

IN THE STATE COURT OF DEKALB COUNTY
STATE OF GEORGIA

CURTIS W. REYNOLDS
ADMINISTRATOR OF THE
ESTATE OF JENNIFER BROOKE

Plaintiff,

v.

DR. BLANCA R. ANTON; DR.
DWAYNE TIMOTHY
DAUGHERTY; DR. MARTHA J.
LITTLE; AND NOVARTIS
PHARMACEUTICAL
CORPORATION

Defendants.

CIVIL ACTION FILE
NO. : 01A-76719-3

Affidavit of Peter R. Breggin, M.D.

In Response to
Defendant Novartis Pharmaceutical Corporation's
Supplemental Memorandum in Support of Summary Judgment

I, Peter R. Breggin, M.D., being first duly sworn, state as follows:

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This response will examine the major issues raised by Defendant Novartis in the company's memorandum for Summary Judgment and in its affidavit by expert Allan Josephson, M.D. In each instance, the company's opinion or its expert's opinion will be summarized and then examined.

I. Controversial Nature of ADHD Diagnosis

The defendant Novartis in its brief claims that ADHD is accepted without controversy in the medical profession and in particular that it is "unquestionably" recognized as "valid and useful" (Defendant Novartis Brief, p. 5). This response will not review the large amount of literature to the contrary (see reviews of literature in Breggin, 1999c reproduced in **Breggin Exhibit A**; and also Breggin 2001b, 2002a). The exhibits provided by expert Allan Josephson, M.D. for Defendant Novartis confirm the highly controversial nature of the diagnosis, including direct challenges to the validity of the diagnosis.

The NIH Consensus Statement (Josephson Exhibit C, 1998, p. 3) states "the disorder has remained **controversial**." It elaborates:

The diverse and conflicting opinions about ADHD have resulted in confusion for families, care providers, educators, and policymakers. The **controversy** raises questions concerning the literal existence of the disorder, whether it can be reliably diagnosed, and, if treated, what interventions are most effective.

One of the major controversies regarding ADHD concerns the use of psychostimulants to treat the conditions. [emphases added]

The NIH Consensus Statement hammered home the theme of controversy surrounding the diagnosis and treatment. Its conclusions repeated its earlier assertion that despite progress in the field, "this disorder and its treatment have remained **controversial** in many public and private sectors" (p. 20) (emphasis added).

Furthermore, the NIH Consensus Statement made clear that ADHD was not an established brain disorder: "Although research has suggested a central nervous system basis for ADHD, further research is necessary to firmly establish ADHD as a brain disorder" (p. 7). Furthermore, "our knowledge about the cause or causes of ADHD remains speculative" (p. 21).

The consensus conference statement was written by professionals without a vested interest who came from various fields in science and medicine and they concluded that the diagnosis and even the treatment remained highly controversial.

Another report cited by Dr. Josephson, Goldman et al. (1998; Josephson Exhibit E) underscores the continuing controversy. Goldman et al. is a publication of the AMA Council, a political committee of the AMA whose publications address issues of policy concern to the AMA. Nonetheless, the report emphasizes the continuing controversy: "Despite an enormous body of research into this disorder, various aspects of ADHD have generated controversy over the years" (p. 1100).

The Surgeon General's Report (Josephson Exhibit F) and the Interagency report on Learning Disabilities (Josephson Exhibit I) are governmental documents with frank political goals including the encouragement of federal spending on the psychiatric diagnosis and treatment of children. Nonetheless, they have a scientific aspect and show indications of the ongoing controversy about the ADHD diagnosis and stimulant treatment. The Interagency report, for example, states that the diagnosis of ADHD as published in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders "has employed neither empiric validation of the DSM III constructs nor operationalization of the diagnostic criteria" (p. 196). In its conclusions, it repeats the theme that the diagnostic criteria for ADHD "represent nonvalidated, nonoperationalized constructs" (p. 211). This contradicts the defendant's contention that the validity of the diagnosis is unchallenged in the medical community.

Based on the exhibits provided by Defendant Novartis and their expert Dr. Josephson, as well as an enormous literature, the concept of ADHD and its treatment with Ritalin remain controversial to this day.

II. Limited Benefits Associated with Short-Term Effects

This report will demonstrate (ahead) that there is little or no evidence for any positive long-term effects from Ritalin, although there is evidence of long-term adverse effects, including growth suppression and abuse potential. This section deals with the limits to the effectiveness of Ritalin even in short-term use. Defendant Novartis and Dr. Josephson take the position that Ritalin is a generally effective medication with robust good effects, and they do this without discussing its significant limits even in short-term use.

Stimulant medication has been used for the control of behavior since the 1930s. During the subsequent six decades, the benefits have been found to be limited to the short-term suppression of spontaneous behaviors (Breggin, 1999, 1998; **Breggin Exhibits A and D**). During those six decades, many attempts by staunch advocates and by drug companies have failed to demonstrate the longer-term (beyond a few weeks) safety or efficacy of Ritalin or any other stimulant. In addition, while behavior is suppressed for a few weeks, there is no substantial evidence for improvement in academic, social, or psychological functioning. To the contrary, there is evidence for cognitive impairment, social withdrawal, and depression as Ritalin effects (see below, Part VII, discussion of adverse effects).

The 1998 NIH Consensus Development Conference (Josephson Exhibit C, p. 10) concluded, "Of concern are the consistent findings that despite the improvement in core symptoms [hyperactive and aggressive behavior], there is little improvement in academic achievement and social skills."

Swanson and his colleagues (1992), based on their extensive review, declared "even now, despite several more years of extensive research, there is very little objective evidence to support the notion that stimulant medication improves learning in ADHD children." They leave no room for uncertainty:

The lack of a pervasive favorable response to stimulation medication represents a severe limitation on the educational benefits of stimulation medication to treat ADD students, and often the unfavorable response is in the area of learning.

Stating that they have been “surprised about the consensus expressed in this large literature,” Swanson and his team (1992) summarized:

We believe that the most important limitations are that **the short-term effects of stimulants on academic performance are minimal compared to the effects on behavior, and that there is no evidence of beneficial effects on learning or academic achievement.** [bold type in original]

Greenhill et al. (1999) reviewed stimulant medications (Josephson Exhibit O). Although Greenhill is a staunch advocate of Ritalin and although he has multiple economic affiliations with drug companies, he too confirmed “long-term academic achievement and social skills have failed to show consistent improvement” (p. 506). Later they note that the failed studies were methodologically flawed (p. 508). However, methodologically failures in drug studies, nearly all of which are conducted by drug advocates and usually drug companies, are almost always skewed toward finding positive results. Therefore the inability of even biased studies to show any long-term improvement takes on added weight.

III. The Failure to Demonstrate Long-Term Efficacy

Defendant Novartis’ Brief speaks of the “consensus” concerning the “utility” of Ritalin in “both short and **long-term**” (p. 5, bold added). In fact, no utility has been demonstrated in the long-term use of Ritalin. The Novartis brief is particularly strong in its summary conclusion that studies are “numerous, ongoing, and consistent in their results” in regard to “evidence of long-term benefits” (p. 10). Instead, the studies, which are indeed numerous, ongoing and consistent, all show no significant positive effects from Ritalin and furthermore many studies show harmful effects.

Ritalin was first approved for the control of behavior disorders in the 1950s. Since then innumerable studies have attempted and have failed to show any long-term benefit from the medication. As a result, NIMH brought together a group of strong advocates for the drug for the treatment of ADHD in an attempt specifically aimed at showing that the drug has long-term benefit (The MTA studies). Before addressing that very flawed series of studies (among other things, they lack placebo-controlled clinical trials and blind observers), it is important to demonstrate that almost fifty years of Ritalin use have failed to show any long-term benefits.

A very extensive review of the literature by James Swanson (Swanson, circa 1993) of the University of California, Irvine, Attention Deficit Disorder Center addressed the question of Ritalin’s long-term effect on behavior. The review came to the unequivocal conclusion that “parents and teachers should not expect long-term improvement in academic achievement or reduced antisocial behavior.”

Swanson's ADD Center team (1992) has taken what it calls "the lead role" in organizing and synthesizing the literature on treatments. As Swanson (circa 1993) described in an Executive Summary for the Department of Education, he and his team produced a comprehensive "review of reviews" of the Ritalin literature based on 300 reviews and 9,000 original articles spanning nearly 55 years. Here, *verbatim*, are the first four conclusions reported by Swanson at a forum sponsored by the Department of Education in 1993:

- Long-term beneficial effects have not been verified by research.
- Short-term effects of stimulants should not be considered a permanent solution to chronic ADD symptoms.
- Stimulant medication may improve learning in some cases but impair learning in others.
- In practice, prescribed doses of stimulants may be too high for optimal effects on learning, and the length of action of most stimulants is viewed as too short to affect academic achievement.

