Brain-Disabling Treatments in Psychiatry

11 - Stimulant-Induced Brain Damage, Brain Dysfunction, and Psychiatric Adverse Reactions

Drugs, Electroshock, and the Psychopharmaceutical Complex


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Chapter 11

Stimulant-Induced Brain Damage, Brain Dysfunction, and Psychiatric Adverse Reactions

Even Newsweek, for whom psychiatry is usually sacrosanct, has begun to wonder if too many "quirky" and otherwise normal kids are being stigmatized with psychiatric labels (Ali, 2007 [2]). The massive increase in diagnosing children with ADHD, bipolar disorder, and autism spectrum disorders such as Asperger's can lead to only one outcome - more psychiatric drugging of America's children...more drugs and less attention to their genuine needs for caring adult role models, improved family life, better schools, and economic opportunity.

Many of the drugs prescribed to children are FDA-approved exclusively or largely for adults and have been discussed in earlier chapters. All of them, including the neuroleptics, mood stabilizers, and antidepressants, cause basically the same adverse effects in children as adults, although they may vary in frequency and intensity. Children are especially vulnerable to developing brain-disabling, spellbinding adverse reactions to psychiatric drugs. For example, antidepressant-induced suicidality was first demonstrated in controlled clinical trials of children and teenagers (chapter 6).

This chapter will focus on the drugs most commonly and specifically prescribed to children: stimulants: such as Ritalin, Concerta, Dextroamphetamine, Adderall, and Strattera. A list can be found in the appendix.

11.1 An Ineffective Treatment

Over the last several years, NIMH has funded a cohort of dedicated stimulant/ADHD advocates to conduct an expensive, nationwide, long-term study under naturalistic conditions in the community to prove effectiveness of stimulants in treating so-called ADHD (Jensen et al., 2001 [57]). The list of authors includes Peter Jensen, Stephen Hinshaw, James Swanson, Larry Greenhill, and even Keith Conners. It was as if the aging Stimulant Club had gone on government relief to produce the NIMH Multimodal Treatment Study of ADHD (MTA), whose results continue to be published.

The MTA researchers led by Swanson [108] were already touting the unpublished results in advance at the 1998 Consensus Development Conference on the Diagnosis and Treatment of ADHD. It seemed to be a foregone conclusion that the upcoming series of publications would be mightily skewed in the direction of proving drug efficacy. Nonetheless, as the various publications began to come out over the ensuing years, the study failed to prove the hoped - for results and began to provide indirect indicators of the superiority of educational and psychosocial interventions (Breggin, 2000a [20], 2001b [22]; Kean, 2004 [59]; Leo, 2004 [68]).

Finally, in 2007 the MTA authors published their evaluation of long-term effectiveness. At the
36-month assessment, stimulant medication was no better than any of several other behavioral and educational approaches (Swanson et al., 2007b[111]). Basically, with or without systematic treatment of any kind, all the children ended up the same. Thus, the best, most experienced minds in the ADHD/stimulant lobby could not put together a study to demonstrate any long-term usefulness for the medications. Meanwhile, they did confirm that the medication stunts growth (Swanson et al., 2007a[110]; see following discussion). As always, these negative results did not cause any of the many investigators to call for more caution in prescribing stimulants to children.

In defense of their drugs, the MTA authors argued that perhaps all of the children simply got better over 36 months; that is, their ADHD went away. First of all, this is contrary to the persistent argument made by drug advocates that ADHD is a real biological disease that does not go away and that requires long-term, even lifetime, treatment. Second, if it is true that so-called ADHD clears up on its own, that makes a good argument for never giving toxic drugs to children.

Ritalin and other stimulants are typically prescribed for months and years at a time. Nonetheless, despite decades of effort, biopsychiatry and the drug companies have not been able to demonstrate any long-term gain for children from taking stimulants. Going back many years to the present day, the FDA-approved labels for Ritalin as found in the Physicians’ Desk Reference (2007)[87] have stated, “Long term effects of Ritalin in children have not been well established” (p. 2273, under “Pediatric Use”). This caveat applies to all of the stimulant drugs. As the National Institute of Mental Health (NIMH) succinctly stated, “The long-term effects of stimulants remain in doubt” (Regier et al., 1992[92]). NIMH had hoped to correct this negative conclusion by paying millions of dollars to drug advocates to conduct the multicenter MTA study that once again failed to prove any long-term effectiveness. NIMH further stated that studies have demonstrated short-term effects such as reducing “class room disturbance” and improving “compliance and sustained attention” (Regier et al., 1992[92]). But it recognized that the drugs seem “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”. Meanwhile, the short-term impacts of reducing disturbance and improving compliance, as well as improving attention, are brain-disabling effects that last only for a few weeks until the brain manages to compensate for the drug toxicity (see following discussion).

