **trust and experience with product**
- **Most data (Relative to Other APS)**
- Low dose availability/oral Solution
- KOL support
- Early onset of action

WEAKNESSES

- **Safety perceptions (Prolactin, EPS, TD, Weight Gain)**
- **Lack of awareness of appropriate dosing**
- Lack of promotional platform/indication
- Lack of sedation relative to other APS

OPPORTUNITIES

- **External data sources (e.g., RUPP)**
- **Clinical partnerships (e.g., Mass General)**
- **Under serviced market/unsatisfied market**
- Zyprexa safety profile (e.g., metabolic)
- JNJ "pediatric" synergy (MCC, OMP, Alza)
- Better diagnosis (DSM - V, consensus guidelines)
- Advocacy is seeking partnership
- Quicksolv

THREATS

- **Further delay of labeling/exclusivity**
- **Negative PR regarding use of APS in C&A**
- **Increased focus of competition on C&A market**
- Perceived legal liability by prescribers
- Sensitivity regarding use of APS in C&A
- Emerging clinical data with other APS
- Migration to other classes of drugs

Subject to legal and regulatory review

2003 Business PLan

Key Issues

- Use of psychotropic medications in child and adolescents remains controversial
- Limited education and awareness of appropriate use of APS
- Physician misperception of Risperdal safety profile: driven primarily by increasingly competitive market
- Lack of indication

Subject: RE: Qualified Protective Order
From: "Bakalar, Elizabeth M (LAW)" <libby.bakalar@alaska.gov>
Date: Tue, 20 Jan 2009 16:58:14 -0900
To: Jim Gottstein <jim.gottstein@psychrights.org>
CC: "Kraly, Stacie L (LAW)" <stacie.kraly@alaska.gov>

Hi Jim,

With all due respect and fully appreciating the need for expedience, we can't really respond to any of the below absent actual and specific discovery requests propounded to us per the Civil Rules. Once we receive those we'll be happy to assist you in meeting their demands to the best of our ability. You are correct that Dave Campana is the state pharmacist. Likewise we'll deal with any deposition noticed to him and/or others in due course.

Libby

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From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Tuesday, January 20, 2009 4:01 PM
To: Bakalar, Elizabeth M (LAW)
Cc: Kraly, Stacie L (LAW); Amanda Metivier; Jim Gottstein
Subject: Re: Qualified Protective Order

Hi Libby,

If you have specific state confidentiality law you believe applies that can be included let me know.

I disagree it is premature to enter such an order. Discovery will also be obtained from non-parties and I need to at least have sought to obtain a Qualified Protective Order before conducting such discovery.

I have (hopefully) attached a draft of a Rule 30(b)(6) deposition notice. There may be some changes to it before I issue the subpoena, but it seems like we can talk about sequence and timing. The first thing I will need are the electronic files pertaining children and youth being administered psychiatric drugs, so I would like first depose the people who know about them. I understand David Campana is probably the person to depose about the Medicaid database, but I also need to get the relevant computer records from OCS, DBH, DJJ, and API. I am happy to work with the AGO informally to the extent we can. Thus, for example, I have (hopefully) attached a list of what I believe are the Medicaid Fields. I'd be happy to get together with Mr. Campana and my computer guy to understand the database and get the records we want. I would want to do the same thing with the other agencies' databases.

Of course, my great preference is to reach some kind of settlement, but in the absence of any movement on that front, I need to pursue discovery with some dispatch.

Bakalar, Elizabeth M (LAW) wrote:
Jim,

We're not averse to the concept of a protective order and we're not trying to be difficult, but until specific discovery

requests are propounded, we think this is a little general/premature. Once we get down to the nitty gritty of discovery, we're going to be dealing with state confidentiality law—not just HIPAA—and any protective order issued should be tailored to the specific request. Obviously if we're talking about raw data, a protective order is probably not needed. So in short we'd prefer to wait until specific discovery requests come in before we jump the gun on this one.

Libby

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From: Jim Gottstein [mailto:jim.gottstein@psychrights.org]
Sent: Tuesday, January 20, 2009 2:43 PM
To: Bakalar, Elizabeth M (LAW); Kraly, Stacie L (LAW)
Cc: Amanda Metivier; Jim Gottstein
Subject: Qualified Protective Order

Hi Libby and Stacie,

We need to get a "Qualified Protective Order" in place under HIPAA for the conduct of discovery and I have taken the initiative to draft the (hopefully) attached one. My preference is to jointly present one, but if we can't agree on its terms, I will go ahead and move for it.

My anticipated schedule got blown up by the Bill Bigley case, essentially losing three months, so I am feeling pressed to move this case along.

--

James B. (Jim) Gottstein, Esq.
President/CEO

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The Law Project for Psychiatric Rights is a public interest law firm devoted to the defense of people facing the horrors of forced psychiatric drugging. We are further dedicated to exposing the truth about these drugs

and the courts being misled into ordering people to be drugged and subjected to other brain and body damaging interventions against their will. Extensive information about this is available on our web site, http://psychrights.org/. Please donate generously. Our work is fueled with your IRS 501(c) tax deductible donations. Thank you for your ongoing help and support.

--

James B. (Jim) Gottstein, Esq.
President/CEO

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Subject: Re: Our Pending Litigation
From: Jim Gottstein <jim.gottstein@psychrights.org>
Date: Mon, 09 Feb 2009 12:49:32 -0900
To: "Bakalar, Elizabeth M (LAW)" <libby.bakalar@alaska.gov>
CC: "Kraly, Stacie L (LAW)" <stacie.kraly@alaska.gov>, Jim Gottstein <jim.gottstein@psychrights.org>
BCC: Amanda Metivier <facing_fostercare@yahoo.com>, V[redacted] C[redacted] <[redacted]>

Hi Libby,

I, too, hope you are not "one of the 'huge wealthy enemies'" referred to in the Huffington Post article. I'm working on configuring our discovery requests and hope to get at least some of them out by the end of this week or early next. I agree we should obtain "concrete facts and figures derived through formal discovery." Analyzing the Medicaid database seems likely to provide the most global picture. I initially proposed we could meet informally in order to formulate the precise request for the Medicaid database, but you want do even that through formal discovery, which is fine.

In addition to the Medicaid Database I understand the Office of Children's Services (OCS) uses "ORCA" and the Division of Behavioral Health (DBH) uses AKAIMS. I don't know what the Alaska Psychiatric Institute (API) and the Division of Juvenile Justice (DJJ) use. We'll just start through the 30(b)(6) deposition, but I am trying to be careful and thorough about putting it together, which is why it hasn't gone out yet.

How about if we set March 19th to start the 30(b)(6) deposition of the state?

Bakalar, Elizabeth M (LAW) wrote:

> We too look forward to working with you, so I truly apologize if it wasn't clear from our January meeting that we were planning to take a hard look at the issues you identified in your agenda. We are doing so as we speak, and just this morning I had a long meeting with DHSS folks to discuss. Settlement (in our opinion) will be helped enormously by concrete facts and figures derived through formal discovery. That way we will have a better idea as to the validity of your allegations, the scope of possible settlement, and the financial impact of any proposals. Our point was simply that there is no need to informally "lobby" the public with respect to issues already being addressed through active litigation. That's our position, but obviously you'll do what you need to do. And no, I was not aware that you were officially scheduled to present at the BTKH meeting. But I sincerely hope that we are not one of the "huge wealthy enemies" referred to in the Huffington Post piece you've attached. We have a common goal of keeping kids in custody safe and healthy. We need to be partners—not combatants—in that endeavor. We are trying to work with you sincerely and in good faith and our point was simply that it's difficult to do so when you're on the sidelines maligning DHSS.
>
> Libby Bakalar
> Assistant Attorney General
> Office of the Attorney General
> P.O. Box 110300
> Juneau, Alaska 99801-0300
> (907) 465-4135 (direct)
> (907) 465-3600 (main)
> (907) 465-2539 (fax)
>
> ---
>
> **From:** Jim Gottstein [mailto:jim.gottstein@psychrights.org]
> **Sent:** Friday, February 06, 2009 7:16 PM
> **To:** Bakalar, Elizabeth M (LAW)
> **Cc:** Kraly, Stacie L (LAW); Amanda Metivier; Jim Gottstein
> **Subject:** Re: Our Pending Litigation

Hi Libby,

It is very encouraging to hear the State is working on settlement issues. I wasn't encouraged when we left our meeting a month ago and this is the first indication I have heard the State is working on settlement issues. You ask that I consider limiting public advocacy efforts "during the the time we have specifically identified to work on settling the issues you raised." What time have you specifically identified to work on settling the issues I raised?

