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STATE OF NORTH CAROLINA)
) ss.
New Hanover COUNTY)

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Anchorage, AK 99501

From: Grace E. Jackson, MD
1201 Clipper Lane
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Date: 31 March 2009

Re: Law Project for Psychiatric Rights
vs.
State of Alaska

Case No. 3AN 08-10115 CI

I. Introduction

Educational and Professional Background

I am a Board Certified psychiatrist residing in North Carolina where I specialize as a clinical psychiatrist, an independent researcher in the areas of neuropharmacology and neurotoxicology, and a writer and lecturer.

I hold a B.A. in political science, a B.S. in Biology, and a Master's degree in Public Administration. I received my medical degree from the University of Colorado School of Medicine in May of 1996. Following medical school, I was commissioned in the U.S. Navy with orders for post-graduate training in psychiatry: internship at San Diego Naval Medical Center (Balboa Hospital - graduating in 1997); residency in Washington, D.C. in the National Capital consortium (a tri-service training program performed at Walter Reed Army Hospital, Bethesda Naval Hospital, and Malcolm Grow Hospital at Andrews Air Force Base). Subsequent to the successful completion of my residency in June 2000, I was assigned as a staff psychiatrist to Bethesda Naval Hospital, where I supervised the work of trainees and provided care to active duty personnel, their dependents, and retirees. Since transitioning out of the military in spring 2002, I have pursued work as a private consultant, and have worked as a clinician within the North Carolina Department of Corrections and the Veterans Administration health care system.

II. Testimony as an Expert in Psychopharmacology

In spring of 2003, I participated as an expert witness in the case of *Myers vs. Alaska Psychiatric Institute* (API). The case was important because of its consideration of my testimony about the efficacy and safety of antipsychotic drugs. Special emphasis was placed upon the Food and Drug Administration's analysis and approval of olanzapine (Zyprexa) as a primary example of the newer therapies. Interestingly, on March 1, 2004, the FDA announced its requirement for warnings about health risks associated with olanzapine and similar chemicals. This FDA alert was consistent with many of the concerns which I had expressed in my affidavit. In considering my testimony in the Myers case, the Alaska Superior Court, and the former Director of Schizophrenia Research at NIMH (National Institute of Mental Health) qualified me as an expert in the area of psychopharmacology.

Subsequent forensic experience and independent research have been preparatory for numerous lectures (both within the United States, and abroad), testimony before the FDA, peer reviewed journal articles, book chapters, and two books explaining the mechanisms through which psychiatric medications often prevent or delay recovery.

My first book (*Rethinking Psychiatric Drugs: A Guide for Informed Consent*) has been adopted by several professors as a required text for students in sociology, psychology, psychotherapy, and social work. Upcoming publications in 2009 include an invited book chapter ("The Case Against Stimulants") in an international compilation entitled *Rethinking ADHD*, and my second solo work (entitled *Drug-Induced Dementia: A Perfect Crime*).

III. Purpose of This Report

This report is written is to provide background information regarding the use of psychotherapy and psychiatric drugs in children and teens. Specifically, this affidavit is intended to provide a brief analysis of a publication which has been used by some legal authorities (e.g., the Bazelon Center for Mental Health Law) and policy makers in preparing recommendations for legislative, educational, and health policy reforms.

IV. Analysis of Key Article

John R. Weisz and Peter S. Jensen, "Efficacy and Effectiveness of Child and Adolescent Psychotherapy and Pharmacotherapy," Mental Health Services Research 1:3 (1999): 125-157.

Funded by three distinct grants and awards from the National Institute of Mental Health (Research Scientist Award K05 MH011561; Research Grants R01 MH49522 and R01 MH57347), Weisz and Jensen undertook a comprehensive review of the benefits of psychotherapy and pharmacotherapy in the treatment of children and adolescents, as demonstrated by the (then) current medical literature. Regrettably, this paper has been repeatedly referenced by policy makers and legal professionals without consideration of the authors' distortions of cited research. This analysis will attempt to clarify and rectify five key distortions of the aforementioned work.

Distortion #1: Scientific forces have ushered in a new era which calls for the rigorous testing of research-based principles and practices for mental health care.

In the introduction to their paper, Weisz and Jensen expressed regret that mental health care had long been guided primarily by "appealing theories" rather than science. They implied that new, scientific forces now called for the performance of evidence based research in order to legitimize treatments.

Fact: There has never been a *scientifically* motivated call for "evidence based" practices or "outcomes" research in mental health care. Rather, the true forces which have given rise to evidence based medicine (EBM) have been political and economic. While a full discussion of the pertinent societal developments lies beyond the purpose of this analysis, suffice it to say that EBM was born in the early 1990s out of the marriage between the pharmaceutical and insurance industries, the federal government, the news media, and the medical profession.

The main consequence of EBM has been the replacement of a rational system of health care with a system based on corporate fraud and illusion. Whereas before, doctors were permitted and encouraged to base treatments upon an understanding of basic science (physiology, pathology, pharmacology); non-corporately dominated journal articles and medical education; direct observation in their own treatment settings; and a health care philosophy which prioritized the eradication or mitigation of root causes of disease, EBM has done exactly the opposite. By privileging the findings of RCTs (randomized controlled clinical trials), EBM has resulted in a system of health care which focuses primarily upon brief symptom suppression, rather than functional improvement or recovery. Furthermore, by emphasizing highly manipulated statistical results from poorly designed trials; and by focusing upon RCT outcomes in highly selected populations, EBM has given rise to standards of care which have little relevance for the long-term treatment experiences of older, sicker, and chronically or multiply medicated patients in the real world.

Distortion #2: The most relevant body of evidence in the treatment of children and adolescences pertains to treatment efficacy and effectiveness.

In performing a review of the medical literature, Weisz and Jensen emphasized outcomes in terms of efficacy and effectiveness. This approach resulted in conclusions that were essentially not applicable for two reasons: 1) the researchers failed to discuss or consider treatment *utility*; 2) the researchers employed inadequate definitions of treatment benefit.

<u>failure to consider treatment utility</u>
The review by Weisz and Jensen focused solely upon treatment efficacy and effectiveness. However, in the real world, clinicians and patients must formulate their decisions about proposed interventions with respect to treatment *utility (utility = risks vs. benefits).* Considerations of potential efficacy and effectiveness (benefits) must be balanced by considerations of potential toxicity. This is particularly important in the case of neuroactive drug therapy, because of the fact that every single class of medication used by psychiatrists has been shown to damage the growth and/or survival of brain cells.