Based on his experience and his "review of reviews" from the ADD Center, Swanson (1993) also concluded about Ritalin:

- *No improvement in long-term adjustment*—Teachers and parents should not expect long-term improvement in academic achievement or reduced antisocial behavior.

Swanson (1993) defines "short-term" as "7 to 18 weeks." Thus, based on a the most extensive review available for the first forty years of scientific literature concerning Ritalin, Ritalin had no proven beneficial effect on behavior beyond 7-18 weeks! Swanson has not been alone in coming to these conclusions. .

A review by a team of Ritalin advocates (Regier and Leshner, 1992), assembled by the National Institute of Mental Health (NIMH) came to the same conclusion: "the long-term efficacy of stimulant medication has not been demonstrated for *any* domain of child functioning." The 1992 NIMH report confirmed that short-term effects are limited to behavioral control such as reducing "class room disturbance" and improving "compliance and sustained attention." They also confirmed that the drug seems "less reliable in bringing about associated improvements, at least of an enduring nature, in social-emotional and academic problems, such as antisocial behavior, poor peer and teacher relationships, and school failure."

In 1995, NIMH continued to justify pumping more millions of dollars into the new MTA Ritalin study on the grounds that the drug's efficacy remained unproven (Richters et al., 1995). The report was authored by a team made up of some of the biggest names in the ADHD/Ritalin field, including Peter Jensen, C. Keith Conners, Laurence Greenhill, William Pelham, and others. The report concluded that there is no evidence for even a short-term positive effect on academic performance. In longer-term studies, their conclusion—as noted above—is even bleaker: “long-term efficacy of stimulant medication has not been demonstrated for *any* domain of child functioning” [italics in original].

In their 1997 review, Whalen and Henker came to the same conclusion as declared in a heading “Unsubstantiated Long-Term Benefits.” Their review would document no “long-term advantage” to taking Ritalin.

The 1998 NIH Consensus Development Conference on the Diagnosis and Treatment of ADHD (Josephson Exhibit C) notes the lack of longer-term demonstrations of efficacy and concludes (p. 3), “conclusive recommendations concerning treatment for the long term cannot be made presently.” The emphasized this observation as one of their major points: “Fourth, there is no information on the effects of long-term treatment (treatment lasting more than 1 year)...” (p. 12). In its section on future directions, the NIH conference called for “studies of long-term treatment” (p. 18).

The American Psychiatric Press Textbook of Psychiatry is probably the most widely read psychiatric textbook and represents mainstream opinion in many of its chapters. All of its recent editions continue to affirm that the long-term efficacy of Ritalin remains unproven.

In the second edition in 1994, the chapter on the treatment of children and adolescents in the American Psychiatric Press Textbook of Psychiatry (Popper and Steingard, 1994) similarly stated unequivocally:

Stimulants do not produce lasting improvements in aggressivity, conduct disorder, criminality, education achievement, job functioning, marital relationships, or long-term adjustment.

In the third edition in 1999, the chapter on the treatment of children and adolescents in the same textbook (Cozza and Dulcan, 1999) stated: “Stimulants have not yet been demonstrated to have long-term therapeutic effects...” The authors then go on to lament the inadequacy of past studies (fifty or more years of studies!) and to look forward to the results of the MTA study.

By the time of the fourth edition, now called the American Psychiatric Publishing Textbook of Clinical Psychiatry (Cozza, Crawford, and Dulcan, 2003), the initial results of the MTA study had been widely published. **The widely disseminated MTA study results failed to modify the prevailing scientific consensus that the safety and efficacy of long-term treatment with Ritalin and other stimulants remained unproven.** The authors concluded, “The long-term therapeutic effect of stimulant medication remains unclear.” In this paragraph, it then cites the MTA study. An analysis of the MTA study (ahead) will indicate that its inadequacies were such that it could not overcome the prevailing opinion that confirms no long-term benefit from stimulant medication, including Ritalin.

Guidelines for stimulant use published by Greenhill et al. (2002) (Josephson Exhibit G), a group consisting of the very most staunch advocates of ADHD and stimulants, admit that benefits have been limited to “short-term controlled studies” and that these benefits are further limited to the “core” symptoms, that is, not including academic, psychological or social improvement. Furthermore, Greenhill et al. state, “the lack of long-term prospective studies with these treatments makes it hard to predict their long-term efficacy or safety” (p. S-91). These are remarkable admissions for the most devoted advocates of the treatments.

The MTA studies are given a great deal of emphasis by Defendant Novartis and their expert Dr. Josephson for allegedly confirming the long-term usefulness of Ritalin. However, the above admissions concerning lack of long-term studies by Greenhill et al. were published after the publication of the MTA studies. Furthermore, the authors of the Greenhill guidelines report include leaders of the MTA team: the director of the project, Peter Jensen, and principal investigators Greenhill, Swanson and Connors. **Thus, even the MTA director and three principal investigators do not think that the MTA studies provide data confirming the long-term efficacy and safety of Ritalin.**

Dr. Josephson in his affidavit cites several very old studies in support of long-term positive results. He has totally misrepresented the results of one and the others don't meet scientific standards.

Mendelson et al. (1971; Josephson Exhibit S) is an old study that did not have a control group (p. 271) and that relied heavily on impressionistic reports and reviews of charts. Furthermore, contrary to the implication of the quote used by Dr. Josephson, the children did not do well: “the children in our study were disobedient and rebellious at home and at school, and were still having difficulties with their schoolwork; a significant minority, perhaps one in four, were involved in enough antisocial behavior to make us pessimistic about their future” (p. 277). This study actually demonstrated how poorly stimulant-treated children turned out; but lacking a control group, no sound conclusions can be drawn. The use of such old and unscientific studies indicates the extremes to which Dr. Josephson had to go in seeking studies to confirm his claim for long-term positive effects from Ritalin.

Dr. Josephson also cited Weiss et al. (1975; Josephson Exhibit Q) as yet another old study demonstrating the effectiveness of Ritalin. Dr. Josephson unaccountably used this totally and unequivocally negative study as evidence for long-term efficacy by taking a quote out of context about the “impression” received by the investigators. Actually, this study unequivocally showed that the Ritalin group did no better and in some areas significantly worse than the control group. These negative findings came despite the fact that the Ritalin group prior to treatment was “slightly less active” and had “better” families (p. 162), two critical factors that would have made the Ritalin group do better. Despite the loading in favor of the Ritalin group, after five years there were no differences between Ritalin and the no-drug group in family ratings, scores of psychiatric and social variables, psychological test scores, or academic performance. Indeed, to a high degree of statistical significance, the controls did better in several academic and behavioral measures including language, arithmetic, French, spelling, attention, restlessness, concentration, and approach to work (p. 163)! (This was probably due to the cognitive toxicity so often caused by Ritalin). To the authors’ credit, they admit that the study results surprised them: “The findings of this study were surprising. All of us had in general been impressed by the efficacy of stimulants for hyperactive children, and we probably all expected the study to demonstrate a better outcome in the children who received methylphenidate than in those who received chlorpromazine or no drugs.” They lament their “failure to demonstrate a better 5-year outcome in adolescence in children who had received methylphenidate...” They speculate, “Possibly when methylphenidate is given 3 years or longer it becomes increasingly less effective and ‘tolerance’ slowly develops” (p. 163). **This controlled study illustrates that as early as the 1970s, studies were demonstrating that children long-term actually did worse on Ritalin than on no drug at all.** The study is so negative in regard to Ritalin—demonstrating the authors’ hoped for positive results never materialized and even suggesting that the drug causes tolerance—that one wonders how Dr. Josephson could have read it and then included it among the positive studies.

Dr. Josephson cited Quinn and Rapoport, 1975; Josephson Exhibit R) as demonstrating long-term positive results. The Ritalin-treated children did do significantly better than the placebo group: “The striking clinical impression at one-year follow-up was that the boys in all three groups continued to have difficulties” (p. 242). At one year, the three groups did not differ on parental ratings or in psychological testing (pp. 243 and 244). The teacher ratings were somewhat improved but even the investigators cast doubt on that result: “These data supporting the long-term effect of medication on classroom behavior must be interpreted with caution because the control group of treatment dropouts may have biased the results” (p. 244). Also, the teachers who rated the children at baseline were not the same who rated the children at the conclusion of the study. In general, it is known that teachers in particular tend to rate children on medication as improved. In this case, they also rated children on the antidepressant imipramine as improved, although that drug is not FDA-approved for behavioral control. Furthermore, the study showed serious adverse behavioral and growth effects (see below). Overall, this old study lack a double-blind, had serious flaws, and showed positive effects only in suppressing classroom behavior, a result that the author themselves cast doubt upon.