When I thought about timing, (a) the Legislature is presumably going to adjourn in mid April, and since (b) the trial is set for February 1, 2010, (c) it was hard to see how we could even get there from here, especially since (d) as far as I am aware, there has been no effort by the Administration to even raise the possibility with the Legislature. If, on the other hand, the Administration has been talking to legislators, I certainly don't see how it can complain about me communicating with it as well. If my e-mail to the Legislature caused the Administration to talk to legislators about the issue, from my perspective that seems good.

My e-mail to all of the legislators was really more of a courtesy, and especially so they could not say they hadn't been informed by me, if, as I hope, absent a settlement, we obtain a court order requiring the State to immediately cease the way it is psychiatrically drugging and paying for the psychiatric drugging of children and youth. Unless requested by legislators for more information, I am not intending to contact them further because I believe, without support from the Administration, it would be a waste of my time, which will be better spent on the litigation. However, as I think you know, I am scheduled to make a presentation to the Alaska Mental Health Trust Authority's Bring the Kids Home workgroup meeting Wednesday afternoon. I am doing that because, as we both know, there will need to be resources devoted to solving the problem and the Trust is potentially part of the solution.

As to PsychRights' general public advocacy efforts, we see that as a key part of the effort. In that regard, you might be interested in the item appearing in the influential Huffington Post blog a couple of days ago at http://www.huffingtonpost.com/dr-peter-breggin/a-hero-protects-americas_b_164020.html . I have also (hopefully) attached the February Nine Star Youth Services Newsletter, "The Teen Beat," which has a couple of articles about the issue starting at page 7.

The State should be ashamed of what it is doing to children and youth, should be immediately taking steps to rectify the situation, and I hope hard questions do start being asked of the Administration and Legislature. In my mind, that would encourage settlement.

I look forward to working with you on these issues.

Bakalar, Elizabeth M (LAW) wrote:
Hi Jim,

It's come to our attention that you've recently contacted the Alaska Legislature regarding our pending litigation (3AN-08-10115). Specifically, you e-mailed members of the Legislature on January 27 to inform them of the alleged "incredible amount of harm the State of Alaska is unnecessarily inflicting" on youth in state custody. We also understand that you have sought to participate in at least one public meeting attended and/or sponsored by

DHSS, possibly for the purpose of addressing issues related to this litigation.

We, along with our clients, attended our January 2009 settlement meeting in good faith. As a result of that meeting we have started to work on many of the issues you identified in the hopes that we could either narrow the scope of this lawsuit or frame future settlement proposals. We understand that you will soon be propounding formal discovery requests, which hopefully will go a long way toward advancing these goals.

So we were a bit surprised and confused by your overtures to the Legislature and others to seek public venues in which to discuss this case. Our clients believe that given our pending litigation, these issues are more appropriately resolved through discovery, settlement, and other established judicial processes.

While no one disputes your right to advocate your position to the public, we ask that you consider limiting these efforts during the time we have specifically identified to work on settling the issues you have raised. It is very difficult and distracting for the Department to engage in settlement discussions while having to simultaneously address and respond to your public advocacy efforts.

Thanks.

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UNITED STATES DISTRICT COURT
EASTERN DISTRICT OF NEW YORK
----------x
IN RE:
ZYPREXA LITIGATION,

MDL 04 1596
United States Courthouse
Brooklyn, New York
----------x
January 17, 2007
11:00 a.m.

TRANSCRIPT OF HEARING
Before: HON. JACK B. WEINSTEIN, District Judge
APPEARANCES
Attorneys for Plaintiff:
DOUGLAS & LONDON, ESQ.
111 John Street
Suite 1400
New York, N.Y. 10038
BY: MICHAEL A. LONDON, ESQ.

THE MILLER FIRM
The Sherman Building
108 Railroad Avenue
Orange, Virginia 22960
BY: MICHAEL J. MILLER, ESQ.

FRED VON LOHMANN, ESQ.
Attorney for Electronic Frontier Foundation
454 Shotwell Street
San Francisco, Ca 94110

MR. HAYES: Right.
THE COURT: I think it's reasonable to read the letter plus the attachment as indicating December 20th as the date for supplying the exhibits.
MR. McKAY: Your Honor --
THE COURT: Do you want to ask anything?
MR. McKAY: No, your Honor. I think that it's really argumentative. It's the date of the deposition and we agree with that.
THE COURT: Then I'm prepared to release the witness.
MR. HAYES: Yes.
THE COURT: Have a good trip back to Alaska, sir?
THE WITNESS: Thank you, your Honor.
(Witness excused.)
THE COURT: Next witness.
MR. LEHNER: At this time we would call Vera Sharav who is still in the courtroom, I believe.
VERA SHARAV, having been called as a witness, first being duly sworn, was examined and testified as follows:
THE CLERK: Could you please spell your name for the court reporter.
THE WITNESS: Vera Sharav, V-E-R-A S-H-A-R-A-V.
DIRECT EXAMINATION

Gottstein, is that correct?
A It was validated in my mind when they appeared on Sunday in the New York Times front page, then again on Monday on the front page. Then of course the editorial calling for congressional hearings about the content of the documents and that is really my interest. My interest is the content because the documents document the fact that Eli Lilly knew that the -- that Zyprexa causes diabetes. They knew it from a group of doctors that they hired who told them you have to come clean. That was in 2000. And instead of warning doctors who are widely prescribing the drug, Eli Lilly set about in an aggressive marketing campaign to primary doctors. Little children are being given this drug. Little children are being exposed to horrific diseases that end their lives shorter.

Now, I consider that a major crime and to continue to conceal these facts from the public is I think really not in the public interest. This is a safety issue.

MR. LEHNER: I move to strike as being nonresponsive to my last question and I would like to ask the court reporter if he is able to -- I think I remember my last question. I'll repeat my last question. Nonetheless, I'll make a motion to strike the last answer.

THE COURT: Denied.

Q My question was was it Mr. Gottstein who conveyed to you the impression that you formed in your mind that these

IN THE SUPERIOR COURT FOR THE DEFENDANTS OF ALASKA

THIRD JUDICIAL DISTRICT AT ANCHORAGE

LAW PROJECT FOR PSYCHIATRIC RIGHTS, an Alaskan non-profit corporation, Plaintiff, vs. STATE OF ALASKA, SARAH PALIN, Governor of the State of Alaska, ALASKA DEPARTMENT OF HEALTH AND SOCIAL SERVICES, WILLIAM HOGAN, Commissioner, Department of Health and Social Services, TAMMY SANDOVAL, Director of the Office of Children's Services, STEVE McCOMB, Director of the Division of Juvenile Justice, MELISSA WITZLER STONE, Director of the Division of Behavioral Health, RON ADLER, Director/CEO of the Alaska Psychiatric Institute, and WILLIAM STREUER, Deputy Commissioner and Director of the Division of Health Care Services, Defendants.	REC'D MAR 30 2009 Case No. 3AN 08-10115 CI

DEFENDANTS' REPLY MEMORANDUM TO PLAINTIFF'S OPPOSITION TO DEFENDANTS' MOTION TO STAY DISCOVERY

In Opposition to defendants' Motion to Stay Discovery, Psych Rights submits a 28-page opposition and close to 200 pages of exhibits[1] arguing two main

[1] The first 22-pages of the exhibits relate to the pending discovery requests in this case and are relevant to the instant motion. The remaining pages appear to relate to Psych Rights "discovery plan" which is discussed, *infra*. As argued in this reply, the discovery plan is beyond the scope of this motion and these documents should be stricken or not relied upon by the court. To the extent the Motion to Stay is not granted, or the underlying Motion for Judgment on the Pleadings is denied, then the defendants will

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points: 1) that the burden and expense of discovery does not outweigh the benefit to Alaska youth in bringing this litigation, and 2) that the Motion to Dismiss, which is the basis for the Motion to Stay, lacks merit. Both these arguments fail for the reasons set forth below. Therefore, the Motion to Stay should be granted.