<u>failure to employ adequate definitions of efficacy versus effectiveness</u>
Weisz and Jensen employed limited definitions of treatment efficacy and effectiveness based primarily upon the location of service delivery. Specifically, they referred to efficacy as "evidence that a treatment has beneficial effects when delivered under carefully controlled conditions designed for experimentation." In contrast, they referred to effectiveness as evidence that a treatment has beneficial effects when delivered to heterogeneous samples of clinically referred individuals treated in clinical settings by clinicians rather than research therapists. However, these conceptualizations both fell short of the contemporary usage of the respective terms.

Today, efficacy and effectiveness studies incorporate temporal and teleological distinctions. The former feature refers to the capacity of a treatment to suppress symptoms over a period of six to eight weeks; the latter feature refers to a treatment's ability to enhance functionality or recovery over the long term.

Distortion #3: Although research has repeatedly shown that psychotherapy is highly efficacious, there is no convincing evidence which suggests that psychotherapy is effective.

Based upon a review of four meta-analyses of psychotherapy in children and teens, Weisz and Jensen correctly opined that the evidence from more than 300 component studies had confirmed highly beneficial effects of these treatments [Effect Sizes of 0.71 to 0.84, where 0.80 = large effect]. Furthermore, they highlighted three important attributes of "talk therapy":

1) the production of durable effects which persist long after the end of the intervention

2) the promotion of language proficiency in children, and

3) the induction of specific, as well as general, therapeutic effects.

Remarkably, Weisz and Jensen then proceeded to denigrate the overall value of psychotherapy on the grounds that research had proven it to be ineffective. In making this claim, they grossly mischaracterized two investigations – both of which had affirmed the long-term benefits of psychotherapy in children who received treatment in typical (rather than experimental) treatment settings.

The Ft. Bragg Study

The Ft. Bragg Demonstration Project was a 94 million dollar project which compared the benefits of a comprehensive range of mental health services (initially called Continuum of Care) to regular community services (outpatient therapy or residential care). The investigation began with a 10-month start-up period and subsequently ran from June 1990 through September 1995.

Participants consisted of children and teenagers between the ages of 5 and 17, from more almost 1000 middle- and low-income military families. Ten long-term outcomes were assessed by employing a variety of standardized rating instruments (e.g., Child Behavior Checklist, Youth Self-Report, Vanderbilt Functioning Index, Caregiver Strain Index). These ratings were obtained at intervals of 6, 12, 18, 36, 48, and 60 months.

Although details of the therapy interventions have never been clearly described in numerous reports of the Ft. Bragg study (e.g., there has been no discussion of the types of psychotherapy performed, and no discussion of the types, doses, or durations of drug therapies employed), subjects in the experimental group received more outpatient sessions and a longer course of treatment.

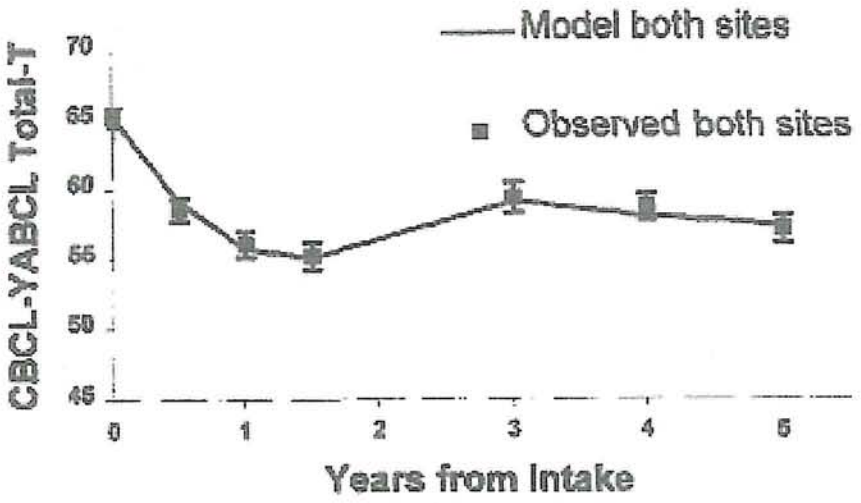
Ft. Bragg Demonstration Project – Key Features

	experimental group * Continuum of Care	control group ** Treatment as Usual
# of subjects	574	410
average age	11	11.4
exposed to medication	59%	60%
# of outpatient sessions in 1 year	27	10

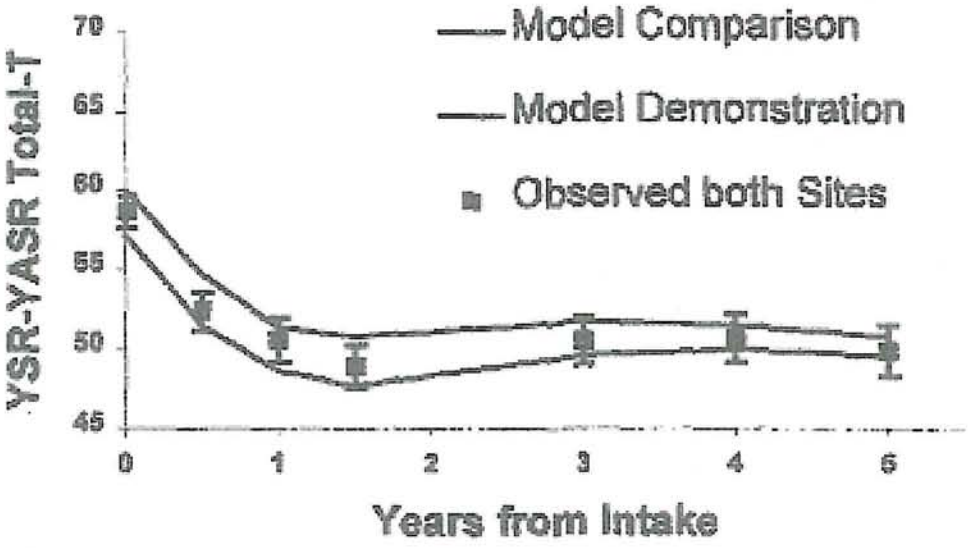
*Continuum of Care = services included comprehensive baseline assessments, case management, outpatient therapy, 24/7 crisis help, inpatient hospitalization, in-home counseling, therapeutic foster homes, group homes, and/or residential care [These families were recruited from Ft. Bragg in Fayetteville, NC]

** Control Group = outpatient therapy, residential care in psychiatric hospitals or residential treatment centers
[These families were recruited from Ft. Stewart and Ft. Campbell in GA and KY]

A critical and careful inspection of the Ft. Bragg literature reveals that all of the children improved significantly over the period of five years. Moreover, ***on three of the ten outcome measures (CBCL/YABCL, YSR, and VFI) intensive psychotherapy services resulted in superior outcomes***. For example, on the Child Behavior Checklist, the Continuum of Care (COC) resulted in an 8.6 point improvement per year (versus 8.2 points per year for controls). On the Vanderbilt Functioning Index, COC subjects fared slightly better than controls (4.11 points better than controls between years 3 and 5). COC subjects also displayed slightly superior results on the Youth Self-Report and Young Adult Self-Report in the first two years of treatment.