In regard to Dr. Josephson citing Quinn and Rapport, it should be noted that Rapoport is a well-known Ritalin advocate who nonetheless has herself discounted this old study of hers since she has authored articles confirming that Ritalin has no proven long-term efficacy [e.g., Greenhill, L., Beyer, D., Finkleson, D., Shaffer, D. Biederman, J., Connors C., Gillberg, C., Huss, M., Jensen P., Kennedy, J., Klein, R., **Rapoport, J.**, Sagvolden, T., Spencer, T., Swanson J., and Volkow N. (2002) (Josephson exhibit G)] .

Dr. Josephson also cited another relatively old study, Satterfield and Satterfield (1981) (Josephson Exhibit T) as demonstrating long-term efficacy of Ritalin. In fact, it is impossible to draw such a conclusion from the data itself because all of the children were subjected to multiple modalities of treatment, including “individualized psychotherapy.” There was no control group to determine whether the drug or the psychological and educational interventions were helping. Also, there was no genuine control group, merely a comparison between children receiving more treatment and children receiving less treatment. The authors themselves note that “One of the problems in attributing favorable outcome to treatment is the difficulty (if not the impossibility) of obtaining a suitable untreated control group” (p. 654). They do not conclude that Ritalin by itself was helpful. Instead they conclude that a “multimodality treatment approach” is helpful (p. 655), with the caveat that it’s hard to determine this without a control group.

From the mid-1950s through 1999, the last year of treatment in the Reynolds case, extensive research and commentary demonstrated that Ritalin had no proven lasting effects (beyond several weeks) and that its only consistently demonstrable short-term effect was the suppression of behavior. To counter these decades of negative findings, advocates of Ritalin at NIMH funded the several-site MTA study with the specific aim of bringing together other lifelong advocates of Ritalin to demonstrate its long-term efficacy. Its purpose was not scientific (i.e., to discover the facts), it was to advocate for the drug’s effect. The study would lack controlled clinical trials and independent or blinded observers. In other words, it would fail to meet the most basic scientific canons. This enabled subjective investigator bias to run riot. I will now address the MTA study.

IV. The MTA Reports

The Defendants Novartis Brief and the Josephson expert report rely most heavily on the MTA study to show long-term efficacy for Ritalin. I have already shown in Part III that the MTA studies did not change the opinion of the most widely read textbook that “The long-term therapeutic effect of stimulant medication remains unclear” (Cozza, Crawford, and Dulcan, 2003). In addition, I have shown that a report authored by three principal investigators for the MTA, as well as the MTA study director, concluded “the lack of long-term prospective studies with these treatments makes it hard to predict their long-term efficacy or safety” (Greenhill et al., 2002).

The first of these multi-site studies was published in 1999 (MTA Cooperative Group (1999a; Josephson Exhibit H). Unless otherwise indicated, the citations in this analysis are to this initial publication.

I am attaching two analyses that I have published that present detailed criticism of the MTA study (Breggin, 2000 & 2001a; **Breggin Exhibits B and C**). Both were published in peer-reviewed journals, including one in the journal in which the original study was published. There are additional critiques of the study in the literature as well.

Overall, the MTA study was so scientifically flawed as to be of little value in coming to conclusions about the safety and efficacy of longer-term MPD treatment. **As demonstrated in Part III of this report, the consensus of fifty years was not changed by this study: There are still no scientific demonstrations of longer-term safety or efficacy.**

A. No Placebo Control

In well-conducted clinical trials, a drug is compared to placebo or "sugar pill." This is because patients or experimental subjects taking medication often experience the "placebo effect": they feel better whether or not the drug has any physical effect on them. They are responding to the belief or the hope that they are receiving a good treatment. Similarly, observers will also rate the subjects as improved because they are biased toward a good outcome on the drugs. Therefore, clinical drug trials usually compare the effects of the drug to the effects of a placebo pill.

As one major textbook remarked, "Placebo effects, which occur in a large percentage of patients, can confound many studies—particularly those that involve subject responses; controls must take this into account" (Nies and Spielberg, 1996, p. 45; also see Fisher and Greenberg, 1989; also Schachar et al., 1997; Josephson Exhibit N). The use of placebos is so important that, for FDA approval, a psychiatric drug must prove superior to placebo in two or more placebo-controlled double-blind studies.

The MTA study had no placebo control group, making it impossible to tell if the stimulant drugs were having a real effect or not.

B. No Double Blind

As a further attempt to assure a degree of scientific objectivity in drug studies, the observers and the subjects must be kept in the dark about which patients are taking the drug and which are taking the placebo. This is called the "double blind."

There were no placebo controls and no double blind in the MTA clinical trials. The parents and teachers who rated the children knew whether or not they were receiving medication that everyone involved in the research expected it would work.

C. Finding Subjects Who Already Favored Drugs

When selecting a group of patients for a clinical trial, it is important to avoid pre-selecting a group that will be highly biased in favor of the drug. However, 32% of the children in the MTA study were already taking stimulant drugs (MTA Cooperative Group, 1999, p. 1074). This indicates that many of these parents, as well as the teachers, were already convinced of the usefulness of stimulants.

D. Building in Bias in the Untrained Observers

Remarkably, the MTA study chose not to use trained observers. Experience and training, as well as objectivity, are required to properly evaluate the impact of psychoactive agents. In nearly all published scientific studies in the field, professionals use rating scales and other tools for evaluating a drug's efficacy and adverse effects. Not here! NIMH relied upon the observations of the parents and teachers who were given preprinted checklists to record both improvement and adverse drug effects.

Many adverse effects of stimulants—such as loss of spontaneity and increased obsessive behavior—are easily mistaken for improvements by parents and teachers (Breggin, 1998, 1999a, b, and c). The use of aware, experienced professionals, rather than parents and teachers by themselves, was absolutely necessary in order to determine the frequency and severity of adverse drug effects.

Borcherding et al. (1990) discussed how teachers and clinicians fail to notice adverse drug effects such as drug-induced obsessions and compulsions unless they are trained to do so and unless the study focuses on discovering these adverse effects. There is no evidence that the MTA parents and teachers received training about how to evaluate drug effects. To the contrary, they were reassured in writing in advance that the drug was safe and that the side effects were not serious. The "Teacher Information" handout informed them that the children would be treated with a "**safe and effective** dose of medication..." (bold in original) (NIMH MTA Study, undated b). This claim provided false and misleading information to the teachers. In the absence of long-term studies demonstrating safety and efficacy, the study purpose was to determine if stimulate medication would be safe and effective over a several month period of time. Parents and teachers should not have been given false reassurances that were yet to be proven and that would, in fact, not be proven by the study.

Since the teachers knew which children were receiving the drugs, this built-in bias further skewed their subjective evaluations of drug safety and efficacy. These printed comments also demonstrate the bias of the investigators who had already pre-determined to their own satisfaction that the stimulants would prove safe and effective over the lengthy study period. The "Information for Parents" handout had similar built-in biases, including a reference to biochemical imbalances and genetic factors in "ADHD"(NIMH MTA Study, undated a).

E. The Fate of Blinded Ratings

The MTA study did utilize one group of observers who carried out "blinded ratings of school-based ADHD and oppositional/aggressive symptoms..." (MTA Cooperative Group, 1999, p. 1074). The data from these raters are produced in Table 5 of the study (pp. 1082-1083). This group observed the children in the classroom without knowing which of them had been placed on drugs. **The blind raters did not find any positive drug effect.** Since this was the only objective rating process in the study, these negative results should have been emphasized as indicating a lack of longer-term stimulant effectiveness. Instead, the finding was buried in a table and was not mentioned in the study conclusions.

F. The Children Did Not Rate Themselves Improved

The study asked the children to rate themselves on an anxiety scale (results in Table 5). The children taking the drugs did not rate themselves as more improved than any of the other children. This result supports the use of the safer non-drug treatment or no treatment at all in comparison to longer-term stimulant drug treatment.

Furthermore, there is reason to believe that the children were also asked to rate themselves on a depression scale. This was confirmed when I obtained a handout provided by the Columbia University project (New York State Psychiatric Institute and Columbia University Division of Child and Adolescent Psychiatry, 1994). It states that the children were going to rate themselves on a depression scale. However, the published study failed to mention that the children had taken a self-rating depression scale. Ritalin commonly makes children depressed.