Dulcan (1994)[37] reviewed stimulant treatment for ADHD children. In regard to long-term control, she found that “stimulants have not yet been demonstrated to have long-term therapeutic effects”. The not yet, it should be emphasized, referred to three decades of trying to prove its effectiveness.

After decades of research, there is still no evidence for efficacy beyond a few weeks’ exposure, and that so-called efficacy is based on the capacity of stimulants to suppress all spontaneous behavior and to enforce obsessive behavior (Breggin, 1999a[17], 2001c[23]; see subsequent discussion). Solanto and Wender (1989)[105] showed that single clinical doses of methylphenidate caused a constriction of cognitive processes and overfocusing on tasks. In the classroom, this is mistaken for an improvement, when in fact it is a drug-induced disorder - a classic example of the brain-disabling principles of psychiatric treatment.

In regard to improvement in learning or educational performance, the record is even worse. There is no convincing evidence for either short- or long-term improvement in cognitive ability or academic performance (reviewed by Breggin, 1991b[13]; Coles, 1987[33]; McGuinness, 1989[77]; Swanson et al., 1992[109]).

Dulcan (1994)[37] also made clear that for the drug to be effective, an array of other interventions are required:

“Specific learning disabilities and gaps in knowledge and skills due to inattention require ed-
ucational remediation. Social skills deficit and family pathology may need specific treatment. Parent education and training in techniques of behavior management are virtually always indicated." (p. 1214)

A program such as Dulcan suggested would in reality do away with the need for drugging children. As a consultant to state programs and clinics, I have found that such a comprehensive program can help the most disturbed and disabled children, including those with more severe diagnoses than ADHD. Such programs are offered to very few children, and even fewer once the decision to medicate has been made.

In May 2006, the Oregon Health and Science University, Oregon Evidence-Based Practice Center issued its final report, “Drug Class Review on Pharmacological Treatments for ADHD” (McDonagh et al., 2006). On the basis of a review of all available research, the 113-page report continued to confirm the shortcomings of the stimulant drugs and, in particular, research surrounding these medications. After reviewing the available literature, the report concluded, “Good quality evidence on the use of drugs to affect outcomes relating to global academic performance, consequences of risky behaviors, social achievements, etc. is lacking.” The report also found that safety evidence was of “poor quality” and that evidence of the drugs helping adults was “not compelling”.

Concerning effectiveness for reducing ADHD behaviors, the report divided its conclusions into age brackets. For preschoolers (age 3-5 years), it found evidence “seriously lacking”. The authors could find only placebo-controlled trials, and only one was of “fair quality”. They also found “no evidence of long-term safety” for drugs in this age group. For elementary school children (age 6-12 years), some studies supported short-term effectiveness but were generally inadequate. For adolescents (age 13-17), McDonagh and Peterson (2006) concluded, “Evidence on the effectiveness of pharmacotherapy for ADHD in adolescence is very limited.”

The study seemed to avoid making definitive comments, but the overall impression was captured in the headline “Are ADHD Drugs Safe? Report Finds Little Proof” (Otto, 2005).

### 11.2 A Wide Variety of Adverse Effects

The stimulant drugs, including all methylphenidate and amphetamine products, produce a wide array of adverse effects on the brain and mind as well as the overall body. Strattera, marketed by Eli Lilly as a nonstimulant, shares most of these adverse effects. Table 11.1 summarize the adverse drug reaction data from eight controlled clinic trials. Table 11.2 compiles many of the stimulant adverse effects. I developed this chart for presentation at the 1998 National Institutes of Health (NIH) Consensus Development Conference on the Diagnosis and Treatment of ADHD to confirm the high frequency and the pattern of adverse stimulant effects.
TABLE 11.1a - Methylphenidate (MPH) and D-Amphetamine (AMP) Adverse Drug Reactions (ADRs) in 8 Double-Blind Placebo-Controlled Studies of Children Diagnosed with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Group*</th>
<th>Dose mg/kg</th>
<th>Duration</th>
<th>Salient Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Firestone et al. (1998) [42]</td>
<td>41, age 4-6</td>
<td>MPH 0.3 and 0.5 BID</td>
<td>7-10 days</td>
<td>Marked deterioration from placebo to 0.5 mg in Sad/unhappy (69% of children), Drowsiness (62%), Uninterested in others (62%). Loss of appetite (75%). Severe symptoms increased 12% for “Uninterested in others” (0-12%) and 28% for “Talks less with others” (22%-50%). Nightmares increased 35% (28%-62%); tics or nervous movements increased 9% (3% to 12%).</td>
</tr>
<tr>
<td>2. Mayes et al. (1994) [75]**</td>
<td>69, age 2-13</td>
<td>MPH most commonly mean 8 days</td>
<td>0.3 TID</td>
<td>6 discontinued because of ADRs. 13 “significantly worse” on drug. 5.8% increase or emergence of “stereotypical behaviors, including hand-wringing,” “arm-waving, teethgrinding and foot-tapping”. 7% severe reactions with one maniclike. 18.8% experience lethargy: “Children with lethargy were variously described by raters as tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive”. 26% “irritability”.</td>
</tr>
</tbody>
</table>

*Placebo subjects were not included in totals.