The parent-rated Child Behavior Checklist / Young Adult Behavior Checklist was a primary measure of general pathology. Children and teens in the COC and control groups experienced improvements which were largely indistinguishable. This graph demonstrates the general effectiveness of psychotherapy for all subjects.



Similar improvements were observed with respect to patient-rated changes over time. This graph demonstrates the longitudinal changes in psychopathology according to the Youth Self-Report and Young Adult Self-Report. For patients in the COC, the benefits of psychotherapy were particularly notable during the early phase of treatment (years 0 to 2, as demonstrated by the slope of the curve).

The Stark County Study

The Stark County (Ohio) investigation was conducted between September 1993 and June 1995. Similar in design to the Ft. Bragg Demonstration Project, this two-year psychotherapy study compared the effectiveness of a variety of integrated services (now designated as System of Care) relative to "usual care." Subjects consisted of 350 children and teenagers under the age of 20. All of these participants displayed serious emotional disturbances for which placement outside of the family home was either in progress or potentially planned. Outcomes were assessed using multiple paper-and-pencil checklists and interviews, with follow-up performed at intervals of 6, 12, 18, and 24 months.

Stark County Psychotherapy Project – Key Features

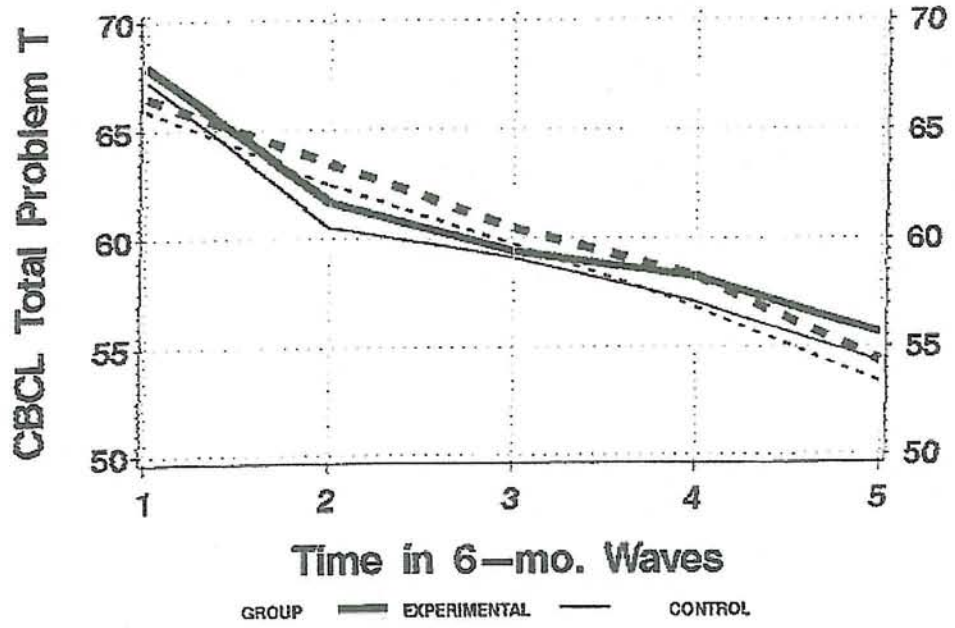
	experimental group * System of Care	control group ** Treatment as Usual
# of subjects	171	179
average age	11.1	11.1
exposed to medication	percentages not disclosed (authors reported equal usage relative to controls)	details not disclosed
using services in first 30 days	80%	37%
using services in first 6 months	93%	66%
attrition	39%	45%

*System of Care = services included comprehensive intake assessments, home based treatment, case management, outpatient therapy, prescription drugs, special classes and other school-based services, and residential treatments in the community

** Control Group = outpatient therapy, residential treatment center services, prescription drugs, special classes and other school-based services

The Stark County Study was limited by high levels of attrition: 39% drop-out rate in the System of Care group, and 45% drop-out rate in the comparison (community) controls. Nevertheless, subjects in both treatment groups improved on almost all of the measured outcomes, as demonstrated by clinically significant improvements in symptoms and higher functioning over time.

Figure 1
Observed and Model-Based CBCL[a] Scores



This graph depicts longitudinal changes in the Child Behavior Checklist, a parent-rated assessment of psychopathology. Children in the experimental and control groups benefited equally from mental health care over the course of five years (as reflected by an approximate 11-point improvement in CBCL scores).

Interestingly, eleven families assigned to the control group eventually crossed over to the System of Care during the run of the study. When the outcomes analysis was repeated by assigning the results of these children to the appropriate subgroup (SOC), the System of Care emerged superior on patient-rated assessments of externalizing, problem behaviors (Youth Self-Report).

Distortion #4: Certain Drug Therapies have been highly efficacious for children and teens.

Although Weisz and Jensen offered meticulous results in their consideration of psychotherapy efficacy (as reflected by the *effect size* calculations reported in the aforementioned meta-analyses), they were either unable to locate or unwilling to report effect sizes for the efficacy of drug therapy. As a substitute, they resorted to a secondary method which emphasized the identification of statistically significant differences between the effects of active therapy (experimental drug) and placebo.

To their credit, Weisz and Jensen humbly acknowledged the striking lack of evidence for the efficacy of most psychiatric drugs in children and teens. However, in the case of one particular antidepressant (fluoxetine, aka Prozac), they seriously mischaracterized the cited research (Emslie et al, 1997).

Emslie Prozac Study #1 (Emslie et al, 1997 - UTSW Medical Center, Dallas)
This 8-week efficacy study enrolled children between the ages of 7 and 17 and ran from April 1, 1991 through January 31, 1995. The goal was to compare fluoxetine versus placebo in children with moderate to severe depression, whose symptoms were not serious enough to require immediate or inpatient (hospital) treatment.

The protocol began with the screening of 256 children via multiple structured interviews conducted over a two-week period (baseline observations). Of the initial sample, 150 children were removed from the study for various reasons. For example, 10% were dropped due to severe symptoms. Interesitngly, *15% (n = 23) were dropped because their depression improved too much during the first three visits.* The remaining 106 children were enrolled in a 1-week placebo "run in" phase of the trial.

[During placebo run in phases of drug trials, all subjects receive capsules which contain an inert ingredient. The goal of placebo run ins, when used, is to permit the elimination of previous active medications, while simultaneously permitting the analysis of each subject's response to non-specific healing effects.]