ARGUMENT

1. Discovery Prior To The Court's Decision On The Motion For Judgment On The Pleadings Is Unwarranted And Burdensome

Psych Rights' primary argument is a policy argument that the benefits of this litigation to Alaska youth are paramount to any burden or expense to the defendants in engaging in discovery at this time. This opinion should not trump legal precedent. Even if Psych Rights is correct that the ultimate benefit to children should be considered primary, the rules of civil procedure still require process to be followed. This ends-justify-the-means argument does not work because in order to get to the end, Psych Rights must have a case that can go forward. This argument also fails to recognize a long line of case law, cited to by the defendants in its motion, that supports the position that discovery is not appropriate because the defendants should not be subjected to the time, expense, and burden of discovery unless there are factual issues in dispute related to the dispositive motion.[2]

In *Karen L. v. Defendants*, the Alaska Supreme Court held that in the case where a dispositive motion related to official immunity was raised, the State defendants were entitled to a stay of discovery because "official immunity shelters government officials, not just from liability, but from *suit*, including pre-trial discovery."[3] In *Karen L.*, a mother sued the Department of Health and Social Services alleging

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work with Psych Rights to establish a mutually agreeable discovery plan, or will seek the court's assistance in developing such a plan. In short, the defendants reserve the right to argue as to the merits of this plan and these documents should it be necessary, and its silence here should not be considered as a waiver of those rights.

[2] *See, e.g., Karen L. v. Defendants Dept. of Health and Social Services, Div. of Family and Youth Services*, 953 P.2d 871, 880 (Alaska 1998), *citing* to *Mitchell v Forsyth*, 472 U.S. 511, 5265, 105 St. Ct. 2806, 86 L.Ed.2nd 411 (1985).

[3] *Id.* (emphasis in original)

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negligent and intentional infliction of emotional harm and loss of filial consortium. In that case, the mother clearly had standing to sue, but the defendants moved for summary judgment alleging that their actions were immune from suit. The superior court granted a motion to stay discovery while the motions related to immunity were litigated.

If, in a case such as *Karen L.*, discovery can be stayed because the issue of immunity from suit was before the court, the same analysis should apply where there is an allegation that the plaintiff cannot meet the case and controversy requirement of standing to sue in the first place.[4] The analysis to grant the stay related to protection from pre-trial discovery is equally, if not more, compelling in a case where there is an allegation that the plaintiff lacks standing. In both cases, there exists a threshold bar to proceeding with the actual litigation, which includes barring pre-trial discovery. This is especially true when cases involve governmental entities because the concept of unfettered discovery may impose "an undue burden on public officials and government agencies."[5]

Psych Rights then argues that the federal cases cited by the defendants do not support its Motion to Stay. Citing to *Chavous v. District of Columbia Financial Responsibility and Management Assistance,* [6] Psych Rights argues that discovery should not be stayed when there are factual issues related to the pending substantive motion. While this statement is correct, it does not apply to this case because there is no need for discovery of factual issues related to whether Psych Rights has standing to bring this suit.

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[4] Psych Rights argues that *Karen L.* is inapplicable because the defendants in that case were sued in their personal and not their official capacities. The undersigned does not see in the case where the defendants were sued in their individual capacity; but even if that was the case the distinction is without merit. The issue that is relevant in this case is when there are dispositive issues that preclude the suit in total, pre-trial discovery to develop a factual record is not allowed.

[5] *Williamson v. U.S. Dept. of Agriculture*, 815 F.2d 368 (5th Cir. 1987), *citing Halperin v. Kissinger*, 606 F.2d 1192 (D.C. Cir. 1979), *aff'd* in pertinent part, 452 U.S. 713 (1981). (The court properly stayed discovery pending resolution of threshold governmental immunity issues).

[6] 201 F.R.D. 1, 3, D.D.C. 2001

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Additionally, Psych Rights argues that the defendants have requested a "blanket stay of discovery without a showing that any of the discovery is in any way unwarranted, or even burdensome, let alone that it would not lead to evidence that might be relevant to the Motion for Judgment on the Pleadings." This statement misses the point. If the Motion for Judgment on the Pleadings is granted and the matter is dismissed, then any discovery conducted prior to that point is *per se* unwarranted and burdensome because there is no case upon which to conduct discovery. In fact, if the court finds that Psych Rights does not have standing (the legal argument in the Motion for Judgment on the Pleadings), then a new lawsuit must be filed with proper plaintiffs who can establish the requisite standing to proceed. Newly named plaintiffs would likely change the factual issues and the claims for relief in the complaint - all of which would render discovery conducted at this time not only costly and burdensome, but quite possibly irrelevant. There is no question that discovery is unwarranted and burdensome in this instance when the named plaintiff does not have standing to bring this suit.

It is well settled that when jurisdictional issues are raised that would bar the litigation in whole, it is well within the discretion of the court to stay discovery. Such a decision should be entered here. While there is a core question remaining as to whether Psych Rights has standing to file the litigation that has been filed, the defendants should not be subjected to the cost and burden on discovery. The Motion to Stay should be granted.

2. Psych Rights Has Not Amended Its Complaint To Add Plaintiffs Therefore, The Motion For Judgment On The Pleadings Is Not Unmeritorious

Psych Rights argues that the dispositive motion is "unmeritorious" and the issue could be addressed by simply naming new plaintiffs. While this statement is hypothetically true, as of this date, Psych Rights has not attempted to amend the Complaint to add new plaintiffs. A hypothetical solution to this problem does not render the Motion for Judgment on the Pleadings unmeritorious. As long there is a real question on whether Psych Rights has standing to proceed, discovery should be stayed.

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3. The Defendants Has Not Gone Outside Of The Motion For Judgment On The Pleadings

In an effort to get to discovery, Psych Rights argues that the underlying motion "goes outside the pleadings," which means that discovery must be allowed. In support of this argument, Psych Rights cites to statements made in the Motion for Judgment on the Pleadings to support its contention that the defendants have "gone outside the pleadings." Psych Rights then claims that discovery is warranted because the motion has "gone outside the pleadings." This argument is misplaced. The statements relied upon by Psych Rights to support the argument that the motion "goes outside the pleadings" is contained in the factual background and the conclusion, not the legal argument. They are statements of the existing law or summaries of positions taken in the defendants' answer and affirmative defenses; they are not part of the defendants' legal argument.[7] A summary of the defendants' position in its answer or on the applicable law does not render the motion outside of the pleadings sufficient to defeat the motion to stay.

4. Psych Rights Discovery Plan Is Premature

The remainder of Psych Rights' motion, close to 20-pages, is devoted to outlining the careful and focused discovery plan that Psych Rights has developed to make this process logical, efficient, and less burdensome. The problem with the "plan" is that it is only logical, efficient, and not burdensome *if* Psych Rights can show the requisite adversity to allow this case to go forward. If Psych Rights wants to know about the defendants' computerized records system, then obtain discovery on how pediatric psychopharmacology is practiced on youth in defendants' custody, and then seek information about negative data related to these medications – it must have standing to do so.

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[7] *See* defendants' Answer to the First Amended Complaint, Affirmative Defenses Nos. 2, 9, and 10.

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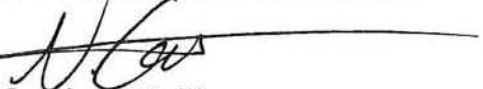
Discovery is the process whereby parties are allowed to develop the factual assumption related to the theory of a case.[8] If a case cannot meet the "case and controversy" test to go forward, there is no need to develop facts as contemplated by the civil rules governing discovery. In the simplest of terms, unless Psych Rights has standing to sue, any factual issues it seeks to develop are not ripe at this time. A logical, efficient, and less burdensome plan should only be implemented after standing has been established.

CONCLUSION

There is no discovery that can be obtained during the pendency of the dispositive motion that will affect the court's decision, thus, discovery is not warranted and is burdensome until standing is established. For the foregoing reasons, the defendants request that the court stay discovery pending the court's decision on the defendants' contemporaneous Motion for Judgment on the Pleadings.

DATED this 27th day of March, 2009.

RICHARD A. SVOBODNY
ACTING ATTORNEY GENERAL

By: 
Nevhiz E. Calik
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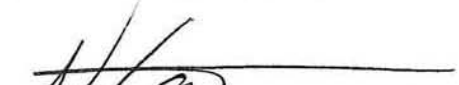
By: 
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[8] Alaska Rules of Civil Procedure 26-36.

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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

LAW PROJECT FOR PSYCHIATRIC RIGHTS, Inc., an Alaskan non-profit corporation, Plaintiff, vs. STATE OF ALASKA, *et al.*, Defendants.	)

Case No. 3AN 08-10115CI

OPPOSITION TO JUDGMENT ON THE PLEADINGS

Plaintiff, the Law Project for Psychiatric Rights (PsychRights®), opposes the Motion for Judgment on the Pleadings (Motion) filed by defendants State of Alaska, *et al.*, (State). Eliminating extraneous matter, the State's sole ground for the motion is the assertion that PsychRights lacks "citizen-taxpayer," standing because there are better parties to bring this suit. This is false. No one else has or is likely to bring such an action and no one else is in a position to competently assert the legal claims made herein.