Why did the investigators fail to report the results of the depression self-rating scale? Stimulants commonly cause or worsen depression in children, and that finding may have shown up on the self-ratings (Breggin, 1999c; also see Section VII ahead). Out of scientific integrity, and especially out of compassion for the millions of children on stimulants, the authors of the MTA study should publish any data they possess on this issue.

The MTA study did not interview any of the children concerning their reactions to the drug. In clinical practice, asking children about any potential adverse drug reactions is central to an effective assessment. A child having drug-related problems, such as twitches, headaches, or "blah" feelings, usually does not understand their source or tell anyone about them until specifically questioned. No interest was shown in how the children experienced or viewed the treatment.

G. Most Children Suffered from Adverse Drug Effects

Despite the strong pro-medication bias built into the study, 64% of children were reported by their parents or teachers to have some negative drug effects. Of these, 11.4% of the adverse drug effects were rated as moderate and 2.9% as severe.

The authors of the study dismissed the severe reactions because more than half of them involved "depression, worrying, irritability." They explained that this suffering "could have been due to nonmedication factors" (MTA Cooperative Group, 1999, p. 1075).

However, depression, worrying, and irritability are common adverse effects of stimulants (literature reviewed in Breggin, 1998, 1999c; **Breggin Exhibits D and A**). In Section VII of this report I will demonstrate from the Josephson Exhibits that these particular Ritalin adverse reactions are commonly reported in the literature. The dismissal of known stimulant-induced side effects, like many of the flaws in this study, resulted from the strong biases of the investigators.

H. No Scientific Measures of Adverse Effects

This relatively long-term study could have provided an all-important opportunity to examine the potentially harmful effects of Ritalin and other stimulants on the physical growth and functioning of children. In my initial critiques of the study, I criticized it for not taking measurements of height or weight to measure for potential growth suppression. As it turns out the MTA did take these measures, but suppressed the data for six years when the results showed growth suppression (see Section VII below).

In addition, no measurements of heart rate or blood pressure were taken, and no electrocardiograms were administered, so that potentially harmful cardiovascular effects were not evaluated. There were no neurological examinations for tics or other abnormal movements and no objective tests of mental function, such as memory or attention.

From the opening statement in the study to its conclusion, the investigators made no serious attempt to evaluate the single most important issue surrounding the long-term use of stimulant drugs—the risks posed to the children.

I. No Improvement in Academic Performance

Although the data is once again hidden within a table (MTA Cooperative Group, 1999, Table 4), the study records no improvement or difference in academic performance in spelling or math. The table seems to indicate marginal improvement in reading. However, according to Bertram Karon, Professor of Psychology at Michigan State University the statistical analysis was flawed. Overall, no academic improvement was found as a result of any treatment. This was an important finding that received no attention from the authors. It confirms many previous studies that have failed to show any improvement in academic performance while taking stimulants.

J. Little or No Effect on Social Skills

The peer group ratings by other children did not rate the medicated children as improved in their social relationships. This is consistent with the majority of published studies that show no improvement in social skills in medicated children. The youngsters simply become more docile and isolated.

K. How Could this Study Have Taken Place?

This highly touted study was grossly marred by scientific flaws, by data that undermine its cheery conclusions, by revelations of adverse effects that were overlooked, by withheld data, and by missed opportunities for important research left by the wayside.

How did well-known scientists produce a study with so many basic design flaws? And why did they pay so little attention to the information of value that they did unearth concerning adverse effects such as growth suppression and lack of efficacy as judged by the only blind raters?

The six principal investigators of the individual projects in North America were Laurence Greenhill, C. K. Conners, William Pelham, Howard Abikoff, James Swanson, and Stephen Hinshaw. Each one of them has devoted his career to promoting the concept of ADHD and the medicating of children for the control of behavior. Conners has been doing so for four decades.

Laurence Greenhill of Columbia University and the New York State Psychiatric Institute exemplifies the conflicts of interest that exist for many researchers in the field. Before the biographical data were removed during a controversy over their funding of dangerous research on children, the New York State Psychiatric Institute and Columbia University web site listed the funding of its researchers. As of December 21, 1998 Greenhill was listed as having research funds or other financial associations with six different drug companies: Richwood, Bristol-Myers, Solvay, Wyeth-Ayerst, Glaxo, and Eli Lilly.

Greenhill, like all scientific presenters at the NIMH Consensus Conference on ADHD and its treatment, was required to report to the conference organizers any financial conflicts of interest. Through Freedom of Information I obtained the financial disclosure forms for all of the participants. Greenhill signed Part A of the "Full Disclosure Statement" which reads, "I, the undersigned, declare that I do not have a financial interest or other relationship with any manufacturer(s) of any commercial product(s)." He then left blank the portion of the form where he should have listed the drug company affiliations noted on his medical center's web site. He signed this apparently false statement.

In summary, the MTA Ritalin study was conducted by highly biased advocates of medication. It failed to adhere to the most important, essential scientific standards for clinical drug trials, including double-blind procedures and placebo controls. Therefore, it cannot be used to draw favorable conclusions about stimulant efficacy or adverse effects. Furthermore, despite the multiple built-in biases, the data it generated tends to confirm that stimulant medication produces no better results than any other intervention and that it causes serious adverse effects.

L. MTA Follow-up Studies

In 2004 the MTA (MTA Cooperative Study, 2004a; Josephson Exhibit K) project produced a follow-up study extending 10 months beyond the original 14 months. This study carried forward all of the scientific flaws describing thus far in this analysis and was essentially invalid. Nonetheless, the study found diminishment of what little beneficial effects they believed they had originally measured.

The MTA authors summarized: "The benefits of intensive MedMgt [medication management] for ADHD extend 10 months beyond the intensive treatment phase only in symptom domains and diminish over time" (p. 754). There was no positive finding for "academic achievement, social skills, or negative/ineffective discipline" (p. 756). In addition, the authors did not count drop outs from medication management, biasing the results in favor of the medication (p. 759). Furthermore, the parent and teacher evaluations remained "nonblinded" (p. 759).

Their “major finding” in the concluding paragraph is oddly couched: “1 major finding from this report is that some children [the medication groups] lost some of the initial benefits during follow-up” (p. 760).

Most startling, in 2004 the MTA group published a second study that also dealt with growth suppression by Ritalin (MTA Cooperative Study, 2004b; Josephson Exhibit L). The group found that during the first fourteen months height and weight studies “reveal initial large and significant effects of assigned treatment on weight ($X^2 = 27.29$, $P < .001$) and height ($X^2 = 37.03$, $P < .001$).” The medication groups had their growth stunted! The NIMH sponsor of the study and the individual researchers failed to make this data public when they were giving out advance results of the study in 1998 at the Consensus Development Conference and they then failed to publish it for six years! Yet the data was available at the end of the fourteen month initial study. This withholding of critical data on growth suppression confirms the extent to which the MTA study participants were willing to go to hide critical data from the public. If this data had been released in 1998, it would have been in the Consensus report and in the media worldwide. Instead, it has gone unnoticed by the public and the professions.

Overall, the withholding of this finding, and the failure of any individual investigator to come forward with it, constitutes an indictment of the ADHD/Ritalin establishment. The researchers involved in this cover-up include NIMH’s Peter Jensen, as well as the six principal investigators, including Laurence Greenhill, C.K. Connors, William Pelham, Howard Abikoff, James Swanson and Stephen Hinshaw.

The growth suppression continued through the next ten months of the study. As biased as the MTA group may be, it’s hard to hide from simple measurements of height and weight. In this regard, and perhaps in this regard only, we can say that MTA has made one scientific contribution—confirming the suppression of growth by Ritalin.

The MTA study (2004b) concludes in convoluted language that in effect admits they gave too much medication to the children: “the medication regimen recommended so far by the MTA may need revision to include provisions for drug holidays and lower doses” (p. 769). This is important news that has been buried.

V. Failure to Demonstrate Safety and Efficacy in Adolescents and Young Adults

The patient, Jennifer Brook Reynolds, continued to be treated with stimulants until her death in her early twenties. **Even less scientific evidence is available to confirm the safety and efficacy of Ritalin in older children and young adults, a fact that the manufacturer has not publicized or included in the label.** The NIH Consensus Development Conference concluded:

All formal diagnostic criteria for ADHD were designed for diagnosing young children and have not been adjusted for older children and adults. Therefore, appropriate revision of these criteria to aid in the diagnosis of these individuals is encouraged. P. 8

Similarly, the NIH Consensus Development Conference Statement emphasized among its major points, “Third, there are no conclusive data on the treatment in adolescents and adults with ADHD.” In regard to “What are the Directions for Future Research,” the NIH Consensus Development Conference called for “Prospective controlled studies, up to adulthood, of the risks and benefits associated with childhood treatment with psychostimulants” (p. 18). Because no adequate studies had been performed, the most basic questions hadn’t been answered about safety and efficacy, even in the treatment of children throughout their exposure and their early adulthood. This point cannot be over-emphasized: Although there have been short-term studies of Ritalin safety and efficacy, few of them follow the children into adolescence, and furthermore, there is a lack of studies of older children and young adults.