During the placebo run-in phase, another 7 children were dropped when their symptoms improved too much (scores on the CDRS-R dropped below 40 – see below).

Following this entire three-week interval (preliminary assessment + placebo run in), 48 children were randomly assigned to the active treatment group (fluoxetine 20 mg per day) and 48 children were randomly assigned to the placebo control group.

Outcomes were subsequently evaluated by clinicians on a weekly basis using four different rating scales (CDRS-R, BPRS-C, CGI, CGAS). Patients performed assessments (CDI or BDI, WSAS) before and after the 8-week period of treatment.

Emslie 1997 – Childhood Prozac Study #1

	fluoxetine	placebo
# of subjects	48	48
mean age	12.2	12.5
with melancholy	15%	25%
anxiety	67%	46%
ADHD	33%	27%
oppositional defiant/ conduct disorder	27%	33%
attrition over 8 weeks	30%	50%

Clinician-Rated Instruments

Main Outcomes	
Clinical Global Impressions (CGI)	score of 1 = much improved score of 2 = very much improved
Child Depression Rating Scale, Revised (CDRS-Revised)	response = CDRS-R of 40 or less remission = CDRS-R of 28 or less
Minor Outcomes	
Children's Global Assessment Scale (CGAS)	a rating scale for overall functioning ranging from 1 to 100 (100 = superior)
Brief Psychiatric Rating Scale for Children (BPRS-C)	a 21-item rating scale for general psychopathology (high score = severe)

Patient-Rated Instruments

Children's Depression Inventory (CDI) for all patients 12 years of age or younger	27-item inventory for evaluating key symptoms of depression
Beck Depression Inventory (BDI) for all patients 13 years of age or older	21-item inventory for evaluating depression
Weinberg Screening Affective Scale (WSAS)	a 56-item questionnaire about mood and behavior

The study was marred by high rates of attrition in both patient groups (30% of fluoxetine patients dropping out; ~ 50% of placebo patients dropping out). This necessitated the analysis of clinician-rated instruments using a technique known as Last Observation Carried Forward (LOCF). In other words, whenever updated weekly evaluations were no longer possible, the most recent scores were simply carried forward from one week to the next. Although the Emslie study has been interpreted as an investigation which demonstrated the efficacy of antidepressant drug therapy, a close inspection of the full protocol and outcomes provides evidence to the contrary. ***On two measures of global functioning (BPRS-C, CGAS), and on all three patient-rated instruments (CDI, BDI, and Weinberg SAS), fluoxetine and placebo were essentially indistinguishable***:

	fluoxetine		placebo	
clinician-rated	start	end	start	end
BPRS-C	47.3	38.9	46.2	41.0
CGAS	47.9	63.9	48.4	60.2
child- rated				
BDI / CDI	15.8	9.9	15.3	11.2
Weinberg SAS	20.6	13.1	20.6	16.7

On the two main outcome instruments, both of which were evaluated by clinicians (CGI and CDRS-R), the Emslie team reported superior benefits for drug therapy:

Emslie Prozac Study #1 – Main Outcomes

	fluoxetine n = 48	placebo n = 48	statistical significance
attrition	29.2%	54%	not disclosed
CGI response			
Last Observation Carried Forward	**56% (2748)**	**33% (16/48)**	**p = 0.02**
Among Treatment Completers	74% (25/34)	58% (15/26)	p = 0.20
CDRS-R remission (LOCF) (# of patients with CDRS < 28)	**31% (15/48)**	**23% (n=11)**	**not disclosed**
CDRS-R final score (LOCF)	42 to 90	42 to 82	not disclosed

However, an accurate interpretation of the Emslie data arguably demands consideration of the children who improved "too much" during placebo run in (n = 7). It is important to appreciate the fact that all 7 of these subjects had originally satisfied the screening criteria for moderate or severe depression. Yet, under the influence of non-specific therapeutic effects (repeated interviews, healing intentions, attention, and possible withdrawal from previous drug therapies), their symptoms dissipated to such a degree that they became ineligible for random assignment within the 8-week trial.

If one assumes that these individuals achieved the status of full remission (data which the published report did not reveal), the Emslie study failed to demonstrate superior benefits for fluoxetine on both of the main outcome instruments. Furthermore, it is quite likely that the differences in CGI response would have been rendered statistically insignificant.

Finally, it is important to appreciate the fact that statistically significant efficacy was demonstrated only by using the technique of Last Observation Carried Forward. Among those subjects who completed 8 weeks of assigned treatment, there was no statistically significant difference between the two groups ($p = 0.20$).

Emslie Prozac Study #1 - Main Outcomes (All Placebo Responders Included)

	fluoxetine n = 48	placebo n = 48 + 7
CGI responders includes 30 more drug-free subjects	**56% (n=27)**	**42% (n=16+7)**
*CDRS-R remission (# of patients with CDRS < 28)	**31% (n=15)**	**33% (n=11+7)**

*Subjects were eliminated from the study during the first three weeks of the study (interviews + placebo run-in) if they obtained CDRS-R scores of 40 or less. The published report by Emslie et al. does not divulge how many of these individuals obtained a CDRS-R score < 28, consistent with the researchers' definition of remission. However, it is theoretically possible that all 7 of the placebo run-in responders attained this level of improvement.

Distortion #5: There is no evidence to suggest that drug therapies are ineffective for children and teens.

In their 1999 publication, Weisz and Jensen claimed that there was no research evidence which had invalidated the effectiveness of childhood pharmacotherapy. However, this contention had presumably been contradicted by the 2- and 3-year outcomes of the federal government's largest investigation on the treatment of Attention Deficit / Hyperactivity Disorder or ADHD (the so-called MTA Study), of which Peter Jensen had been a leading researcher and co-author. As revealed by subsequent publications (2004, 2007, 2009), Jensen and his colleagues eventually conceded the ineffectiveness *and* harmfulness of medication, based upon their discoveries that treatment with stimulant drugs resulted in the long-term worsening of impulsivity, a 4- to 5-fold higher rate of depression and anxiety, and a two-fold higher rate of substance misuse between the ages of 11 and 13 (***see Appendix***).

In Sum:

1) **the Weisz and Jensen publication has been repeatedly misused**

Weisz and Jensen's 1999 publication has been repeatedly cited by policy makers and legal authorities as a document which demonstrated the superior benefits of specific drug therapies for children and teens. It has also been cited as a document which confirmed the relative *ineffectiveness* of psychotherapy. However, these interpretations have been inaccurate because they have failed to consider five major distortions in the paper.