I. Standards for Considering Motions for Judgment on the Pleadings

Civil Rule 12(c) provides:

> **(c) Motion for Judgment on the Pleadings**. After the pleadings are closed but within such time as not to delay the trial, any party may move for judgment on the pleadings. If, on a motion for judgment on the pleadings, matters out-side the pleadings are presented to and not excluded by the court, the motion shall be treated as one for summary judgment and disposed as provided in Rule 56, and all parties shall be given reasonable opportunity to present all material made pertinent to such a motion by Rule 56. A decision granting a motion for judgment on the pleadings is not a final judgment under Civil Rule 58. When the decision adjudicates all unresolved claims as to all parties, the judge shall direct the appropriate party to file a proposed final judgment. The proposed judgment must be filed within 20 days of service of the decision, on a separate document distinct from any opinion, memorandum or order that the court may issue.

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In *Prentzel v. State, Dept. of Public Safety*,[1] the Alaska Supreme Court held a movant for judgment on the pleadings can prevail only if the "pleadings contain no allegations that would permit recovery if proven." The Alaska Supreme Court in *Prentzel* also made clear that "a party should be permitted to amend if there is no showing that amending would cause injustice," reversing the superior court's denial of such a motion.[2]

In *Hebert v. Honest Bingo*,[3] which was cited by the State, the Alaska Supreme Court reversed the granting of a motion for judgment on the pleadings, saying:

> [A] Rule 12(c) "motion only has utility when all material allegations of fact are admitted in the pleadings and only questions of law remain."

The Court also held"

> When a court considers a motion for judgment on the pleadings, it must "view the facts presented in the pleadings and the inferences to be drawn therefrom in the light most favorable to the nonmoving party."[4]

II. Standing

The only legal ground actually asserted in the State's Motion for Judgment on the Pleadings is the affirmative defense that PsychRights lacks standing. In *Hebert*, the Alaska Supreme Court discussed the special situation posed when a motion for judgment on the pleadings is based solely on an affirmative defense.[5]

> A Rule 12(c) motion based solely upon an affirmative defense poses a special situation because a plaintiff is not permitted to reply to affirmative defenses or new material contained in the defendant's answer absent a court order to the contrary. Accordingly, judgment on the pleadings is inappropriate if the defendant seeks

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[1] 53 P.3d 587, 590, (Alaska 2002).
[2] 53 P.3d at 590-91.
[3] 18 P.3d 43, 46 (Alaska 2001), footnote omitted.
[4] 18 P.3d at 46-47, footnote omitted.
[5] 18 P.3d at 47, footnotes omitted.

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relief based upon any factual matters raised in the answer to which the plaintiff has not had an opportunity to respond: "Thus, when material issues of fact are raised by the answer and defendant seeks judgment on the pleadings on the basis of this matter, his motion cannot be granted."

The seminal case for "citizen-taxpayer" standing in Alaska is *Trustees for Alaska v Alaska Department of Natural Resources*,[6] in which the Alaska Supreme Court laid out the requirements as follows:

> First, the case in question must be one of public significance. . . . Second, the plaintiff must be appropriate in several respects. For example, standing may be denied if there is a plaintiff more directly affected by the challenged conduct in question who has or is likely to bring suit. The same is true if there is no true adversity of interest, such as a sham plaintiff whose intent is to lose the lawsuit and thus create judicial precedent upholding the challenged action. Further, standing may be denied if the plaintiff appears to be incapable, for economic or other reasons, of competently advocating the position it has asserted

A. Citizen-Taxpayer Standing

(1) Pleading Citizen-Taxpayer Standing

The State raises that PsychRights did not include a specific allegation of citizen-taxpayer standing. In *Hebert*, the Court said:[7]

> [J]udgment on the pleadings is appropriate where the defendant raises an affirmative defense that is supported by the undisputed facts. For example, when the statute of limitations is alleged as a bar to the plaintiff's claims, a Rule 12(c) motion may be an appropriate avenue for relief if the statute of limitations defense is apparent on the face of the complaint and no question of fact exists

Assuming *arguendo*, that the Amended Complaint is technically insufficient for failing to include the allegation that PsychRights has citizen-taxpayer standing, PsychRights will be

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[6] 736 P.2d 324, 329-30 (Alaska 1987), footnotes omitted.
[7] *Id.*, footnote omitted.

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moving for leave to amend the Complaint to do so. Allowance of such an amendment appears to be mandatory.[8]

(2) This Case is of Public Significance

The State does not dispute that this case raises issues of public significance.[9] This can not be seriously disputed.

(a) Psychiatric Drugs Are Being Pervasively Prescribed to Children & Youth in State Custody and Through Medicaid In Spite of the Lack of Scientific Support for the Practice

Attached hereto as Exhibit 1 is a copy of the CriticalThinkRx Curriculum, which is funded by the Attorneys General Consumer & Prescriber Education Grant Program, overseen by the Attorney General offices of Florida, New York, Ohio, Oregon, Texas, Vermont and two rotating states (CPGP).[10] The CriticalThinkRx Curriculum was specifically developed to inform non-medically trained professionals working in child welfare and mental health and was the result of systematic literature searches selecting materials based on relevance and accuracy.[11]

Among the CriticalThinkRx findings are:

> "Basic empirical support of efficacy in children is lacking for most individual [psychotropic] medication classes and no studies have established the safety and efficacy of combination treatments in children."[12]

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[8] *Prentzel*, 53 P.3d at 590-91; *Fomby v. Whisenhunt*, 680 P.2d 787, 790 (Alaska 1984).
[9] Motion for Judgment on the Pleadings, page 16.
[10] Exhibit 1, p. 2. The funds available to the CPGP came from the settlement of a lawsuit against the manufacturer of the anticonvulsant Neurontin for the illegal marketing of Neurontin for unapproved ("off-label") use. *Id.*
[11] *Id.*
[12] Exhibit 1, p, 17, CriticalThinkRx Curriculum, citing to Bhatara, V., Feil, M., Hoagwood, K., Vitiello, B., & Zima, B. (2004), National trends in concomitant psychotropic

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In spite of this, the number of children and youth in the United States administered these drugs tripled during the 1990s and is still rising in this decade.[13] Seventy-five per cent of all psychiatric medication use in children is for uses not approved by the Food and Drug Administration (FDA).[14]

> "The bottom line is that the use of psychiatric medications [in children] far exceeds the evidence of safety and effectiveness."[15]

Psychotropic drugs given to children and youth increase behavioral toxicity, causing apathy, agitation, aggression, mania, suicidal ideation and psychosis, leading to additional mental illness diagnoses and more psychiatric drugging.[16]

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medication with stimulants in pediatric visits: Practice versus knowledge. Journal of Attention Disorders, 7(4), 217-226; Jensen, P.S., Bhatara, V.S., Vitiello, B., Hoagwood, K., Feil, M., and Burke, L.B. (1999). Psychoactive medication prescribing practices for U.S. children: Gaps between research and clinical practice. Journal of the Academy of Child and Adolescent Psychiatry, 38(5), 557-565; Martin, A., Sherwin, T., Stubbe, D., Van Hoof, T., Scahill, L., & Leslie, D. (2002). Use of multiple psychotropic drugs by Medicaid-insured and privately insured children. Psychiatric Services, 53(12), 1508; Vitiello, B. (2001). Psychopharmacology for young children: Clinical needs and research opportunities. Pediatrics, 108(4), 983-989

[13] Exhibit 1, page 16, citing to Olfson, M., Blanco, C., Liu, L., Moreno, C., & Laje, G. (2006). National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. Archives of General Psychiatry, 63(6), 679-685; Olfson, M., Marcus, S.C., Weissman, M.M., & Jensen, P.S. (2002). National trends in the use of psychotropic medications by children. Journal of the American Academy of Child and Adolescent Psychiatry, 41(5), 514-21; and Zito, J. M., *et al.*, (2003), Psychotropic practice patterns for youth: A 10-year perspective. Archives of Pediatric & Adolescent Medicine, 157(1), 17-25.

[14] Exhibit 1, page 17, citing to Vitiello, B. (2001). Psychopharmacology for young children: Clinical needs and research opportunities. Pediatrics, 108(4), 983-989; and Zito, J. M., *et al.*, (2003), *supra*.

[15] Robert Farley, The 'atypical' dilemma: Skyrocketing numbers of kids are prescribed powerful antipsychotic drugs. Is it safe? Nobody knows, *St. Petersburg Times*, July 29, 2007, quoting Ronald Brown, Chair, 2006 American Psychological Association Task Force on Psychotropic Drug Use in Children.