**Only the preschoolers were double-blind placebo-controlled.

Note: QD = once daily; BID = 2x daily; TID = 3x daily.
TABLE 11.1b - Methylphenidate (MPH) and D-Amphetamine (AMPH) Adverse Drug Reactions (ADRs) in 8 Double-Blind Placebo-Controlled Studies of Children Diagnosed with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Group*</th>
<th>Dose mg/kg</th>
<th>Duration</th>
<th>Salient Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Barkley et al. (1990) [7]</td>
<td>83, age 5-13</td>
<td>MPH 0.3 and 0.5 BID</td>
<td>14-20 days</td>
<td>Decreased appetite, insomnia, stomachaches, and headaches. Proneness to crying increased at least 10% during low dose. Tics/nervous movements increased 10% at the high dose. Decreased appetite and insomnia “serious” in 13% and 18% at both doses compared to 1% and 7% on placebo. 3.6% dropped out due to “serious” ADRs. One case of “excessive speech and disjointed thinking”.</td>
</tr>
<tr>
<td>4. Schachar et al. (1997) [98]</td>
<td>46, age 6-12</td>
<td>MPH approximately 4 months 0.5-0.6 — BID</td>
<td>10% drop out due to ADRs, 3 due to “sadness and behavioral deterioration, irritability, withdrawal, lethargy, violent behavior, or rash”; 1 due to “withdrawal and mild mania”; 1 due to “withdrawal and dysphoria”. 45% experienced an increase in at least 1 ADR (p &lt; .005). Increased severity of affective ADRs (mostly withdrawal, sadness, crying) (p &lt; .01). Increased severity of physiological ADRs (mostly anorexia and stomachaches) (p &lt; .005).</td>
<td></td>
</tr>
<tr>
<td>5. Gillberg et al. (1997) [48]</td>
<td>62, age 6-11</td>
<td>AMPH varying doses</td>
<td>4-15 months</td>
<td>3 cases of hallucination, 1 with severe tics. 32% abdominal pain occasionally or often. 56% poor appetite.</td>
</tr>
</tbody>
</table>

*Placebo subjects were not included in totals.

Note: QD = once daily; BID = 2xdaily; TID = 3xdaily.
### Table 11.1c - Methylphenidate (MPH) and D-Amphetamine (AMPH) Adverse Drug Reactions (ADRs) in 8 Double-Blind Placebo-Controlled Studies of Children Diagnosed with ADHD

<table>
<thead>
<tr>
<th>Study</th>
<th>Group*</th>
<th>Dose mg/kg</th>
<th>Duration</th>
<th>Salient Adverse Drug Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Borcherding et al. (1990) [11]</td>
<td>46 boys, age 6-12</td>
<td>Average weekly dose: 3 weeks MPH 0.5, 0.8, and 1.3 BID. AMPH 0.2, 0.5, and 0.7 BID</td>
<td>Studied compulsive and tic ADRs. 58% develop abnormal movements. 51% develop obsessive/compulsive or perseverative ADRs. 1 persistent tic. Many severe OCD ADRs. See Table 11.6.</td>
<td></td>
</tr>
<tr>
<td>7. Solanto and Wender (1989) [105]</td>
<td>19, age 6-10</td>
<td>MPH 0.3, 0.6 and 1.0 QD</td>
<td>3 separate days</td>
<td>Studied cognitive functions. 42% “overaroused” with “cognitive perseveration” (overfocused, OCD reaction).</td>
</tr>
<tr>
<td>8. Castellanos et al. (1997) [31]</td>
<td>20, age 6-13; all comorbid for Tourette’s</td>
<td>AMPH means 0.2, 0.41, 0.64 BID. MPH means 0.43, 0.67, and 1.20 BID</td>
<td>3 weeks</td>
<td>25% develop obsessive ADRs on MPH. 3 stopped medication at completion due to increased tics. One-third experienced worsened tics.</td>
</tr>
</tbody>
</table>

*Placebo subjects were not included in totals.