2) **contestable deference to Evidence Based Medicine**

Contrary to the opinions of Weisz and Jensen, Evidence-Based Medicine (EBM) within psychiatry has never been driven by considerations of science. Rather, due to the political and economic pressures exerted by the pharmaceutical industry, EBM emerged in the 1990s as a substitute for America's traditional model of healing. That model had long emphasized the role of basic science, clinical intuition, direct observation, and abductive reasoning in treating patients. Under the influence of EBM, the U.S. system of health care has enshrined the randomized, placebo controlled trial as the arbiter of medical propriety. This has deflected the attention and efforts of medical providers away from the goal of disease eradication by creating sham "standards of care" which focus primarily upon the short-term modification of symptoms, rather than long-term measures of recovery and functionality.

RCTs also very susceptible to manipulation by Drug Cos

3) **misuse of the terms "efficacy" and "effectiveness"**

The conclusions of Weisz and Jensen with respect to treatment benefits were limited by a failure to consider treatment utility. Without addressing the potential *benefits and risks* of potential therapies, their discussions of the research evidence were arguably irrelevant because they were incomplete. Furthermore, although Weisz and Jensen employed a qualitative distinction between efficacy (benefits observed in academic research settings) and effectiveness (benefits observed in typical clinical settings), these definitions did not go far enough.

Contemporary use of these two terms distinguishes "efficacy" and "effectiveness" on the basis of *temporality* (short-term vs. long-term outcomes) and teleology or primary goal (symptom modification vs. restoration of function). Ultimately, what physicians and patients need to know is the utility of competing interventions with respect to long-term recovery and safety in the real world.

4) unsubstantiated denigration of psychotherapy effectiveness

Weisz and Jensen mischaracterized two long-term studies of psychotherapy and used these interpretations to defend their view that psychotherapy was ineffective outside of experimental or research settings. In fact, a careful inspection of the protocols and outcomes from the Ft. Bragg and Stark County studies reveals that ***all of the patients enrolled in these experiments experienced clinically significant improvements over a 2- to 5-year period***. Moreover, on several rating scales of psychopathology, intensive psychotherapy strategies (Continuum of Care, System of Care) produced superior benefits.

5) dubious validation of pharmacotherapy efficacy

Weisz and Jensen correctly identified numerous limitations (failed efficacy) associated with various classes of drug therapies when used in children and teens. However, in defending the use of fluoxetine (Prozac) as a treatment for childhood depression, they failed to discuss the methodological and interpretive flaws of the earliest study published by Emslie et al (1997).

I Wonder what the effect would have been.

Contrary to the implications of Weisz and Jensen, and contrary to the narrative report of the University of Texas researchers, the Emslie study confirmed ***equivalent efficacy for placebo and drug therapy on all three patient-rated assessments, and on ½ of the clinician-rated instruments***. Furthermore, had Emslie's team integrated data from the seven individuals who improved "too much" during the placebo run-in, it is highly likely that the medication and placebo differences would have become statistically as well as clinically insignificant on the remaining instruments (CGI, CDRS-R). In other words, ***the 1997 Emslie Prozac trial was a highly problematic study which presented dubious evidence of antidepressant drug efficacy.***

6) mischaracterization of drug therapy ineffectiveness

In their 1999 publication, Weisz and Jensen asserted that there was no research evidence to suggest that drug therapies were ineffective in children and teens. In fact, by 1999, Jensen had already been a leading member of the multi-site research team commissioned by the federal government to determine the effectiveness of treatments for ADHD. Given the fact that the MTA Study was initiated in 1991, Jensen more than likely possessed inside knowledge of the 2- and 3-year MTA outcomes by the time he collaborated with Weisz. Even if he did not, however, the subsequent publications of the MTA research team have clearly demonstrated that the use of stimulant drugs by children results in poorer long-term outcomes, including greater substance misuse; higher levels of depression and anxiety; and, in a subset of children, a steady worsening of ADHD symptoms.

Appendix

The MTA Study

Coordinated by the National Institute of Mental Health and initiated in 1991, the MTA was a multi-site study which randomly assigned 579 ADHD children to four different groups for 14 months of treatment. Participants were recruited from six different research facilities throughout the United States. At the time of enrollment, the patients ranged in age from 7 to 10 years (mean age: 8.5). Initial results were not published until 1999. However, in an effort to provide prognostic data about this cohort, the MTA researchers published the first of several long-term, follow-up assessments of this cohort in 2004, 2007, and 2009.

MTA Study Methodology

Patients in the MTA study were randomly assigned to one of four treatment conditions. For a variety of reasons (perceived lack of efficacy, side effects, familial decisions), many patients changed treatment during the course of the study. Subsequently, this change in treatment status has necessitated careful analyses of all outcome data using both "intention to treat" (assigned treatment) and "naturalistic" (actual treatment) subgroups.