The guidelines proposed by the American Academy of Pediatrics (2000), cited by the defense (Josephson Exhibit D), limits itself to the age range of 6-12. **This remarkable limitation is critical to this case in which the patient Jennifer Reynolds was treated in her adolescence and early adulthood.** The guidelines stated, “there is, as yet, inadequate information about its applicability to individuals younger or older than the age range for this guideline [6-12 years old]” (p. 1168).

VI. Abuse Potential

At the conclusion of its conference on ADHD and Ritalin in December 1996, the Drug Enforcement Administration (DEA) declared:

[T]he use of stimulants for the short-term improvement of behavior and underachievement may be thwarting efforts to address the children’s real issues, both on an individual and societal level. The lack of long-term positive results with the use of stimulants and the specter of previous and potential stimulant abuse epidemics, give cause to worry about the future. The dramatic increase in the use of methylphenidate in the 1990s should be viewed as a marker or warning to society about the problems children are having and how we view and address them.

The Defendant Novartis brief admits that Ritalin is a Schedule II substance [A DEA category confirmed by the international agency, the INCB] and further admits that Ritalin “by definition possesses a potential for abuse” (p. 12). Other stimulants commonly used to treat ADHD are also in this category, including amphetamine. Most research lumps Ritalin and amphetamine together as essentially similar. This is confirmed by several papers included as Josephson Exhibits as well as in any textbook of pharmacology. In addition, the defendant expert, Dr. Josephson, refers to Ritalin “and similar stimulants” (p. 15). The DEA has repeatedly stated that Ritalin has at least the same addiction and abuse potential as amphetamines (Drug Enforcement Administration, 1995, 1996; Feussner, 1998; Sannarud and Feussner, 2000). **In this light, the label for Ritalin is grossly inadequate compared to the label for Dexedrine or Adderall (amphetamines). The labels for Dexedrine and Adderall have much stronger warnings about abuse. For example, the Dexedrine and the Adderall labels both begin at the very top with a boxed, capitalized warning (see the 1998 Physicians’ Desk Reference). The warning begins:**

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED.

This warning is in dramatic contrast to the Ritalin label which, as the defendant admits, states that Ritalin “should be given cautiously to emotionally unstable patients, such as those with a history of drug dependence or alcoholism,” as if only these vulnerable individuals had any risk.

Defendant Novartis in a footnote (p. 21) says I am “simply incorrect” for stating that the Ritalin label “fails to mention that Ritalin is a controlled substance in Schedule II of the DEA.” The defendant points to the existence of a minute symbol at the top of the label. In fact, I am not wrong. I am correct in stating that the label never mentions this important fact, although it does display the poorly visible symbol as required by law. By contrast, for example, the label for Oxycontin specifically mentions in the label that it has “an abuse liability similar to morphine and is a Schedule II controlled substance (quote from the label in the 1998 Physicians’ Desk Reference). Indeed, the Dexedrine (amphetamine) label also specifically states in its section on Drug Abuse and Dependence that is “a Schedule II controlled substance.” The appropriate equivalent for the Ritalin label would be to actually mention that Ritalin has “an abuse liability similar to amphetamine and is a Schedule II controlled substance.” No such mention is found in the Ritalin label.

The 1998 NIH Consensus Development Conference (Josephson Exhibit C, p. 13) minces no words in regard the abuse risk of Ritalin and other stimulants used to treat ADHD: “It is well-known that psychostimulants have abuse potential” (p. 13).

Also at the NIH Consensus Development Conference, the subject of abuse potential was examined in depth by the representative from the DEA, Janet Feussner (1998), who warned, “An extensive scientific literature spanning more than 30 years of research unequivocally indicates that MPH has a high abuse liability...” (p. 202). Rather than repeating her pithy analysis, her article is appended (**Breggin Exhibit I**). A more detailed version of her report was later published as well (Sannarud and Feussner, 2000). In numerous reports, the Drug Enforcement Administration (DEA) (1995, 1996) and the world-wide equivalent, the International Narcotics Control Board (INCB) (1996, 1997), have published numerous warnings about Ritalin abuse.

In addition at the conference, researcher and educator Nadine Lambert (1998; **Breggin Exhibit G**) presented the most carefully conducted scientific study ever published on the subject of Ritalin as an agent that predisposes to cocaine abuse in young adulthood. Her study is one of the only ones in the literature that is prospective in nature, following and evaluating the children specifically in regard to this problem over a period of several years. Lambert followed up this initial publication at the conference with a 1998 peer-reviewed article (Lambert and Hartsough, 1998; **Breggin Exhibit H**).

The AMA Council Report (Goldman et al., 1998; Josephson Exhibit E) noted that one reason for the controversy surrounding ADHD is that “its treatment often includes stimulant medications that have abuse or diversion potential” (p. 1100). Although the AMA Council was somewhat more optimistic, it confirmed, “A great deal of concern has been raised by the DEA and others about the potential for abuse or diversion of stimulant medication...” (p. 1104). The Council Report confirms the DEA’s observations on the increasing mentions of Ritalin as a drug of abuse (also see Feussner, 1998, and Sannerud and Feussner, 2000, for original DEA data).

Despite extensive studies and warnings from the DEA (Drug Enforcement Agency) and the INCB (International Narcotics Control Board.), and despite the conclusions of the Consensus Development Conference, advocates of the ADHD/Ritalin model with strong ties to the drug companies continue to lament this emphasis. Thus Greenhill et al. (1999) cited the DEA’s Feussner (1998) and complained, “Even MPH has been cited in the NIH Consensus Development Conference as having “a high abuse liability” (p. 510). Actually, the NIH Consensus Conference Statement itself reflected the scientific concerns expressed by the DEA and others at the conference, including myself. As noted, the NIH Consensus Development Conference concluded, “It is well-known that psychostimulants have abuse potential” (p. 13). Greenhill also presented his views at the conference. Having heard all sides, with a heavy weighting of presentations by drug-company associated professionals, the independent NIH Consensus Development panel concluded that Greenhill and other advocates were wrong in denying the abuse potential of Ritalin.

Dr. Josephson cites Biederman et al. (1999; Defendants' Exhibit U) as evidence that Ritalin treatment actually protects against substance abuse. This is not the first time that Biederman has rushed into print to try to counter scientific publications indicating adverse stimulant effects. The faculty disclosure associated with the Journal of Clinical Psychology, 2003, 64, Supplement 11 revealed that Dr. Biederman has received research support not only from defendant Novartis but also from other drug manufacturers, some of whom make stimulants, including Shire Richwood, Eli Lilly, Wyeth, Pfizer, Cephalon, Janssen, and Noven Pharmaceuticals. He is on the speakers bureaus not only of defendant Novartis but also GlaxoSmithKline, Eli Lilly, Pfizer, Wyeth, Shire Richwood, Alza, and Cephalon. He is on the advisory board not only of defendant Novartis but also Eli Lilly, Celltech, Shire Richwood, Noven Pharmaceutical, Alza, McNeil, and Cephalon. Other authors of the Biederman et al. report also have significant ties to drug companies, but not as extensively as Dr. Biederman, the lead author.

The Biederman study is too flawed to have any validity. I will summarize some of the worst aspects:

(1) The treatment and control groups were pruned and manipulated so that only individuals 15 years old and older were included. This is a study of late teenagers, 15-19 year olds.

(2) These late teenagers were studied while they were receiving Ritalin from their doctors. They were on the drugs during the study of drug abuse! In fact, not one of the drug-treated group members was abusing illicit drugs at baseline; they were being provided licit drugs by doctors, so they didn't have to seek illicit drugs. The authors don't even discuss this fatal flaw to their study.

(3) The control group of non-medicated ADHD late teens were substantially different from the Ritalin-treated group in ways that predisposed the control group to become active users of illicit drugs. To a statistically significant degree, the control group was older (therefore more prone to use illicit drugs), was of lower socioeconomic status, and at baseline had a higher future risk of conduct disorder. Indeed, the so-called control group with its vulnerabilities to drug abuse was already abusing drugs at a high rate at baseline (Table 1) whereas the medicated group was not abusing any drugs at all. In other words, the control was not a control group at all, but instead was a group of young men (average age 18) who were much more likely to abuse drugs, some of whom were already abusing drugs. The authors claim to try to correct these distortions through statistical means but the control was already so much smaller than the treatment group (56 to 19) that statistical corrections would be meaningless. Besides, it is not scientifically valid to take a non-control group and make it a control group by statistical assumptions. The authors put it mildly when they warned about "the lack of an ideal control group for assessing the independent effect of pharmacotherapy on SUD [substance abuse disorder] onset" (p. 5 of exhibit). That is, they admit that their control group was inadequate to the task of the study.