Note: QD = once daily; BID = 2x daily; TID = 3x daily.
### TABLE 11.2a - Harmful Effects Caused by Ritalin, Concerta, Dexedrine, Adderall, and Similar Stimulants

<table>
<thead>
<tr>
<th>Brain and Mind Function</th>
<th>Cardiovascular Function</th>
<th>Gastrointestinal Function</th>
</tr>
</thead>
</table>

### TABLE 11.2b - Harmful Effects Caused by Ritalin, Concerta, Dexedrine, Adderall, and Similar Stimulants

<table>
<thead>
<tr>
<th>Endocrine and Metabolic Function</th>
<th>Other Function</th>
<th>Withdrawal and Rebound Reactions</th>
</tr>
</thead>
</table>


The high rates of psychiatric adverse effects in controlled clinical trials have been largely ignored by the medical profession. However, they have not gone entirely unacknowledged. Table 11.3 is excerpted from a handbook of psychiatric medications (Maxmen et al., 1995 [74]).

The Drug Enforcement Administration (DEA, 1995b) [34] provided a summary comparing the adverse effects of methylphenidate and amphetamine. For the central nervous system (CNS), it found excessive CNS stimulation, psychosis, dizziness, headache, insomnia, irritability, and attacks

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of Tourette’s or other tic syndromes. It also listed for both drugs a variety of cardiovascular symptoms, including increased blood pressure and heart rate; various gastrointestinal symptoms, including vomiting, stomach pain, and anorexia; and weight loss and growth suppression. For methylphenidate alone, it listed leukopenia (abnormally low white cells in the blood), anemia, hypersensitivity reaction, and blurred vision. For amphetamine, it lists skin rash or hives.

The DEA (1995b) \[34\] also observed that adverse effects of irritability or sadness have not been well studied but have been reported in up to 22% of children on stimulant medication. Elsewhere in the same document, the DEA noted that with both Ritalin and amphetamine, “psychotic episodes, violent behavior and bizarre mannerisms have been reported” (p. 16). Emotionally disturbing adverse effects are even more common with the youngest children. Dulcan and Popper (1991) \[36\] noted that in preschool children, there is a greater risk of side effects, “especially sadness, irritability, clinging, insomnia, and anorexia” (p. 188).

**TABLE 11.3 - Rates of Adverse Mental Effects Reported in Stimulant Clinical Trials**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Methylphenidate</th>
<th>Amphetamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness, less alert</td>
<td>5.5%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Confused, dopey</td>
<td>10.3% (8% to 12%)</td>
<td>3.9% (2% to 10%)</td>
</tr>
<tr>
<td>Depression</td>
<td>39%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Agitation, restlessness</td>
<td>10%</td>
<td>6.7% (3.3% to 10%)</td>
</tr>
<tr>
<td>Irritability, stimulation</td>
<td>25% (17% to 29%)</td>
<td>17.3% (11% to 19%)</td>
</tr>
</tbody>
</table>

Note. The data are from Maxmen and Ward (1995, p. 366) \[74\]. The numbers are percentages of patients reported in studies to suffer from the adverse effect. Numbers in parentheses represent the range reported in studies.

Given the high rates of adverse effects caused by stimulants, it is a wonder that doctors tend to see these drugs in such a benign light, cavalierly prescribing them to children for the control of their behavior.

### 11.3 More Extreme Intoxication Reactions

One way to understand the routine effect of any psychiatric drug is to look at its more extreme or toxic effects (Breggin, 1991b \[13\]). According to the brain-disabling principles described in chapter 1, the clinical or therapeutic effect will be nothing more than a less intense expression of the toxic effect. In discussing methylphenidate’s so-called cognitive toxicity, Swanson et al. (1992) \[109\] summarized the literature:

“In some disruptive children, drug-induced compliant behavior may be accompanied by isolated, withdrawn, and overfocused behavior. Some medicated children may seem ‘zombie-like’ and high doses which make ADHD children more ‘sober,’ ‘quiet,’ and ‘still’ may produce social isolation by increasing ‘time spent alone’ and decreasing ‘time spent in positive interaction’ on the playground.”

These findings are very similar to even more extreme reactions with larger, chronic doses. Schirring (as cited by Spotts et al., 1980 \[107\]) studied amphetamine intoxication in monkeys and in humans. In monkeys, mothers on amphetamine lost contact with their infants and became obsessed in a stereotypical fashion:
“In mother-infant dyadic relationships, amphetamine eliminated the eye contact, the specific
gaze that is an importatn cue for contact in these animals. In addition, the parental care
behavior partem was disrupted. The mother lost her interest in the infant. She did not react to
the calling signals of the infant, spent most of the time away from the infant and was preoccupied
with stereotyped self-grooming behavior.”