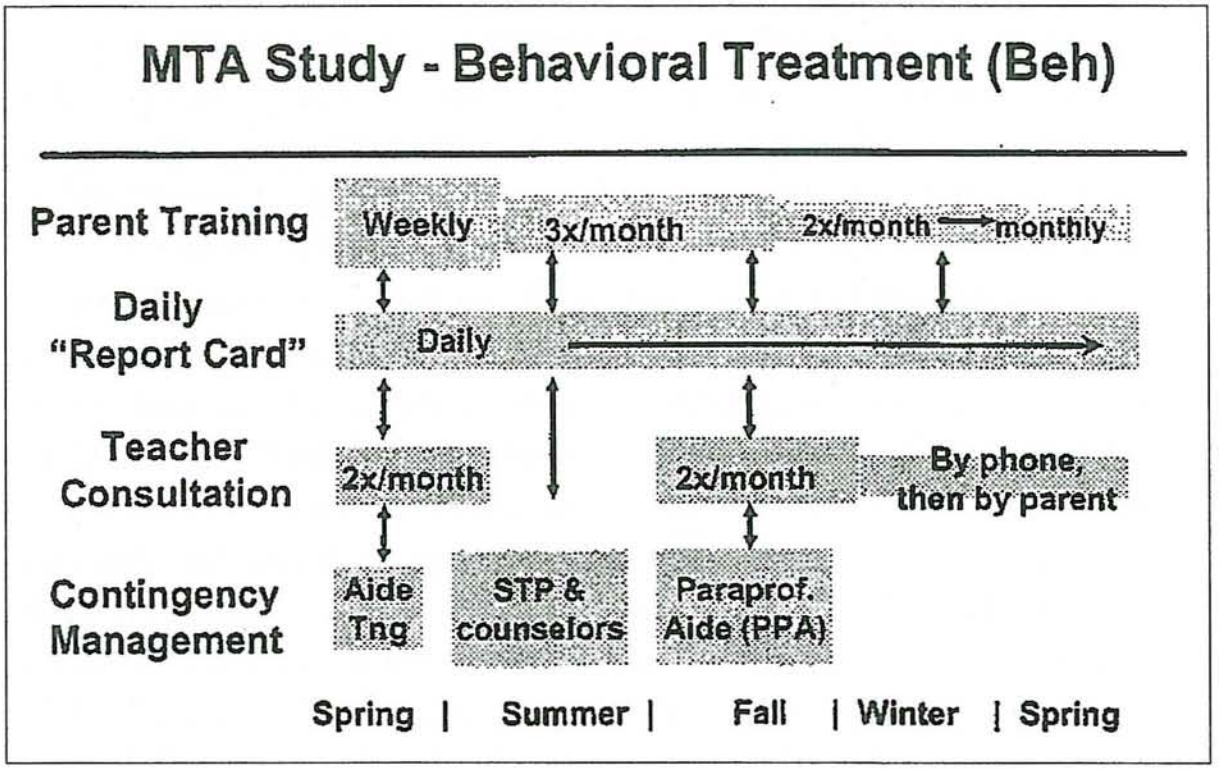
Group 1: medication management only

Stimulant medication was initiated and increased over a period of 28 days, then adjusted monthly to find the best dose. Patients were continued on medication indefinitely, receiving an average daily dose of 30.5 mg/day of Ritalin. This dose was divided into three portions (morning, noon, late afternoon).

Group 2: behavioral therapy

The behavioral therapy arm of the study consisted of parent training, child training, and teacher training. Parents received a maximum of twenty-seven group and eight individual sessions. The child-focused therapy was delivered in the form of an eight-week summer camp (Summer Treatment Program = STP). The STP included daily intensive behavioral interventions, academics, social skills, and recreation. During the school year, teachers received ten to sixteen biweekly consultations. In addition, a trained aide was placed in the classroom for twelve weeks of on-site assistance (coaching) with each ADHD child.

A key aspect of the behavioral therapy intervention was its emphasis upon training. As time progressed, the direct involvement of mental health professionals was gradually tapered and withdrawn. The chart below demonstrates the sequence of these changes:



Group 3: medication combined with behavioral therapy

Individuals assigned to this treatment group received the same medication and behavioral elements described above. Behavioral therapy was gradually reduced over the course of six to nine months, while medication was continued indefinitely.

Group 4: community comparison

The community comparison arm of the study assigned children to treatment as usual in the community. This consisted of stimulant medication (generally at lower doses and twice a day instead of three times a day) in approximately two-thirds of the group. The remaining patients did not receive medication. Details of non-pharmacological interventions for these children were either unavailable or not reported.

MTA Design Flaws & Limitations

Arguably the most important American study of ADHD children to date, the MTA featured significant methodological deficiencies which limit the applicability of its findings and the validity of its conclusions. Among the chief confounds were the following features:

1) study was not blinded

Teachers, parents, evaluators, and patients all knew whether or not a child was receiving an active drug treatment. This may have led to exaggerated ratings of behavior, based upon the expectancies of adults and children alike.

2) more than 1/3 of the children had received previous treatment with stimulants

This would have led to functional and/or anatomic brain changes in the drug-exposed. When some of these same subjects were randomly assigned to the unmedicated, behavioral therapy subgroup, they were vulnerable to initially poorer outcomes for psychological and physiological reasons.

3) treatments were not delivered with the same intensity over the 14 months

By the 14-month endpoint of the study, the teacher and child portions of the behavioral therapy intervention had been over for six to nine months. Formal parent contacts had ended within four weeks of assessment. This essentially converted the MTA study into a comparison between *actively* treated children (those remaining on drugs) and *previously* treated children (those whose intensive therapies had ended months before).

4) compliance within each intended treatment group was limited

During the initial 14-month phase of the study, non-compliance was considerable:

medication management:	22% did not comply
behavioral therapy:	37% did not comply
combined treatment:	19% added medication 36% stopped behavioral therapy

5) psychotherapy was limited to behavioral therapy (operant conditioning)

To the extent that ADHD children experienced cognitive deficits in skill sets, and not just deficits in performance, the emphasis upon "contingency" therapy may have been inadequate to meet the needs of many children. Similarly, the apparent failure to consider psychodynamic, existential, and familial concerns may have eroded the quality of the non-drug intervention even further.

MTA Outcomes

14-Month Outcomes

Subjects in all four treatment groups demonstrated significant improvements in core ADHD symptoms. However, as the effectiveness of the non-drug interventions have been repeatedly mischaracterized by the media and by medical professionals since 1999, several points deserve emphasis here.

First, subjects in the MTA study were compared on nineteen possible outcome variables. Medication -- either alone or combined with behavioral therapy -- was associated with superior outcomes only on a minority of these variables (3 variables for medication, 5 variables for combined treatment).

Second, over 75% of the behavioral therapy subjects were successfully maintained throughout the entire study *without the use of medication.*

Third, for the 34% of subjects who displayed anxiety symptoms along with ADHD, behavioral therapy was equally effective as medication and combined therapy.

Fourth, for the families who received disability payments, the use of medication alone was associated with a significant worsening of parent-child relations.

Fifth, when outcomes were analyzed according to actual medication use (naturalistic vs. assigned treatment), there was little difference between the initially medicated subjects who continued or stopped drug therapy. However, ***among the patients who began the study without medication, symptom reduction was greater for those remained drug free:***