Dr. Josephson also cites Barkley et al. (2003, Josephson Exhibit V) as evidence that Ritalin does not cause stimulant abuse. Dr. Barkley, like Dr. Biederman, is one of the most active, staunch, and devoted promoters of the ADHD concept and the use of stimulant drugs. In fact, he travels around the world promoting these concepts. Yet when the study is actually read (rather than its conclusions), the study shows an association between stimulant treatment and later cocaine. For example, when examining the contribution of stimulant treatment in high school to adult drug use, the authors found that “Those who had received stimulant treatment used cocaine more frequently ($P=0.43$). In other words, they found a direct correlation between stimulant treatment and cocaine abuse. This is buried in a paragraph that goes on to explain that when they examined other co-existing variables, “stimulant treatment was no longer significant ($P = .062$). Actually, this was, at the least, a red flag for the risk of stimulant use in association with later cocaine abuse. Clearly, the authors were doing everything in their statistically tool box to try to modify the finding; yet after the statistical manipulations, the correlation between stimulant treatment and later cocaine abuse was still very close to what is generally considered statistically significant ($P = .062$ rather than 0.05).

Barkley et al.’s discussion section contains the following remarkable admissions:

Whether children had been treated with stimulants, either in childhood, or in high school, was not associated with risk for their ever having used these substances by young adulthood, with 1 exception. That exception was the risk of using cocaine. There, we found that stimulant treatment in childhood or in high school increased the risk of ever using cocaine. High school stimulant treatment was also associated with a greater frequency of cocaine use. (p. 105)

The authors then go on to argue that the actual correlation was with severity of lifetime conduct disorder symptoms. This makes no medical or scientific sense. There is no reason why lifetime severity of conduct disorder symptoms should be associated exclusively with cocaine abuse and not with the abuse of other drugs, especially cigarettes and alcohol. But it makes medical and scientific sense why treatment with prescribed stimulants would predispose to specific abuse of the most potent illicit stimulant, cocaine. Furthermore, treatment with stimulants may also cause or exacerbate symptoms of conduct disorder. When stimulant treatment leads to cocaine abuse, the treatment by definition has caused or exacerbated conduct disorder. Whether or not the Barkley statistical analysis has validity (and the outcome was borderline at best as described above), the Barkley report cannot be used as an argument against the association between Ritalin treatment and later cocaine abuse. Instead, it strongly confirms it.

The Barkley report authors conclude “The present study found no consistent or convincing evidence that stimulant treatment in childhood or during high school was associated with risk for adolescent or adult substance abuse...” (p. 107). A conclusion like this could only be based on the hope that no one would actually read the study.

Dr. Josephson cites another study, a review and analysis of other studies by the same group of individuals with their close connections to the drug industry (Wilens et al., 2003; Josephson Exhibit W). A review of the literature depends not only on the objectivity of those reviewing the studies but also upon the quality of the studies. We have already looked at the misleading nature and poor quality of some of those studies, including those involving Biederman and his team, and Barkley.

In summary, the world's narcotic control agencies have repeatedly pointed to the addiction and abuse risks associated with Ritalin and have warned about increasing abuse resulting from the increasingly widespread prescription of Ritalin. These agencies include the DEA of the United States (Drug Enforcement Administration 1995, 1996; Feussner, 1998) and the International Narcotics Control Board of the World Health Organization (International Narcotics Control Board. 1996, 1997). Furthermore, the NIH Consensus Development Conference in 1998 confirmed that it is well-known that stimulants are subject to abuse. The best prospective study yet published (Lambert, 1998; Lambert and Hartsough, 1998; **Breggin Exhibits G and H**) confirmed the connection between Ritalin use and later cocaine abuse. As we have seen, even the most die-hard advocates, Barkley and his team, have generated data confirming the connection between stimulant treatment in childhood and high school and later cocaine abuse.

VII. Adverse Drug Effects Other than Abuse

The Defendant Novartis, in an incomplete sentence, claims that “Second, the mainstream medical community not only does not recognize the supposed risks Dr. Breggin would have Novartis put on the label” (p. 16). A claim like this flies in the face of the fact that I was selected by NIH to be **the single scientific presenter on the subject of adverse drug effects in children** at the 1998 NIH Consensus Development Conference on the Diagnosis and Treatment of ADHD.

The array of adverse effects that I describe are documented with dozens of citations to the scientific literature in my report to the NIH Consensus Development Conference (Breggin, 1998; **Breggin Exhibit D**). The documentation can also be found in my medical books (for example, Breggin 1997) and even more extensively in my peer-reviewed articles (for example, Breggin 1999c; **Breggin Exhibit A**) that review hundreds of scientific studies.

This report has documented the lack of academic improvement on stimulant medication. There are strong indications that children in fact perform more poorly while taking Ritalin (reviewed in Breggin, 1999c; Breggin Exhibit A). Swanson, Cantwell, Learner, McBurnett, Pfiffner and Kotkin (1992) describe cognitive toxicity in detail with multiple citations to the literature. They summarize, “The clinical procedure of using parent and teacher reports to titrate the dose of stimulant medication may result in treatment of some ADHD children with doses that produce cognitive toxicity in as many as 40% or more of the typically treated cases.” In other words, almost half of the children treated many develop a Ritalin-induced worsening of their cognitive abilities.

Rather than review once again the literature I have already reviewed in many publications, including the available controlled clinical trials, I have appended my most comprehensive publication (Breggin, 1999c; **Breggin Exhibit A**). To show how thoroughly the literature confirms my published findings, I will review some of the articles provided as exhibits by Dr. Josephson as confirmation of my reports about the frequency and severity of adverse effects from Ritalin.

The 1998 NIH Consensus Development Conference (Josephson Exhibit C, p.13) noted that “high doses” of central nervous system stimulants “may cause central nervous system damage, cardiovascular damage, and hypertension.” It also noticed an association between high doses and “compulsive behaviors” and “movement disorders,” as well as rare “hallucinogenic responses.” The caveat of high doses is not correct. As the individual who presented the most scientific material on adverse reactions, I made clear that all of these adverse effects were reported in routine doses (as an example, see Borcharding et al., 1990, attached to this report as **Breggin Exhibit F** for high rates of obsessive reactions and abnormal movements during average dose trials).

Schachar et al. (1997), provided by the defendants (Josephson Exhibit N), confirms my analysis of the frequency, severity and range of adverse drug effects caused by Ritalin. The study was double-blind with a placebo group. Of the original 46 Ritalin patients, 37 continued to the end of the study. Adverse effects were frequent, covered a broad range and were sometimes severe. Here is a brief summary (taken from pp. 760-761):

(1) A high percentage of children withdrew due to adverse effects (5 or 11%);

(2) The five children (11%) withdrew because of the kind of severe psychiatric reactions described in my reports and initial affidavit in this case: “three withdrew during titration (because of sadness and behavioral deterioration, irritability, withdrawal, lethargy, violent behavior, or rash), one discontinued in the second month of treatment (because of withdrawal and mild mania), and one discontinued during the third month of treatment (because of withdrawal and dysphoria).” By contrast, none of the placebo children withdrew for any of these reasons. The one placebo withdrawal was for stuttering.

(3) The adverse psychiatric effects related to withdrawal and depression increased with dose, confirming their causal relationship to the drug: “withdrawal, sadness, and crying, [were] the most common affective side effects that increased with MPH.”

(3) Anorexia and stomachaches were the most common physiological side effects.

(4) The children on Ritalin failed to gain weight, and in fact lost some weight, in comparison to the control group; that is, weight gain was suppressed. This was statistically significant. [Note also that the recent report from the MTA (2004b, see analysis above) that documented the suppression of weight and height from short-term and long-term treatment with Ritalin with lasting effects at the end of the study at 24 months.]

(5) Many children had adverse effects. “Significantly more children receiving MPH than receiving the placebo experienced clinically significant side effects.” Of the 37 children who continued for four months, 30 (81%) showed increased symptoms above baseline.

Schachar et al. emphasize the high rate of drop outs and the seriousness of the adverse drug effects: “Second, side effects of MPH were evident, even though every effort was made to keep them to a minimum through careful and continuous monitoring, dosage adjustment, and use of twice-daily dosing” (p. 761).