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Children in foster care are 16 times more likely to receive psychotropic drugs than their non-foster care counterparts.[17] Children in welfare settings, such as those enrolled in Medicaid, are two and three times more likely to be given psychiatric drugs than children in the general community.[18]

These alarming facts apply to Alaska as the State admits in its Answer.[19] From April 1, 2007, through June 30, 2007, at least the following number of Alaskan children and youth under the age of 18 received the following psychiatric drugs through Medicaid:

- second generation neuroleptics -- 1,033
- first generation neuroleptics -- 15
- stimulants -- 1,578
- supposedly non-stimulant drugs such as Strattera --293
- antidepressants -- 871
- anticonvulsants marketed as "mood stabilizers" -- 723
- noradrenergic agonists, most likely Clonidine to counteract problems caused by the administration of neuroleptics -- 470[20]

In fact, Facing Foster Care in Alaska (FFCA), the statewide group of foster Youth and Alumni in Alaska,[21] held a statewide retreat in November of 2008, and issued its report, "Mental Health Services and Foster Care," (FFCA Report) in which they state:

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[16] Exhibit 1, page 18, citing to Safer, D. J., Zito, J. M., & dosReis, S. (2003). Concomitant psychotropic medication for youths. American Journal of Psychiatry, 160(3), 438-449.
[17] Zito, J. M., *et al.* (2003), supra.
[18] Exhibit 1, page 20, citing to Breland-Noble, A.M., Elbogen, E.B., Farmer, E.M.Z., Dubs, M.S., Wagner, H.R., & Burns, B.J. (2004). Use of psychotropic medications by youths in therapeutic foster care and group homes. Psychiatric Services, 55(6), 706-708; Raghavan, R., Zima, B. T., Andersen, R. M., Leibowitz, A. A., Schuster, M. A., & Landsverk, J. (2005). Psychotropic medication use in a national probability sample of children in the child welfare system. Journal of Child and Adolescent Psychopharmacology.Special Issue on Psychopharmacoepidemiology, 15(1), 97-106.
[19] Paragraphs 229-235 of the Amended Complaint herein and the State's Answer pertaining thereto.
[20] *Id.*

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In their 2008 Policy Agenda, FFCA members called for Decreased use of Psychotropic Medication for Alaska's foster youth. Many of Alaska's youth and alumni complain about being prescribed psychotropic medications after entering the foster care system for symptoms of depression, anxiety, trauma, attachment issues, and misbehavior. The youth and alumni of FFCA feel that these are all normal symptoms of child maltreatment and dealing with all that comes out of being placed in foster care. There has been a national focus on the use of psychotropic medications being over-prescribed for children and youth in foster care. FFCA members have also complained about side-effects caused by these medications resulting in a decreased ability to focus on their education as well as function in everyday society. The youth and alumni of FFCA would like to see that the prescription of psychotropic medications for Alaska's foster children and youth is decreased and reviewed more closely.[22]

Among the comments in the FFCA Report made about children and youth in foster care being given psychiatric drugs are:[23]

- Too young for drugs
- Worse Afterwards
- Makes you Worse
- Lies & deception
- In hell
- Messes with life
- No Choice
- Constant Labeling
- False Accusations
- No advocating What-so-ever
- Guinea pigs
- Other alternatives
- No reason
- Forced
- Over-mediating
- Prolific diagnosis
- Taking away childhood
- Normality-shouldn't we be like this?

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[21] FFCA defines "Youth" as "a young person in foster care" and "Alumni" as "a person who was in foster care at some point during their life." Exhibit 2, p. 7

[22] Exhibit 2, p. 4, emphasis added.

[23] Exhibit 2, p. 3.

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Interestingly, the solutions suggested by the FFCA Youth and Alumni correspond closely to those the scientific evidence set forth in the CriticalThinkRx Curriculum and incorporated into the Amended Complaint herein show are effective.

There is no doubt this case raises issues of public importance.

(3) There is No More Directly Affected Plaintiff Likely to Bring Suit For A Systemic Injunction Against The Improper Psychotropic Drugging of Alaskan Children and Youth In State Custody or Paid For Through Medicaid.

PsychRights satisfies the citizen-taxpayer standing requirement that there be no more directly affected plaintiff likely to bring suit. The State asserts "there is no reason to presume [a minor Medicaid recipient or child in state custody who has been prescribed or is taking psychotropic medication] would not sue."[24] This fundamentally misconstrues the lawsuit by ignoring that individual affected persons may not be able to obtain the relief requested. Individuals can assert the right that they, or their child or ward, not be subjected to such inappropriate psychiatric drugging and perhaps even obtain a declaratory judgment to that effect. However, the most important relief requested is the injunction against the State improperly administering or paying for the administration of psychotropic drugs to any Alaskan children or youth. This was one of the reasons PsychRights brought this action in its own name, and did not name any other plaintiffs.

(b) The State Would Not Be a Proper Plaintiff

The State asserts:

> To the extent [PsychRights] purports to represent the general public interest of children in state custody . . ., representation of the general public interest of children

[24] Motion for Judgment on the Pleadings, pages 17-18.

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> in state custody "rests with the Attorney General for the State of Alaska, the Department, and/or the parents and guardians of individual children in state custody or the children themselves -- not [PsychRights]."[25]

Would that it were so that the Alaska Attorney General was protecting the legal rights of children and youth in State custody and through Medicaid from the improvident, largely ineffective, and harmful administration of psychotropic drugs. Instead, it is defending the indefensible.

Would that it were so that the Department of Health and Social Services was fulfilling its obligations with respect to the improper administration of psychotropic medication to children and youth of whom it has seized custody and paying for through Medicaid.

The State's attention was directed to the CriticalThinkRx Curriculum on June 11, 2008, which was two and one half months before this action was even filed,[26] yet when answering the Amended Complaint on these same facts,[27] responded it was without sufficient information to admit or deny them.[28] Instead, the State asserts it is powerless to stop the harm to children and youth of whom it has seized custody:

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[25] Motion for Judgment on the Pleadings, pages 14-15.
[26] Exhibit G to Amended Complaint.
[27] The vast majority of the allegations in the Amended Complaint regarding (1) the FDA Drug Approval Process, (2) Undue Drug Company Influence Over Prescribing Practices, (3) Pediatric Psychotropic Prescribing, (4) Neuroleptics, (5) Antidepressants, (6) Stimulants, (7) Anticonvulsants Promoted as "Mood Stabilizers," and (8) Evidence-Based, Less Intrusive Alternatives: Psychosocial Interventions, as well as (9) the "CriticalThinkRx Specifications," come from the CriticalThinkRx Curriculum.
[28] Answer, ¶s 38- 84, 86-92, 94-106, 108-110, 113-132, 134-135, 138, 140-143, 145-148, 152, 154-158, 162-163, 166-167, 169-181, 186, 190-199, 201-211.

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> A reading of the Complaint makes obvious that the true subject of plaintiff's grievances is not the Department, but prescribers of psychotropic pharmaceuticals, the pharmaceutical companies which produce and market them, and the overall culture of pediatric psychiatry. The implication that the Department possesses meaningful authority and control over these matters-or is in any realistic position to administer the relief requested even if the court were to order it-is a fiction.[29] . . .
>
> Insofar as plaintiff disagrees with the practice of pediatric psychiatry and the culture of pharmaceutical marketing and prescribing practices related to psychotropic medication, those matters are not within the Department's meaningful control.[30]

As set forth below, it is not only within the State's control to stop the immense harm caused by the administration of psychotropic drugs to children and youth in its custody, it is its obligation to do so. It is clear from the State's abdication of responsibility that this Court must step in to protect these most vulnerable of Alaskan children and youth from the harm being inflicted upon them through the State's abdication of responsibility.

At pages 3-4 of its Motion for Judgment on the Pleadings, citing to AS 47.10.084, AS 47.12.150, and AS 47.30, the State asserts only parents or the courts can authorize the administration of psychotropic medication, going on to say:

> In short, the administration of psychotropic medication to children in Alaska is a decision left to the parent or legal guardian of the child, or to the superior court. None of the named defendants is permitted to prescribe, authorize, or administer psychotropic medication to any child in the state absent consent from that child's parent, legal guardian, a superior court judge, or, in some circumstances, the child himself or herself. The named defendants simply do not administer psychotropic medication to children in custody in the manner portrayed by plaintiffs Complaint. Rather, there exist well-established statutory schemes-none of which is referenced in the Complaint-to seek individual approval to make such decisions.[31]

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[29] Motion for Judgment on the Pleadings, page 2.
[30] Motion for Judgment on the Pleadings, page 20.
[31] Motion for Judgment on the Pleadings, page 5

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First, this is clearly untrue because AS 47.10.084(a) provides that when parental rights have been terminated the State assumes the parents' residual right to give consent.