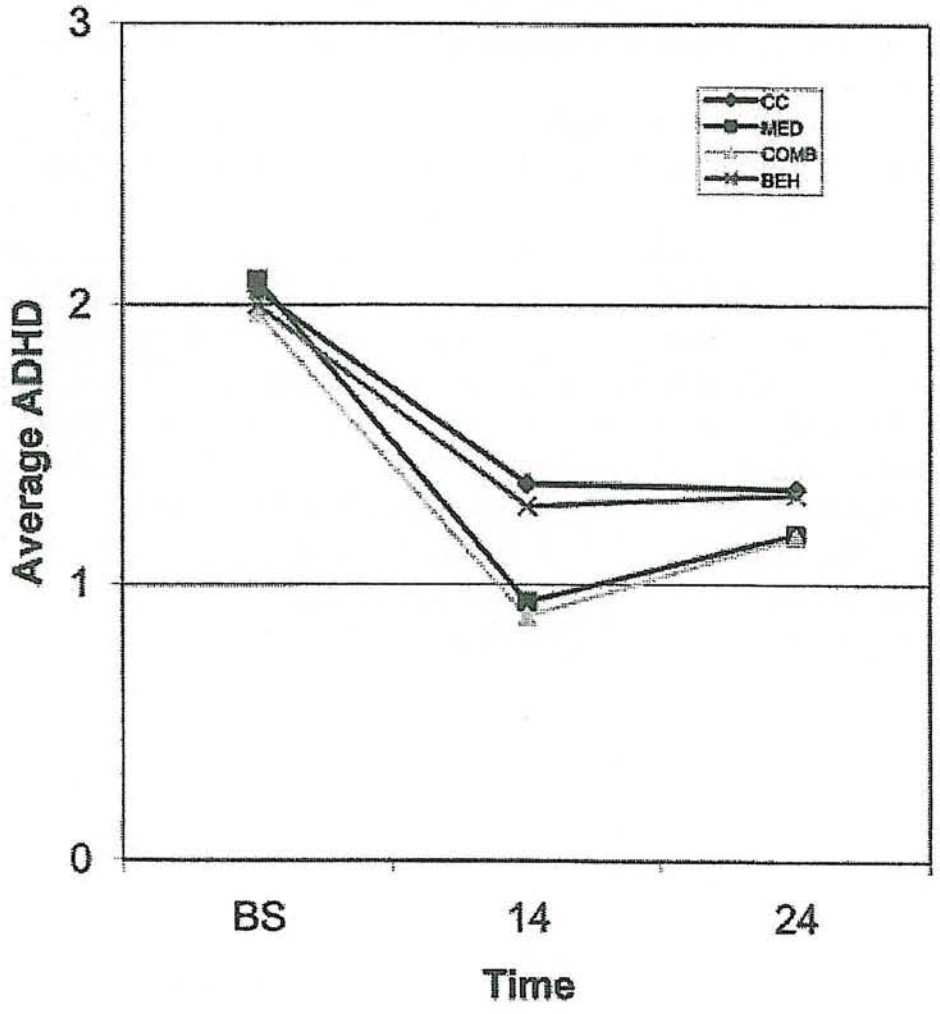
	change in SNAP ratings scores between 0 and 14 months
consistently medicated	- 1.10
medicated >> changing to drug free	- 1.00
consistently drug free	- 0.68
unmedicated >> change to medication	- 0.50

[Note: A negative change in SNAP score signifies symptomatic improvement]

24-Month Outcomes

As the MTA study was designed to follow a cohort of individuals prospectively over time, further assessments were planned and achieved. At 24 months, 540 of 579 original subjects were re-examined on ***five domains of functioning***: ADHD symptoms rated by parent and teacher, ODD (Oppositional Defiant Disorder) symptoms rated by parent and teacher, social skills rated by parent and teacher, Wechsler Individual Achievement Test reading score, and a "negative parental discipline" score. ***Children who received stimulant medication worsened on the first three of these conditions***.

The ITT (intention to treat) analysis showed a reversal of recovery trajectories by year two:



However, these results were partly confounded by changes in treatment:

	% on meds at 14 months	*% on meds at 24 months*
medication management	*93*	*69*
combined therapy	*87*	*68*
behavioral therapy	*23*	*38*
community care	*55*	*61*

When investigators reevaluated the two-year outcomes according to the actual pattern of medication use, **patients who began the period on stimulants experienced the greatest deterioration in ADHD symptoms, whether or not drug therapy was continued:**

	Change in SNAP Scores 14 to 24 Months
stimulants, changing to no medicine	+ 0.33
continuous stimulants	+ 0.15
unmedicated, continuing without stimulants	+ 0.10
unmedicated, changing to stimulants	- 0.15

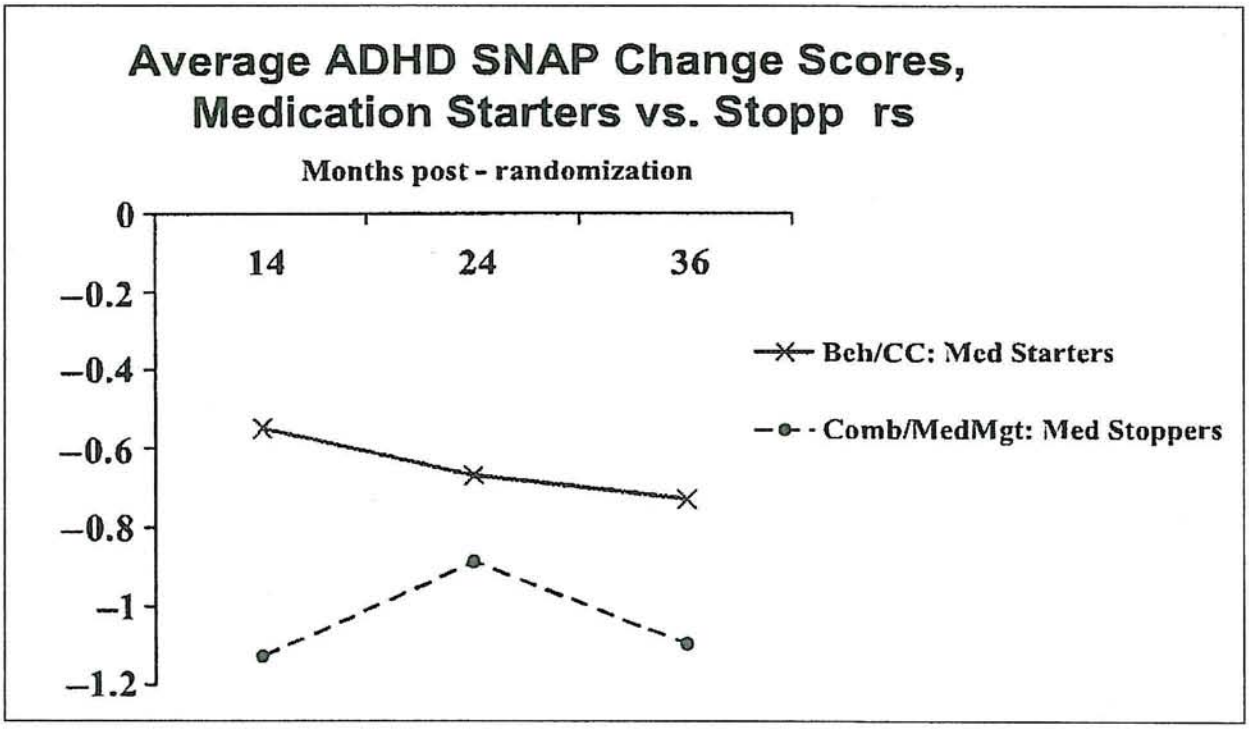
[Note: A negative change in SNAP scores signifies improvement in symptoms.]