They also noted the importance of placebo controls, because the placebo control group also improved over time.

The study by Schachar et al., one of the few placebo-controlled studies with a length of four months, confirms the observations in my reports and initial affidavit concerning the frequency and severity of adverse drug reactions to Ritalin. Not only was this study included as a defendants exhibit, I have used it my reviews of the literature, along with other controlled studies, to demonstrate the high rate and severity of adverse drug reactions to Ritalin (Breggin, 1998, 1999a,b and c).

Another study offered by Dr. Josephson (Quinn and Rapoport, 1975; Josephson Exhibit R) again demonstrates the harmful impact of Ritalin on many children. The study was not blind so that investigator bias was not controlled (p. 241). Nine out of 38 (24%) boys dropped out. At least seven (18%) suffered obvious behavioral abnormalities commonly caused by the drug (“2 for irritability and excitation, 5 for worsening behavior”) (p. 242). Furthermore, 47% suffered anorexia. The Ritalin group suffered significant weight loss and some height suppression (p. 242).

Defendant Novartis is incorrect in suggesting that I exaggerate adverse drug effects or rely on something other than the scientific method and scientific literature.

VIII. Criticism of Peter R. Breggin, M.D. by Defendant Novartis

A. Defendant Novartis states that my views concerning the adverse effects of Ritalin are not held within the medical community

My publications, including my medical books and peer-reviewed publications, are based on the medical literature and as much as possible on controlled clinical trials, including my medical book, Brain-Disabling Treatments in Psychiatry (1997). My appended peer-reviewed 1999 publication is probably the most detailed and documented review and analysis in the entire medical literature (Breggin 1999c; **Breggin Exhibit A**). Furthermore, as indicated in Section VII of this report, several of the studies provided by Defendant Novartis confirm my observations on the frequency, severity and nature of Ritalin adverse drug reactions.

I am frequently asked to consult and lecture on adverse drug effects at universities and hospital grand rounds, including at CME seminars used to maintain the credentials of medical doctors. Specifically in regard to Ritalin adverse effects, I was asked by the Office of the Director of the National Institutes of Health (NIH) to be the scientific presenter on adverse drug effects in children at the 1998 NIH Consensus Development Conference on the Diagnosis and Treatment of ADHD. I have been hired by the FAA (Federal Aviation Agency) to consult concerning the adverse effects of medications on the performance of flyers.

B. Defendant Novartis questions my expertise in labeling, stating, “Dr. Breggin claims no expertise in product warning” (p. 16).

1. Forensic Experience Regarding Labeling

Defendant Novartis is grossly wrong when it states that I make no claim for expertise in producing warning. I not only claim to have expertise in labeling, I have been exercising that expertise in the courtroom for two decades, including some landmark cases. My testimony has been accepted in many criminal cases, malpractice cases and product liability cases. Some of these cases include the following:

Andre v. Somatics, Inc. 5.31.91. Supreme Court: New York County: IAS: Part 29. Index No. 9220/87. Product liability. The judge used my report, citing it for several pages, to reject the ECT manufacturer's request for summary judgment in the product liability case against them that involved labeling issues extensively.

Kuss v. 1991. Houston, Texas. Malpractice. A woman believed she was injured by multiple psychiatric drugs. I testified in trial concerning standard of care and multiple psychiatric drugs, including the benzodiazepine Xanax and the antidepressant Prozac, as well as the FDA approval process and labeling.

Piechotta v. 1992. Malpractice and Product Liability. Philadelphia, Pennsylvania. A child developed tardive dyskinesia after treatment with neuroleptic drugs. After deposition testimony concerning neuroleptics, the FDA and labeling, and product liability of the pharmaceutical industry, my credentials and scientific method were challenged by the defendant drug company and the judge affirmed my report.

Fentress (the Wesbecker case) vs. Shea Communications; Jefferson Circuit Court. 1994. Louisville, Kentucky. Product liability. A man committed multiple murders within days of his doctor recording that Prozac might be making him psychotic. This was the first and only one of the combined Prozac cases to go to trial. I was the scientific medical expert for the entire discovery process for the more than one hundred combined cases. Labeling was a central issue. I testified in trial as an expert concerning pharmaceutical company negligence (Eli Lilly and Company), the FDA and the drug approval process including labeling, clinical trial evaluation, the spontaneous reporting system, and medication effects on behavior.

State of Alabama versus Parker. 1996. Criminal case appeal. A boy who had been given Ritalin as a child became addicted to stimulants as a teenager, and committed drug-related violence. I testified in a hearing before the judge on an Appeal of a Capital Punishment Verdict. My testimony covered the standard of care for psychiatry and the addictive effects of Ritalin on children, including the implications of labeling in regard to addiction and abuse.

Accardo v. Cenac. 1997. Baton Rouge, Louisiana. Malpractice. A woman developed tardive dyskinesia after treatment with neuroleptic drugs. I testified in the malpractice trial concerning neuroleptic drugs, tardive dyskinesia and dystonia, as well antidepressants and benzodiazepines, the FDA and labeling, the pharmaceutical industry, standards of care, and adverse drug effects.

Mitchell v. Upjohn, 1998. Los Angeles Superior Court. Product liability. A woman believed she was addicted by prescription Xanax. After a rigorous challenge by the defendant drug company, I was allowed to testify on all issues in the product liability trial concerning the benzodiazepine Xanax, addiction, drug testing, clinical trial evaluation, and the FDA and labeling.

Ungar v. Pike, 1998. No. 92 L 728. Chicago. State of Illinois in the Circuit Court of Cook County. A man committed suicide while taking the benzodiazepine sleeping pill, Halcion. I gave deposition testimony on malpractice and product liability, and trial testimony on malpractice concerning the standard of care in internal medicine in regard to mental health issues, on benzodiazepines and specifically Halcion as a cause of depression and suicide, and on drug labeling by the FDA.

Franko v. Worthington et al., Court of Common Pleas, County of Philadelphia, Pennsylvania, June 2001. Malpractice. In 1988 a man died from the combination of Prozac, Ritalin and other drugs with the MAOI antidepressant, Parnate. I testified concerning the effects and interactions of Prozac, Ritalin, and Parnate, and also drug development and FDA regulation and labeling.

Commonwealth of Virginia v. John Lowe. July 2001. 28th Judicial Circuit, Abington, Virginia, Judge Charles H. Smith, Jr. presiding. Criminal trial. A man who shot his estranged wife and a deputy sheriff was charged with many crimes, including kidnapping and malicious wounding. At the time of the incidents, he was being treated with Prozac, Remeron, and BuSpar. The judge accepted my testimony in all areas, including adverse drug reactions, drug labeling, FDA procedures, and criminal responsibility, including involuntary intoxication.

State of South Carolina v. Brooke Jewell. Before Judge Edward E. Cottinham, Charleston County General Sessions Court. November 15, 2001. Sentencing hearing for a 27 year old man with no prior history of violence who pleaded guilty to rape charges. I presented evidence that Paxil can cause mania with disinhibition and aggressive sexuality, and that a Paxil-induced Mood Disorder caused or contributed to his actions. The judge accepted my testimony in all areas, including SSRIs, Paxil, the FDA approval process, labeling, and related topics. I focused on an analysis of the label.

Kernke v. The Menninger Clinic. U.S. District Court for the District of Kansas, Judge Gerald Vanbebber. Case No. 00-22630GTV. December 11-12, 2001. Malpractice. In the case of a man who wandered off the hospital grounds and died of exposure, I testified concerning standards of care in a residential treatment center and a mental hospital ward, as well as the standards of conduct of physicians in charge of a drug-company sponsored clinical trial of an experimental drug, including the determination of inclusion/exclusion criteria, informed consent, coercion in the consent process, and the monitoring and reporting of potential adverse drug effects.

Frye v. Stretch, June 26, 2002. Circuit Court of Jefferson County, Mississippi. In a malpractice case against a pediatrician concerning the prescription of Ritalin, I testified concerning the standards of care for evaluating children and prescribing stimulant medication, as well as the adverse effects of Ritalin, the label, and the Ritalin label including aspects related to the potential for addiction to cocaine.

Commonwealth of Pennsylvania v. Eric Gadsden, January 2004. Court of Common Pleas of Monroe County, Forty-Third Judicial District, No. 683 Criminal 2002. In the case of a man who shot and wounded his wife and a friend, I testified by video deposition concerning the role of Paxil and other SSRIs in causing violent and suicidal behavior. My testimony included discussions of the FDA drug approval process and interpreting the FDA spontaneous reporting system data.

Matley v. Minkoff, January 2004. Lowell, Massachusetts. A mentally retarded woman was treated with neuroleptics from age 18-22 and developed tardive dyskinesia. I testified concerning the treatment of mental retardation, neuroleptic drugs, and tardive dyskinesia, including the drug label.