Second, the State is clearly wrong on the law regarding its responsibility under AS 47.12.150 even if parental rights have not been terminated. In *Matter of A.E.O*,[32] in another context, the Alaska Supreme specifically rejected the State's interpretation that the existence of residual parental rights and responsibilities relieved it of the same responsibilities:

> The term "subject to" in section .084(a) best connotes the idea that the state's responsibility is subordinate to that of the parent, not that it is eliminated because the parents are also responsible.

Frankly, the State's interpretation that AS.47.10.84 divests it of responsibility for the psychiatric drugging of children and youth in its custody doesn't make sense.

As set forth above, *Matter of A.E.O.* rejects the State's interpretation of the language in another context. Accepting the State's interpretation creates a conflict within AS 47.10.084. AS 47.10.084 provides in pertinent part:

> (a) When a child is committed under AS 47.10.080(c)(1) to the department, . . . or committed to the department or to a legally appointed guardian of the person of the child under AS 47.10.080(c)(3), a relationship of legal custody exists. This relationship imposes on the department and its authorized agents or the parents, guardian, or other suitable person the responsibility of physical care and control of the child, . . . the right and duty to protect, nurture, train, and discipline the child, the duty of providing the child with . . . medical care . . .. These obligations are subject to any residual parental rights and responsibilities . . .. When parental rights have been terminated . . . the responsibilities of legal custody include those in (b) and (c) of this section. . . .
>
> (b) When a guardian is appointed for the child, the court shall specify in its order the rights and responsibilities of the guardian. . . . The rights and responsibilities

[32] 816 P.2d 1352, n9 (Alaska 1991).

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> may include, but are not limited to, having the right and responsibility of . . . consenting to major medical treatment . . ..
>
> (c) When there has been transfer of legal custody or appointment of a guardian and parental rights have not been terminated by court decree, the parents shall have residual rights and responsibilities. These residual rights and responsibilities of the parent include, but are not limited to . . . consent to major medical treatment except in cases of emergency or cases falling under AS 25.20.025, . . . except if by court order any residual right and responsibility has been delegated to a guardian under (b) of this section. In this subsection, "major medical treatment" includes the administration of medication used to treat a mental health disorder.[33]

As the Alaska Supreme Court held in *A.E.O.*, the proper way to interpret this is that the "subject to" does not divest the State of its "right and duty to protect, nurture, train, and discipline the child, the duty of providing the child with . . . medical care . . ."

It is also the State's responsibility to provide the proper non-psychopharmacological approaches identified in PsychRights Amended Complaint in compliance with its AS 47.10.084(a) "duty to protect, nurture, train, and discipline" when that is in the child or youth's best interests, instead of immediately reaching for the pill bottle.[34]

In addition to these statutory obligations, the State has the constitutional obligation to protect children in its custody. The United States Supreme Court has held if a state,

> fails to provide for his basic human needs-e.g., food, clothing, shelter, medical care, and reasonable safety-it transgresses the substantive limits on state action set by the Eighth Amendment and the Due Process Clause.[35]

Third, it is PsychRights understanding, the "consents" are virtually always obtained because one or more of the defendants seek such consent (or court order). In seeking such

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[33] Emphasis added.
[34] *See*, AS 47.10.084(a). §A(1) of PsychRights Amended Complaint seeks this relief.
[35] *DeShaney v. Winnebago County Department of Social Services*, 489 U.S. 189, 200, 109 S.Ct. 998, 1005 (1989).

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consents from parents and guardians, and for that matter, court orders, the State provides the parents and guardians with inaccurate information in order to obtain the consents and court orders.[36] In addition, it is PsychRights' understanding parents are often subjected to extreme pressure to agree to the psychiatric drugging of their children.[37] The State's protestations of non-involvement are disingenuous.

It is clearly the State's responsibility to prevent the children and youth in its custody from being harmed by inappropriate psychiatric drugging. It is shameful the State is abdicating its responsibility when it should be working to correct the problem. If, as the State asserts through the Attorney General, that "representation of the general public interest of children in state custody rests with the Attorney General for the State of Alaska," it should not be using the full weight of its office to defending the defendants indefensible position, but instead insisting the State fulfill its statutory, constitutional, and moral duty to the children and youth of Alaska.

In *Trustees for Alaska*, the Alaska Supreme Court rejected the possibility that the United States Attorney General might bring suit as a sufficient basis for finding it was "a plaintiff more directly affected by the challenged conduct in question who has or is likely to bring suit" and thereby divest Trustees for Alaska of standing.[38] Here, it is clear the

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[36] §A(iii) of PsychRights' Prayer for Relief is "the person or entity authorizing administration of the drug(s) is fully informed of the risks and potential benefits." This includes parents giving consent under AS 47.10.084(c).

[37] PsychRights also understands parents are often threatened that they will have no chance of getting their child(ren) back if they don't consent to the psychotropic drugs. These facts are expected to be established through discovery.

[38] 736 P.2d 330.

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State is not likely to be such a plaintiff and if it did file such a suit, it would be acting as exactly the type of sham plaintiff that is not permitted.[39]

(c) No Affected Child or Youth, Parent or Guardian Is Likely to Sue

The State asserts "there is no reason to presume [a minor Medicaid recipient or child in state custody who has been prescribed or is taking psychotropic medication] would not sue."[40] This is a far cry from *Trustees for Alaska's* requirement of "likely to sue" as the grounds for divesting PsychRights of citizen-taxpayer standing.[41] It is also untrue. There is every reason to presume that neither the children or youth themselves, nor parents or guardians parties, would sue.

First, none have. In *Ruckle v. Anchorage School Dist.*,[42] cited by the State, the Alaska Supreme Court affirmed dismissal because a more directly affected plaintiff already had filed suit. In *Trustees for Alaska*,[43] itself, the Alaska Supreme Court, citing to *Carpenter v. Hammond*[44] and *Coghill v. Boucher*,[45] made it very clear that no one else having filed suit is a strong indication that no one else is likely to file suit.

Second, these children and youth, as well as their parents, lack the resources to do so, and are subject to severe retribution if they tried. They are uniformly poor and otherwise disadvantaged. Guardians are perhaps sometimes in a different situation, but

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[39] *Id.*
[40] Motion for Judgment on the Pleadings, pages 17-18.
[41] 736 P.2d at 329.
[42] 85 P.3d 1030, 1035 (Alaska 2004).
[43] 736 P.2d at 330.
[44] 667 P.2d 1204, 1210 (Alaska 1983), as cited in *Trustees for Alaska* 736 P.2d at 330.
[45] 511 P.2d 1297 (Alaska 1973).

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often, the guardian is the State itself. With respect to non-state guardians for adults, PsychRights knows of a case where a guardian was not allowed to object to forced psychiatric drugging of her ward, and another one where the guardian, the wife of the ward, was removed as guardian because she didn't want him forced to take psychiatric drugs. Part of the discovery planned by PsychRights is to flesh out the State's overwhelming influence if not outright coercion of parents and guardians. Guardians are simply not usually in a position to mount such a lawsuit.

It is known that children and youth attempting to assert their rights are punished therefor. The FFCA Report on Mental Health Services evidences, "one member commented that he did know his rights, but if he did refuse medication he would be placed in North Star."[46] It is also known that if parents don't "toe the line" they are told they will have no chance of reunification.

Third, the potential for being subjected to an award of attorney's fees against them, is a powerful disincentive to bringing such a lawsuit.[47]

Fourth, the State is almost certain to assert children and youth in state custody do not have the right to bring such a lawsuit on their own behalf.

(4) PsychRights Satisfies the Adversity Requirement

In *Trustees for Alaska*, the Alaska Supreme Court described the adversity requirement as follows:

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[46] Exhibit 2, p.4.
[47] *See*, discussion of this issue in §II.B., below.

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> [Standing may be denied] if there is no true adversity of interest, such as a sham plaintiff whose intent is to lose the lawsuit and thus create judicial precedent upholding the challenged action

The State does not contest that PsychRights is sufficiently adverse, conceding PsychRights is a "legitimate public advocacy organization."[48]

The Alaskan not-for profit corporation, tax-exempt,[49] public interest law firm of Law Project for Psychiatric Rights was founded in late 2002 to mount a strategic litigation campaign against forced psychiatric drugging and electroshock.[50]

> The impetus was the book *Mad in America: Bad Science, Bad Medicine, and the Enduring Mistreatment of the Mentally Ill*, by Robert Whitaker. PsychRights recognized this as a possible roadmap for demonstrating to the courts that forced psychiatric drugging is not achieving its objectives but is, instead, inflicting massive amounts of harm.[51]

"In 2006, due to what can only be considered an emergency, PsychRights adopted strategic litigation against the enormous and increasing amount of psychiatric drugging of children as a priority."[52] Because it is the adults in their lives rather than they who are making the decisions, children are essentially forced to take psychiatric drugs[53] and thus this lawsuit fits squarely within PsychRights' mission.