In amphetamine addicts, similar behaviors were observed, including stereotypical, bizarre move-
ments, repetition of single words or phrases, stereotyped writing or drawing, talking without listening,
and social withdrawal and isolation (see also Schiørring, 1981 [101]).

In discussing amphetamine abuse, Kramer (1970) [63] again compared the stereotypical behavior
of animals to some of the reactions in human beings:

“Perhaps the most curious effect of amphetamines is their capacity to induce behavior which is
persisted in or repeated for prolonged periods. If the issue is not too disorganized the activity
may, on the surface at least, be useful. Dwellings may be cleaned, automobiles polished, or
items arranged to an inhuman degree of perfection. Analogous to this compulsive behavior in
man is what has been termed stereotypy in animals. Rats, mice, guinea pigs, cats, and squirrel
monkeys, almost without exception, perform repetitive acts.”

Notice the author’s remark that the behavior may “on the surface at least, be useful”. In treating
children with Ritalin, Concerta, Adderall, and other stimulant medications, we settle for a surface
or cosmetic change in behavior without dealing with the underlying problems in the family, school,
and elsewhere. We do so at grave risk to the child’s physical and mental integrity.

The label for Ritalin lists the symptoms associated with severe intoxications, while noting that
these reactions can also occur at lower doses. Table 11.4 summarizes this information, providing
another window into the primary effect of the drug.

**TABLE 11.4 - Toxic Reactions to Stimulants: Usually in
Overdose and Occasionally at Low Doses**

<table>
<thead>
<tr>
<th>Psychiatric manifestations</th>
<th>Sweating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agitation</td>
<td>Flushing</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Headache</td>
</tr>
<tr>
<td>Confusion</td>
<td>High fever</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Elevated heart rate</td>
</tr>
<tr>
<td>Delirium</td>
<td>Palpitations</td>
</tr>
<tr>
<td>Panic states*</td>
<td>Cardiac arrhythmias</td>
</tr>
<tr>
<td>Assaultiveness*</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Enlarged pupils</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonpsychiatric manifestations</th>
<th>Dry mouth, nose, and eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremors</td>
<td>Increased respiration*</td>
</tr>
<tr>
<td>Increases neurologic reflexes</td>
<td>Nausea, vomiting, diarrhea, and cramps*</td>
</tr>
<tr>
<td>Muscle twitching</td>
<td>Muscle breakdown*</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Hypotension, shock, and circulatory collapse*</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
</tr>
</tbody>
</table>

*Item taken from the 2002 FDA-approved overdose section of the labels for Dexedrine, Adderall,
and Adderall XR, but not Ritalin. The remainder was taken from the Ritalin label with some overlap.
The Dexedrine and Adderall labels both state that “individual patient responses to amphetamines vary widely” and “toxic symptoms occasionally occur as an idiosyncrasy at doses as low as 2 mg”.

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The Adderall XR label also states that patient responses “vary widely” and “toxic symptoms” may occur “at low doses”. Any of the symptoms can occur with any of the stimulants at routine clinical doses.

11.4 Atomoxetine (Strattera)

Eli Lilly promoted and continues to promote Strattera as the nonstimulant drug to treat ADHD (Eli Lilly and Company, 2006 [38]). While the company maintains this position, the drug is nonetheless listed under “Central Nervous System Stimulants” in the Physicians’ Desk Reference (2007, p. 208 [87]). Lilly’s extremely shrewd marketing ploy of promoting Strattera as a nonstimulant is meant to allay the concerns of parents and doctors about their children taking stimulants for ADHD.

It is true that Strattera has not been demonstrated to cause dependence and abuse like Ritalin, Adderall, and the other stimulant drugs used to treat ADHD and therefore has not been placed in Schedule II by the DEA. But Strattera is a highly stimulating drug. According to the label for Strattera, as found in the Physicians’ Desk Reference (2007, p. 1817, Table 1 [87]), in the clinical trials used for FDA approval, irritability was reported in 8% of subjects, crying in 2%, and mood swings in 2%.

The real-world effects of Strattera are even more ominous in regard to overstimulation. Henderson and Hartman (2004) [53] examined data from 153 sequential patients at two clinics: “We have observed extreme irritability, aggression, mania, or hypomania induction in 51 cases (33%).” Of the 51 cases, 88% displayed verbal aggression; 49%, physical aggression; 96%, irritability; 96%, mood swings; 69%, grandiosity; 18%, decreased sleep; 14%, hyperactivity; 10%, increased goal behavior; and 6%, hypersexuality. They diagnosed 10 of the 51 patients with mania, and 3 were hospitalized.