State of Michigan v. Christopher Bernaiche. Circuit Court for Wayne County, Detroit, Michigan, Case No. 03-01733. February 2004. A few days after his dose of Prozac was doubled, a twenty-six year old man was beaten up in a bar and returned to shoot five people killing two. I testified on the effects of SSRIs on violence and suicide, as well as the FDA drug approval process, drug labels, and drug company misrepresentation.

Some of my more important legal cases involving labeling were settled before coming to trial. There have been several dozen over the years. Recently I was the expert in a case against the manufacturer involving allegations of false labeling concerning Paxil's capacity to cause withdrawal reactions. The case was "resolved" in association with label changes that gave greater emphasis to these withdrawal reactions. The Paxil withdrawal suit was brought in San Jose, California on August 19, 2000 as a "Complaint for Injunctive Relief under Business and Professions Code" (Nguyen & Farber, plaintiffs vs. SmithKline Beecham Corporation, Case No: CV791998).

On many occasions I have conducted discovery inside pharmaceutical firms specifically examining the labeling processes for their drugs, including Ritalin, Paxil, Prozac, Xanax and others. In these cases, I have been the primary scientific expert involved in this process.

Most notably perhaps in the mid-1990s I was selected by a consortium of lawyers to be the scientific expert examining and analyzing the total discovery materials for the combined Prozac suits (more than one hundred suits). In that capacity, I reviewed the FDA and drug company documents concerning the labeling process. I also interviewed other experts, including FDA officials, concerning labeling, and read everything available on the subject. The central issue of the cases, of course, was labeling.

More recently my publications and medical-legal consultations with the attorneys provided the basis for several Ritalin class actions suits that were based in part on alleged mislabeling of the drug. I participated only as a consultant in the initial formulation of the suits and not in their failed progress through the courts.

Especially in regard to psychiatric medication, my forensic experience with labeling issues may be as great or greater than anyone else in the psychiatric profession.

2. Publications Concerning Labeling

I have been writing about the labeling process for many years in scientific books and peer-reviewed articles.

In 1994 in my book Talking Back to Prozac I performed an in-depth analysis of the labeling process for Prozac based on interviews with FDA officials, Freedom of Information Inquiries to the FDA, the scientific literature, and my involvement in the discovery process in product liability suits. I further developed this analysis in my medical book, Brain-Disabling Principles in Psychiatry, in 1997.

Two of my books deal specifically and extensively with the labeling of Ritalin (The Ritalin Fact Book, 2002, and Talking Back to Ritalin Revised, 2001). The Ritalin Fact Book (chapter 12, pp. 112-120) traces the development of stimulant labels over the years based on my own research.

A number of my peer-reviewed journal publications also deal with the FDA approval process and labeling. One example that focuses exclusively on labeling is my peer-reviewed article "Fluvoxamine as a cause of stimulation, mania, and aggression with a critical analysis of the FDA-approved label" (Breggin, 2002; **Breggin Exhibit E**). Another that deals with the FDA approval process and labeling is my peer-reviewed article entitled "Analysis of Adverse Behavioral Effects of Benzodiazepines with a Discussion of Drawing Scientific Conclusions from the FDA's Spontaneous Reporting System (Breggin, 1998a).

3. Presentations to Professional Bodies Concerning Labeling

As my resume indicates (**Breggin Exhibit J**), I frequently give talks to professional bodies concerning adverse medication effects, including seminars at which physicians earn professional education credits (CME credits). I commonly address the issue of labeling in these presentations, since physicians and other professionals want to know why, for example, there are discrepancies between a drug's label and the known facts about the drug's effects. Often I have to explain the origin and organization of FDA-approved drug labels. I have also presented on the subject of labeling at national legal conferences (see part D below).

4. Special Training in the Arena of Labeling

I have presented at and/or attended a number of lengthy several-day-long training workshops on the drug approval process that dealt with labeling, often in great depth. The following seminars, including the three at which I made presentations, all dealt extensively with the labeling process:

(1) "Regulatory Training Course I: IND [Investigative New Drug] Phase." A course in how drug companies develop an IND for the FDA in accordance with FDA statutes, regulations, and guidelines. DIA (Drug Information Association). Bethesda, Maryland, February 26-28, 1996

(2) Regulatory Training Course II: Marketing Application & Post Approval Phase." A course in how drug companies develop an NDA [New Drug Application], as well as post-approval activities, in accordance with FDA statutes, regulations, and guidelines. DIA (Drug Information Association), Bethesda, Maryland, March 27-29, 1996

(3) "Clinical Therapeutics and the Recognition of Drug-Induced Disease: How Health Care Professionals and the FDA Can Work Together to Reduce the Risks of Adverse Drug Events." A workshop focused on the spontaneous reporting system presented by the Center for Drug Evaluation and Research (CDER) of the FDA, Georgetown University School of Medicine, Washington DC, June 10, 1994

(4) "The Application of GCP [Good Clinical Practices] for Study Site Coordinators and Business Administrators." Described as "a comprehensive, practical overview of the responsibilities of the investigator, the clinical study coordinator assisting the investigator, and the sponsor in the conduct of a clinical trial" for FDA approval of a drug. DIA (Drug Information Association), Philadelphia, December 11-13, 1995

(5) "Pharmaceutical Industry Crisis Management Workshop." Purpose described as "to develop the participants knowledge of the fundamental elements of crises and crisis management in the pharmaceutical industry." Initial day covered handling of a variety of issues, including New Drug Applications (NDAs), FDA regulations and industry relations, recalls, adverse drug event reporting, and clinical trial standards. DIA (Drug Information Association), Washington, DC, December 4, 2000.

(6) "Ritalin Litigation." Described as "The medical and legal roadmap to trying or defending your Ritalin suit successfully," including presentations on stimulant drug treatment, ADHD, and the role of the FDA and DEA in monitoring industry activities. I presented on "The science behind the lawsuits" (including labeling issues) and also attended. The American Conference Institute, New York City, March 29, 2001.

(7) "Emerging Drug Litigation Conference." One-half day on class action suits at which I presented on "The Science and Medicine of Ritalin" (including labeling issues) and also attended. Mealey's (Lexis/Nexis). New Orleans, May 17, 2001.

(8) "Adverse Effects of SSRI Medications: A Medical Legal Conference." Labeling was a key issue at this conference focused on product liability. I presented on "Adverse Psychiatric Effects of SSRI Antidepressants" (including labeling issues) and attended conference. Extant Medical Legal Consulting. Philadelphia, October 4-5, 2002.

IX. Conclusions

My responses to the Defendant Novartis are contained in the above affidavit. This affidavit should be viewed as a supplement and expansion of my original affidavit. In summary, none of the criticisms by Defendant Novartis have merit. In fact, the exhibits provided by the defendant's expert, Dr. Josephson, further confirm and supplement my original affidavit.

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XI. Exhibits

Exhibit A. Breggin, P. (1999). Psychostimulants in the treatment of children diagnosed with ADHD: Risks and mechanism of action." *International Journal of Risk and Safety in Medicine*, 12 (1), 3-35. [Reproduced on www.breggin.com]

Exhibit B. Breggin, P. (2000). The NIMH multimodal study of treatment for attention-deficit/hyperactivity disorder: A critical analysis. *International Journal of Risk and Safety in Medicine* 13:15-22. [Reproduced on www.breggin.com]

Exhibit C. Breggin, P. (2001). MTA study has flaws. (letter) (2001) *Archives of General Psychiatry*, 58, 1184.

Exhibit D. Breggin, P. (1998). Risks and mechanism of action of stimulants. NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder, November 16-18, 1998, Program and Abstracts, pp. 105-120. National Institutes of Health, Bethesda, Maryland.

Exhibit E. Breggin, P. (2002) Fluvoxamine as a cause of stimulation, mania, and aggression with a critical analysis of the FDA-approved label. *International Journal of Risk and Safety in Medicine*, 14: 71-86. [Reproduced on www.breggin.com]

Exhibit F. Borcharding, B.V., Keysor, C.S., Rapoport, J.L., Elia, J., & Amass, J. (1990). Motor/vocal tics and compulsive behaviors on stimulant drugs: Is there a common vulnerability. *Psychiatric Research*, 33, 83-94.

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Exhibit H. Lambert, N. and Hartsough, C. (1998). Prospective study of tobacco smoking and substance dependence among samples of ADHD and non-ADHD subjects. *Journal of Learning Disabilities* 31, 533-534.

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Exhibit J. Recent Summary Resume of Peter R. Breggin, M.D.