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[48] Motion for Judgment on the Pleadings, p. 16.
[49] *See*, Internal Revenue Services Advance Ruling Letter, dated April 1, 2003, and Public Charity Ruling Letter, dated July 11, 2007, which can be downloaded from the Internet at http://psychrights.org/CorpSec/501c3.pdf and http://psychrights.org/about/Finances/IRSPublicCharityLtr073007.pdf, respectively.
[50] J. Gottstein, "Involuntary Commitment and Forced Psychiatric Drugging in the Trial Courts: Rights Violations as a Matter of Course," 25 Alaska L. Rev. 51, 53 (2008).
[51] *Id.*
[52] *Id*, n. 2.
[53] *See*, also Exhibit 2, p. 4 (older youths will be hospitalized and drugged against their will there if they exercise right to refuse the drugs).

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PsychRights has been successful in pursuing its mission. First, it won *Myers v. Alaska Psychiatric Institute*,[54] in which the Alaska Supreme Court held Alaska's forced drugging statute unconstitutional for failing to require the court to find the drugging to be in the person's best interest and there is no less intrusive alternative. Next, it won *Wetherhorn v. Alaska Psychiatric Institute*,[55] in which the Alaska Supreme Court held it was unconstitutional to involuntarily commit someone as gravely disabled unless, the level of incapacity is so substantial that the respondent is incapable of surviving safely in freedom. In the preface of the 2007 pocket section of his five-volume treatise on mental health law, noted scholar Michael Perlin stated the following:

> *Wetherhorn* . . . reflects how seriously that state's Supreme Court takes mental disability law issues. Last year, we characterized its decision in *Myers v. Alaska Psychiatric Institute*, as "the most important State Supreme Court decision" on the question of the right to refuse treatment in, perhaps two decades. This year, again, the same court continues along the same path, in this case looking not only at the "grave disability issue," but also building on its *Myers* decision.

Of course, it takes a litigant to bring a case to the Alaska Supreme Court in order to give the Court an opportunity to rule. Until PsychRights commenced its strategic litigation campaign, it appears the attorneys appointed to represent psychiatric respondents in involuntary commitment and forced drugging cases failed to bring even one appeal.[56]

Most recently, in *Wayne B.*,[57] the Alaska Supreme Court required strict compliance

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[54] 138 P.3d 238 (Alaska 2006).
[55] 156 P.3d 371 (Alaska 2007).
[56] "Involuntary Commitment and Forced Psychiatric Drugging in the Trial Courts," *supra.*, 25 Alaska L. Rev. at 53.
[57] 192 P.3d 989 (Alaska 2008).

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with Civil Rule 53(d)(1)'s transcript requirement, invalidating the longstanding practice of the superior court, in Anchorage at least, of approving the recommendations of probate masters in involuntary commitment and forced drugging cases without having such a transcript.[58]

Currently, PsychRights has two cases on appeal to the Alaska Supreme Court, *W.S.B. v. Alaska Psychiatric Institute*,[59] in which the issue is whether it is permissible for the Superior Court to close the court file to the public when the respondent has elected to have the hearing open to the public as was his right under AS 47.30.735(b)(3) and desires to have the court file open to the public as well, and *William S. Bigley v. Alaska Psychiatric Institute*,[60] in which PsychRights asserts Mr. Bigley is constitutionally entitled to the provision of an available less intrusive alternative to being forced to take psychotropic drugs against his will.[61]

PsychRights has adversity.

(5) PsychRights is Able to Competently Advocate the Position Asserted

Because of the improvident, largely ineffective and counterproductive, and extremely harmful yet pervasive administration of psychiatric drugs by the State of Alaska of children and youth of whom it has seized custody and through Medicaid payments, PsychRights filed this action seeking declaratory and injunctive relief that Alaskan

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[58] The Court did hold where the superior court "actually listens" to the recording the failure to have a transcript is cured. 192 P.3d at 991.
[59] Case No. S-13015.
[60] Case No. S-13116.
[61] Mr. Bigley also raised other issues, such as the denial of due process in having less than one business day's notice to defend against the forced drugging petition there.

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children and youth have the right to prevent defendants from authorizing the administration of or paying for the administration of psychotropic drugs to them unless and until:

(i) evidence-based psychosocial interventions have been exhausted,

(ii) rationally anticipated benefits of psychotropic drug treatment outweigh the risks,

(iii) the person or entity authorizing administration of the drug(s) is fully informed of the risks and potential benefits, and

(iv) close monitoring of, and appropriate means of responding to, treatment emergent effects are in place.[62]

PsychRights is able to competently advocate this position.[63]

Counsel for PsychRights in this action is James B. (Jim) Gottstein, Esq., the founder, President and CEO of PsychRights, where he works *pro bono* to advance PsychRights' mission.[64] Mr. Gottstein has been practicing law in Alaska since 1978, when, in addition to being admitted to the Alaska bar, he was admitted to practice before the United States District Court, District of Alaska and the Ninth Circuit Court of Appeals.[65] Mr. Gottstein was admitted to the United States Supreme Court in 1994.[66]

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[62] *See*, ¶1 of Amended Complaint and §A of PsychRights' Prayer for Relief.
[63] In reviewing the status of the pleadings, PsychRights realized it should add to the relief requested to effectuate ¶22 of the Amended Complaint, to wit that the State be enjoined from paying for outpatient psychiatric drugs for anything other than indications approved by the Food and Drug Administration (FDA) or included in the following compendia: (a) American Hospital Formulary Service Drug Information, (b) United States Pharmacopeia-Drug Information (or its successor publications), or (c) DRUGDEX Information System. A motion to amend the complaint to include this relief will be forthcoming shortly.
[64] 25 Alaska L. Rev at 51.
[65] Exhibit 3, p.1.
[66] *Id.*

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Mr. Gottstein represented the class of people diagnosed with serious mental illness in *Weiss et al v. Alaska*,[67] the lawsuit over the State of Alaska's illegal misappropriation of the one million acre federal land grant in trust first for the necessary expenses of the mental health program, resulting in a settlement in 1994 valued at approximately $1.3 Billion and creation of the Alaska Mental Health Trust Authority.[68]

From 1998 to 2004, Mr. Gottstein was appointed to and served on the Alaska Mental Health Board,[69] which, among other things, is the state agency charged with planning mental health services funded by the State of Alaska.[70] In 2007, Mr. Gottstein was appointed by the Chief Justice of the Supreme Court to the Probate Rules Subcommittee on Involuntary Commitments and the Involuntary Administration of Psychotropic Medication established to recommend court rules to govern these proceedings.[71]

In 2008, Mr. Gottstein published the law review article, Involuntary Commitment and Forced Psychiatric Drugging in the Trial Courts: Rights Violations as a Matter of Course,[72] in which he documented the lack of efficacy, life shortening and threatening, and otherwise extremely harmful nature of the neuroleptics, which is the class of drugs normally forced on adults faced with court proceedings to force them to take psychiatric drugs against their will, and identified a number of ways in which Alaskans' fundamental

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[67] 4FA 82-2208Civ.
[68] *Weiss v. State*, 939 P.2d 380 (Alaska 1997).
[69] Exhibit 3, p. 1.
[70] AS 47.30.666.
[71] Exhibit 4.
[72] 25 Alaska L. Rev. 51.

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liberty rights in being free of psychiatric confinement and unwanted psychiatric drugs are improperly infringed by the courts of Alaska.

Psychiatrists ought to be able to rely on the information they receive through medical journals and continuing medical education.[73] The State ought to be able to trust that psychiatrists recommending the administration of psychiatric drugs are basing these recommendations on reliable information. Unfortunately, neither of these things which ought to be true are true. Thus, one of the key questions in this case is why psychiatrists are prescribing and custodians are authorizing the administration of harmful psychotropic drugs of little or no demonstrated benefit to children and youth. The answer is that the pharmaceutical companies have been very effectively illegally promoting their use. Section V of PsychRights' Opposition to Motion to Stay Discovery describes some of this and rather than repeat it here, PsychRights hereby incorporates it herein as though fully set forth, including exhibits.