36-Month Outcomes

As before, the MTA treatment groups differed in their exposures to medication during the 24- to 36-month time interval:

Initial Treatment Group	% Using Stimulants 24 to 36 months
medication management	72%
combined therapy	71%
community treatment	62%
behavioral therapy	45%

The assigned treatment (intention to treat) analysis revealed that ***medication use between 24 and 36 months was a significant predictor of symptomatic worsening***, rather than improvement. A naturalistic analysis of the same database replicated this finding. Relative to medication initiators (average SNAP change of 0.05), medication stoppers (average SNAP change of 0.21) showed a greater improvement in ADHD symptomatology:



In other words, starting medication between years 2 and 3 produced very little change in symptoms. However, ***stopping medication between years 2 and 3 produced a four-fold greater improvement in ADHD*** (0.21 ÷ 0.05 = 4.2).

A secondary analysis of the 3-year dataset demonstrated that efficacy findings were *not* the result of a self-selection bias. Using a sophisticated technique to evaluate outcomes according to propensities for pharmaceutical therapy, researchers rejected the hypothesis that medication was continued or initiated only in those patients with the worst prognosis. In other words, the severity of baseline symptoms failed to predict the negative association between stimulant drug therapy and "recovery" from ADHD.

Delinquency and Substance Misuse

Only recently (August 2007) has the MTA research group disclosed data from a separate analysis of treatment effects upon delinquency and the emerging use of addictive substances. Based upon a series of parent- and child-rated evaluations, investigators compared the prevalence and severity of delinquent behaviors at 24- and 36-months in the 579 members of the ADHD cohort, relative to 289 slightly younger "normal" controls. In addition, the child participants (ADHD and controls) were interviewed confidentially about the lifetime ("ever") or current use (i.e., within the past six months) of various legal and illegal chemicals. Findings were remarkable for the following:

1) Relative to controls, the MTA subjects demonstrated a significantly higher prevalence of moderate to serious delinquency:

	Moderate to Serious Delinquency	
	24 months	36 months
MTA	20%	27%
controls	7%	7%

2) ***The use of stimulant medication was positively associated with delinquency at 24 and 36 months.*** This relationship was statistically significant at both time points ($p = 0.005$ and $p = 0.034$, respectively). *Children with higher ratings of delinquency at 24 and 36 months were more likely to have been medicated within the past year*

3) Subjects assigned to the behavioral therapy treatment group experienced lower rates of substance misuse between the ages of 11 and 13:

Initial Treatment	Substance Misuse at 36 Months
behavioral therapy	13%
combined therapy	16%
community care	19%
medication management	22%

After controlling for changes in the seriousness of delinquency, researchers found that behavioral therapy continued to predict lower substance misuse at 24 months (logistic regression analysis, $p = 0.02$) and at 36 months ($p = 0.11$).

6- and 8-Year Outcomes

Attrition continued over an extended period of follow-up, with 22% and 25% of the participants dropping out at six and eight years, respectively. By the time of the 8-year re-assessment, 17% (70 of 406) of the MTA participants had received stimulant therapy continuously, while 20% of the subjects (83 of 406) had remained drug-free. [Regrettably, the MTA research team has not published a comparison of long-term outcomes using the data from these discrete subgroups.]

Nevertheless, it is significant that the most recent evidence confirmed stark outcomes for childhood recipients of pharmacotherapy. For example, using a structured diagnostic interview instrument (the Diagnostic Interview Schedule for Children, or DISC) to evaluate subjects at six years, researchers observed that the children exposed to behavior therapy had experienced the most favorable outcomes. In contrast, ***children exposed to stimulant drugs (with or without psychotherapy) experienced a four- to five-fold higher prevalence of depression or anxiety.***

	medication management	combined therapy	community control	behavior therapy
anxiety or depression	19%	18%	16%	4%

Between three and six years, the use of stimulant medication was associated with a deterioration of hyperactivity and impulsivity, aggression, and general psychopathology (the latter, based upon the Columbia Impairment Rating Scale). These changes stabilized but did not reverse between years six and eight.

Although the overall prevalence of diagnosable, full-syndrome ADHD decreased in all four patient groups by the time of adolescence (43% with ADHD at 6 years, 30% with ADHD at 8 years), the MTA children remained significantly more impaired than age-matched controls in terms of their behaviors, their academic achievement, and their overall level of functioning.

Ultimately, children who were still taking prescription stimulants at six or eight years fared no better than their unmedicated counterparts. This finding compelled the MTA researchers to conclude:

> **"these long term follow-up data fail to provide support for long-term advantage of medication treatment beyond 2-years for the majority of children..."**

Summary

1) The MTA Study was characterized by numerous design flaws which biased results *in favor of the medicated subjects.*

2) Many children changed therapies over time. This necessitated post-hoc comparisons of subjects according to "naturalistic" (actual medication use), as well as assigned conditions.

3) By 14 months, behavioral therapy proved to be ***more effective than standard drug treatment in the community on 6 of 19 measures, and equally effective on the remaining 13 variables***. Moreover, behavioral therapy was equal or superior to intensive treatment with medication or combined therapy on *14 of 19 variables.

4) Between 14 and 36 months, the continuing use of stimulant medication was associated with a deterioration of ADHD symptoms. In contrast, the benefits of past treatment with behavioral therapy proved to be stable and enduring.

5) Relative to those subjects who initiated stimulant therapy between 24 and 36 months, patients who stopped medication experienced a *four-fold* greater improvement in the severity of ADHD.

6) Past or continuing exposure to drug therapy was associated with higher ratings of delinquency by 24 and 36 months. Relative to those who avoided stimulants and so-called normal controls, the ***ADHD subjects who used stimulants ultimately displayed a higher prevalence of substance misuse between the ages of 11 and 13***.

7) Long-term outcomes from the MTA study have only recently been disclosed (March 2009). According to these revised findings, exposure to stimulants between years three and six was associated with higher rates of depression and anxiety, and with the deterioration of impulsivity, hyperactivity, aggression, and general functioning. By the eighth year of follow-up, stimulant therapy presented no distinguishable advantages in terms of "normalizing" the symptoms of ADHD, preventing or reducing delinquency, or enhancing general academic performance.

*The fourteen measures were: hyperactivity/impulsivity (ranked by teacher and by classroom observer); aggression (ranked by teacher and classroom observer); teacher ranked social skills; internalizing symptoms (ranked by teacher, child, and peers); parent-child relations (power assertion, personal closeness); and academic achievement (reading, mathematics, spelling)

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Affirmation and Notarization of Work

DATED this 31ST day of March 2009, in WILMINGTON, North Carolina.

Grace E. Jackson MD

Grace E. Jackson, MD

SUBSCRIBED AND SWORN TO before me this 31st day of March, 2009.

Notary Public in and for North Carolina
My Commission Expires: 04/02/2011