Henderson and Hartman (2004) [53] reported dramatic examples of the symptoms as described by parents, including “blows up at everything”; “huge tantrums”; “yelling threats, ‘I’m going to get a gun and shoot you,’ ‘I’ll kill you’ ”; and “physical aggression, physical attacks on another, punching a female peer in the face, strangling a peer, attacking parents, brandishing a weapon”. The onset of the symptoms covered a broad range, with an average of 6.39 weeks.

In overdose, like any stimulant, Strattera can cause severe seizures (Sawant et al., 2004 [97]).

11.4.1 Strattera-Induced Suicidality

Strattera is the one ADHD treatment that has received a black-box warning concerning increased suicidality. After a review and analysis of 13 clinical trials conducted with children, all but one for the treatment of ADHD, the FDA (2005c) [43] “identified an increased risk of suicidal thinking for Strattera”. The bold black-box warning included in the label can be found in the 2007 Physicians’ Desk Reference [87]:

“Suicidal ideation in Child and Adolescents-STRATIERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit Hyperactivity Disorder (ADHD). Anyone considering the use of STRATIERA in a child or adolescent must balance this risk with the diniGal needs. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior.”

Once again, Eli Lilly has managed to promote one of its drugs as especially safe, when it is in fact especially dangerous.
11.5 The Food and Drug Administration Continues to Minimize the Risks of Stimulants

For many years, I have criticized the FDA-approved labels for stimulant drugs, including amphetamine products such as Adderall and Dexedrine and methylphenidate products such as Ritalin and Concerta. The labels have been especially weak in warning about addiction and serious psychiatric side effects such as psychosis, mania, aggression, and suicide. The FDA (2006b) recently admitted, “Current approved labeling for drug treatments of ADHD does not clearly address the risk of drug-induced signs of symptoms of psychosis and mania (such as hallucinations) in patients without identifiable risk factors, and occurring at the usual doses” - a point I had been making for nearly a decade.

The process of beginning to reassess the risks of stimulants began in June 2005, when the FDA (2005d) first gave notice that it was receiving a large number of reports of adverse psychiatric reactions, including suicidality, for methylphenidate products such as Concerta and Ritalin:

“Post-marketing reports received by FDA regarding Concerta and other methylphenidate products [e.g., Ritalin] include psychiatric events such as visual hallucinations, suicidal ideation, psychotic behavior, as well as aggression or violent behavior.”

“We intend to make labeling changes describing these events.”

The FDA provided a summary of 52 adverse psychiatric reactions reported over the prior year for Concerta and Ritalin, including cases of overstimulation (agitation and mania), depression, psychosis, aggression and violence, and suicidal behavior (FDA, 2006b). Notice the similarity to the dangerous effects that the FDA previously recognized as associated with the newer antidepressants. The similarity between stimulant and antidepressant adverse effects is probably due to the stimulating effects of the newer antidepressants.

The FDA announced plans for a September 2006 hearing focused on revising the stimulant labels in regard to cardiovascular and psychiatric adverse effects. The agency’s Division of Drug Risk Evaluation (Gelperin et al., 2006) published an extensive memorandum reviewing reports received concerning “Psychiatric Adverse Events Associated With Drug Treatment of ADHD”:

“The most important finding of this review is that signs and symptoms of psychosis or mania, particularly hallucinations, can occur in some patients with no identifiable risk factors, at usual doses of any of the drugs currently used to treat ADHD. Current labeling for drug treatments of ADHD does not clearly address the risk of drug-induced signs or symptoms of psychosis or mania (such as hallucinations) … A substantial proportion of psychosis related cases were reported to occur in children age ten years or less, a population in which hallucinations are not common.” (pp. 3-4)

According to the March FDA (2006b) report, every type of stimulant drug had caused psychosis, and for each type of drug, there had been reports of rechallenge, where the drug, when administered a second time, once again caused psychosis. The drugs shown to cause psychosis with positive rechallenge reports included all those involved in treating ADHD: various preparations of amphetamine (Adderall and Dexedrine), various preparations of methylphenidate (Focalin, Concerta, Metadate, Methylin, Ritalin), methylphenidate transdermal systems (skin patches), Stratera, and Provigil.

The FDA’s (2006b) report also cited reports of stimulant-induced aggression:

“Numerous postmarketing reports of aggression or violent behavior during therapy of ADHD have been received, most of which were classified as non-serious, although approximately 20%
of cases overall were considered life-threatening or required hospital admission. In addition, a few cases resulted in incarceration of juveniles."

Once again, positive rechallenge reports were found for each drug.