As set forth in the discovery plan set forth by PsychRights in its Opposition to Motion to Stay Discovery, establishing through discovery the bases upon which psychotropic drugs are prescribed to Alaskan children and youth in state custody and through Medicaid is an essential part of this litigation. For example, at page 21 of PsychRights' Opposition to Stay of Discovery, it stated:

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[73] They should be skeptical, however, about "information" provided by drug companies.

> Even with respect to the stimulants, such as Ritalin, which have been approved for children and youth, the truth is there is a lack of data supporting long-term efficacy or safety,[74]

In other words, PsychRights has cited studies that show such practice is improvident and it is necessary to establish upon what bases psychiatrists and others prescribers are prescribing stimulants to Alaskan children and youth. PsychRights can conduct this discovery.

Interestingly, in the short time since PsychRights filed its Opposition to Motion to Stay Discovery, the Washington Post ran a story on just this subject:

> New data from a large federal study have reignited a debate over the effectiveness of long-term drug treatment of children with hyperactivity or attention-deficit disorder, and have drawn accusations that some members of the research team have sought to play down evidence that medications do little good beyond 24 months.
>
> The study also indicated that long-term use of the drugs can stunt children's growth.
>
> The latest data paint a very different picture than the study's positive initial results, reported in 1999.
>
> One principal scientist in the study, psychologist William Pelham, said that the most obvious interpretation of the data is that the medications are useful in the short term but ineffective over longer periods but added that his colleagues had repeatedly sought to explain away evidence that challenged

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[74] Citing to ¶s 154, 156-165 of the Amended Complaint herein; APA Working Group on Psychoactive Medications for Children and Adolescents. (2006); and Report of the Working Group on Psychoactive Medications for Children and Adolescents. Psychopharmacological, psychosocial, and combined interventions for childhood disorders: Evidence-base, contextual factors, and future directions, Washington, DC: American Psychological Association; National Institute of Mental Health Multimodal Treatment Study of ADHD Follow-up: 24-Month Outcomes of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder, MTA Cooperative Group, *American Academy of Pediatrics*, 113;754-761 (2004)

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> the long-term usefulness of medication. When their explanations failed to hold up, they reached for new ones, Pelham said.
>
> "The stance the group took in the first paper was so strong that the people are embarrassed to say they were wrong and we led the whole field astray," said Pelham, of the State University of New York at Buffalo. Pelham said the drugs, including Adderall and Concerta, are among the medications most frequently prescribed for American children, adding: "If 5 percent of families in the country are giving a medication to their children, and they don't realize it does not have long-term benefits but might have long-term risks, why should they not be told?"[75]

Indeed, why haven't the psychiatrists and other prescribers been telling people the truth about these drugs?

As set forth above and in the Opposition to Motion to Stay Discovery, the answer is the drug companies have provided the psychiatrists with inaccurate information. PsychRights will develop this in discovery and through presenting the evidence to this Court. It also seems worth noting here that it is virtually inconceivable that any parent or guardian, or any child or youth, not represented by PsychRights would or could effectively pursue this information, which further buttresses the argument in §II.A.(3) that no other plaintiff is likely to adequately pursue the claims in this action.

B. Interest-Injury Standing

The State argues that PsychRights has not claimed interest-injury standing and it is correct about that. PsychRights could move to amend the Complaint to add individual children and youth, their parents, or guardians, or any combination thereof, to achieve such interest-injury standing, but is reluctant to do so. The original Complaint did not include

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[75] Exhibit 5, p. 1.

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such plaintiffs for a number of reasons, which PsychRights carefully considered before filing the Complaint in this action.

First, as set forth above, the most important relief requested is for systemic relief, especially an injunction, to which individual affected parties would appear not entitled. Naming PsychRights as the plaintiff allows the lawsuit to narrowly tailor the requested relief to the deprivation of rights suffered by Alaskan children & youth in State custody and enrolled in Medicaid.

Second, while PsychRights anticipates being the prevailing party, it seems unfair to expose such plaintiffs to the possibility of attorney's fee awards against them. Counsel has experience with the Alaska Attorney General obtaining attorney's fees against people on welfare who unsuccessfully sought to vindicate their rights in court and understands it is the Attorney General Office's policy to always seek fees against non-prevailing parties, even if they can't afford them.

Until 2003, such plaintiffs named in this action could expect to be found public interest litigants and exempt from such an award. In 2003, however, in ch. 86, § 2(b), SLA 2003, codified at AS 09.60.010 (b)-(e), the Legislature abolished the public interest exception from Rule 82 awards against non-prevailing parties. Under AS 09.60.010(c)(2) an award against such plaintiffs is still not allowed for attorney's fees devoted to claims concerning constitutional rights and under (e) relief can be granted for "undue hardship."

This case raises constitutional claims, as well as substantial non-constitutional claims, thus potentially subjecting such individual plaintiffs to an award of attorney's fees

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against them. This would potentially subject the named plaintiffs to an award of attorney's fees.

Even though PsychRights expects to be the prevailing party and even though the undue hardship exemption under AS 09.60.010(e) seems applicable, PsychRights feels it needs to consider the other possibilities and decided this was another reason not to name individual children and youth, their parents or guardians. It just seemed unfair to expose them to the possibility of having to carry another big brick on their already heavy load.

Should this Court decide that PsychRights does not have citizen-taxpayer standing to bring this suit, PsychRights will consider whether to amend the Complaint to add such named plaintiffs or whether to appeal instead. It is a conundrum because any delay in granting the requested relief is doing great harm to Alaskan children and youth. However, as set forth above, PsychRights has citizen-taxpayer standing and no such amendment is necessary.

III. The Motion is Untimely

Finally, Civil Rule 12(c) requires that a motion for judgment on the pleadings be brought "within such time as not to delay the trial" and the State's Motion for Judgment on the Pleadings is untimely, especially when considered in conjunction with its contemporaneously filed Motion to Stay Discovery.

This action was filed September 2, 2008 and the State filed its Answer to the Amended Complaint on or around October 14, 2008. The instant Motion for Judgment on the Pleadings was not filed until on or around March 12, 2009, some six months after this action was commenced and five months after the State's Answer was filed.

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PsychRights commenced efforts to conduct discovery in January, with which the State originally cooperated, but then at the last minute filed its Motion to Stay Discovery contemporaneously with the filing of the instant Motion for Judgment on the Pleadings. In its Motion to Stay Discovery, the State seeks to stay discovery pending determination of the instant Motion for Judgment on the Pleadings.

In support of its Motion for Expedited Consideration of the State's Motion to Stay, the State submitted an affidavit swearing to the following:

> In preparing for Mr. Campana's deposition, counsel began to review the underlying Complaint more extensively and developed concerns about engaging in further discovery at that time.[76]

The trial is set to commence February 1, 2010, and pretrial deadlines are looming. Decision on this motion may potentially take some time. If discovery remains stayed, it will likely delay the trial and prejudice PsychRights. Frankly, in light of the State's concurrent Motion to Stay Discovery, and what seems to PsychRights to be a patently unmeritorious Motion for Judgment on the Pleadings, it is hard to see how it was made for any reason other than to obstruct and delay the conduct of discovery and thereby jeopardize the trial date and/or prejudice PsychRights' ability to present its case.

IV. Conclusion

Because PsychRights has citizen-taxpayer standing, the State's Motion for Judgment on the Pleadings should be **DENIED**. To the extent that there may be some

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[76] Affidavit of Elizabeth Bakalar, dated March 12, 2009.

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technical deficiency in the Amended Complaint, PsychRights should be allowed leave to amend.

DATED: March 31, 2009.

Law Project for Psychiatric Rights

By: _____
James B. Gottstein
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IN THE SUPERIOR COURT FOR THE STATE OF ALASKA
THIRD JUDICIAL DISTRICT

LAW PROJECT FOR PSYCHIATRIC RIGHTS, Inc., an Alaskan non-profit corporation, Plaintiff, vs. STATE OF ALASKA, *et al.*, Defendants,	)

Case No. 3AN 08-10115CI

EXHIBITS TO
to
OPPOSITION TO MOTION FOR JUDGMENT ON THE PLEADINGS

1. June, 2008, CriticalThinkRx Curriculum, June, 2008.
2. Facing Foster Care in Alaska Report on Mental Health Services, November 2008.
3. Curriculum Vitae of James B. (Jim) Gottstein, Esq., September 12, 2008.
4. Appointment of James B. Gottstein to the Probate Rules Subcommittee on Involuntary Commitments and the Involuntary Administration of Psychotropic Medication, June 28, 2007.
5. Washington Post Article, "Debate Over Drugs For ADHD Reignites Long-Term Benefit For Children at Issue," March 27, 2009.