Finally, suicide also appeared as a risk. However, except for Strattera, there was less demonstrable causality:

Suicidality has been identified as a safety issue for STRATTERA (atomoxetine), and this information is clearly conveyed in current labeling. A causal association between other drug therapies of ADHD and suicidality cannot be ruled out on the basis of this review. Further evaluation of this issue is recommended. (FDA, 2006b [45])

11.6 Once Again, Too Little, Too Late

In publishing these observations in March 2006, the FDA finally caught up with strong warnings I had issued 8 years earlier, in November 1998. On that occasion, I was selected by the director’s office of the NIH to be the scientific presenter on adverse drug effects at the government’s Consensus Development Conference on the Diagnosis and Treatment of ADHD. In addition to presenting these data in a verbal exchange on a panel with another expert who was denying the risk of stimulant-induced psychosis, I presented my analysis of the data in my published report in the Consensus Development Conference proceedings (Breggin, 1999b [18]).

In preparation for my presentation, I used the Freedom of Information Act to obtain a summary of all adverse event reports for Ritalin sent into the FDA. When I tabulated the results, it became apparent that there were strong signals indicating that Ritalin was causing many psychiatric adverse events. I found hundreds of psychiatric adverse drug reactions coded in the FDA’s summary as agitation, hostility, depression, psychotic depression, psychosis, hallucinations, emotional lability, and abnormal thinking as well as overdose, overdose intentional, and suicide attempt. I then broadened this warning in my publication “Psychostimulants in the Treatment of Children Diagnosed with ADHD: Risks and Mechanism of Action” (1999c) [19] and in my book Talking Back to Ritalin (2001c) [23].

If I was able to pick up the signal in 1998, then the FDA and the drug manufacturer Novartis, with their vast resources, should have been able to do so even more easily and more quickly. After I publicized the problem at the 1998 conference, the FDA and the drug companies no longer had any excuse for failing to conduct their own analyses to test and to confirm my observations. But they delayed for nearly a decade.

I presented at the 2006 FDA hearings on stimulant medication in the hope of encouraging the agency to take seriously our seemingly mutual concerns about psychiatric adverse stimulant effects such as suicide and violence. But the FDA was already withdrawing from its previous declarations about the risks associated with stimulants. Except for keeping the already existing Strattera black-box warning about suicide, the Pediatric Advisory Committee decided not to scare parents by adding a black box warning about suicide to the stimulant labels. In reality, the panel members, many with ties to drug companies, did not want to scare their patrons about potential lost profits. The committee did, however, recommend mentioning in the stimulant labels that there have been reports of aggressive and suicidal events in association with these drugs, but the FDA would not even go that far.

In February 2007, nearly half a year after the conference, the FDA finally issued a press release announcing its intention to require label changes indicating psychiatric side effects such as “hearing voices, becoming suspicious for no reason, or becoming manic,” but at a rate of only 1 per 1,000. This
rate estimate of 1 per 1,000 (0.1%) actually made the threat seem less than doctors had previously
supposed since a higher rate of 1% had been bandied about for many years.

There is no basis for the FDA’s ridiculously low estimate of the risk of psychosis and similar
reactions from stimulants. The study that looked most closely at the rates for psychotic-like reactions
in children taking stimulants found that nearly 10% displayed these symptoms at some point during
treatment (Cherland et al., 1999 [32]). Even more negligent, the FDA-approved label made no
mention of stimulants causing suicide. Once again, the agency had grossly failed America’s children.

11.7 A Triumph for the American Psychiatric Association

The FDA’s cowardly retreat on the issue of stimulant adverse effects took place under fire from the
psychiatric establishment. Earlier, in February 2006, the FDA’s panel of advisors had shocked the
agency and medical authorities by recommending a black-box warning for all stimulant drugs used in
the treatment of ADHD concerning cardiovascular risks, including heart attack, stroke, and sudden
death.

The impetus came not from psychiatrists and psychopharmacologists in the financial thrall of
drug companies, but in particular, from a cardiologist named Steven Nissen, a consultant to the
panel, and from professor of public health Curt Furberg, a panel member. The physicians saw a need
to alert their colleagues to the risk and hopefully slow down the utilization of these drugs, a real
no-no among the psychiatric and psychopharmacological leadership. Nissen went so far as to say,
“I want to cause people’s hands to tremble a little bit before they write that prescription” (Rosack,
2006 [95]). Nissen noted the FDA’s estimate that 2.5 million children and 1.5 million adults are now
taking stimulant medications during any 30-day period, presumably for ADHD. He called this “a
major public health concern” and urged the FDA to consider much broader issues, including the
effects of pharmaceutical industry marketing and direct-to-consumer advertising.

Did Nissen make the hands of drug prescribers shake? Instead, drug company hands began to
tremble, and Steven Sharfstein (2006) [103], as president of the American Psychiatric Association
(APA), came to their aid, along with drug company-funded lobbying groups like CHADD. Sharf-
stein - reaching well beyond his role as APA president but well within his role as defender of the
psychopharmaceutical complex - responded that the FDA panel’s stance was “unsupported by clear
evidence at this time”. Within hours, the APA had issued a formal statement criticizing some FDA
panel members for taking an action that was “beyond the scope of their mission”. He really meant
that they threatened the mission of the APA and its partnership with the drug industry. The FDA
listened and withdrew its fervor for improving the stimulant labels.

11.8 Stimulant Dependence

An editorial comment in the 1995 Archives of General Psychiatry stated, “Cocaine, one of the
most reinforcing and addictive of abuse drugs, has pharmacological actions very similar to those of
MPH [methylphenidate], one of the most commonly prescribed psychotropic medications for children
in the United States” (“Editorial,” 1995). Using PET, Volkow et al. (1995) [115] found that the
distributions of cocaine and methylphenidate in the brain were identical, but that the latter remained
for a longer period of time.

Parents are seldom told that methylphenidate is speed - that it is pharmacologically classified
with amphetamines and causes the very same effects, side effects, and risks. Yet this is well known in
the profession. For example, Treatments of Psychiatric Disorders (American Psychiatric Association
[APA], 1989 [4]) observed that cocaine, amphetamines and methylphenidate are “neuropharmaco-
logically alike" (p. 1221). As evidence, the textbook pointed out that abuse patterns are the same for the three drugs, that people cannot tell their clinical effects apart in laboratory tests, and that they can substitute for each other and cause similar behavior in addicted animals (APA, 1989 [4]; see also Breggin, 1991a [12]; Breggin et al., 1994a [26], 1994b [27]). The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; APA, 1994 [3]) confirmed these observations by lumping cocaine, amphetamine, and methylphenidate abuse and addiction into one category. The federal government classifies methylphenidate in the highest addiction category, Schedule II, which also includes amphetamines, morphine, opium, and barbiturates (Goodman et al., 1991 [50]).

Before it was replaced by other stimulants in the 1980s, methylphenidate was one of the most commonly used street drugs (Spotts et al., 1980 [107]). Youngsters in middle school, high school, and college nowadays self their prescribed methylphenidate to classmates, who abuse it along with other drugs, often by snorting it. In working with community groups, we often hear anecdotal reports of individuals who have graduated from using medically prescribed methylphenidate to alcohol or street drugs. I have seen cases in my own practice.

Youngsters selling their prescribed Ritalin made The Washington Post (Welsh, 1995 [121]) in a discussion of conditions at local private schools:

"Students report that at two prestigious Virginia boarding schools, boys with prescriptions for Ritalin - a drug for attention deficit disorder - have been selling their pills to classmates looking to get high. At one school,  a student said, 'Ritalin rivals acid and marijuana.'"

Like any addictive stimulant, methylphenidate and amphetamine can cause withdrawal symptoms such as crashing with depression, exhaustion, withdrawal, irritability, and suicidal feelings. However, parents and teachers almost never recognize a withdrawal reaction when their student or child gets upset after missing a single dose. Instead, they mistakenly believe that the child needs to be kept on the medication.

11.9  Concern At the Drug Enforcement Administration

On October 25, 1995, the DEA (1995a) [35] published a press release as an introduction to a substantial document (DEA, 1995b [34]) concerning the extensive use of methylphenidate and the serious hazards associated with it. The press release began with the following series of points:

"Methylphenidate (MPH), most commonly known as Ritalin, ranks in the top 10 most frequently reported controlled pharmaceuticals stolen from licensed handlers."

"Organized drug trafficking groups in a number of states have utilized various schemes to obtain MPH for resale on the illicit market."

"MPH is abused by diverse segments of the population from health care professionals and children to street addicts."

"A significant number of children and adolescents are diverting or abusing MPH medication intended for the treatment of ADHD."

"In 1994, a national high school survey (Monitoring the Future) indicated that more seniors in high school in the U.S. abuse Ritalin than are prescribed Ritalin legitimately."

"Students are giving and selling their medication to classmates who are crushing and snorting the powder like cocaine. In March of 1995, two deaths in Mississippi and Virginia were associated with this activity."

The DEA (1995a) [35] press release concluded its list of concerns with the following statement:
“Every indicator available, including scientific abuse liability studies, actual abuse, paucity of scientific studies on possible adverse effects associated with long-term use of stimulants, divergent prescribing practices of U.S. physicians, and lack of concurrent medical treatment and follow-up, urge greater caution and more restrictive use of MPH.”

In 2000, in response to continuing drug company pressure to view Ritalin as a mild stimulant, the DEA’s Christine Sannerud and Gretchen Feussner [96] wrote an article asking “Is Ritalin an Abused Drug? Does It Meet the Criteria of a Schedule II Substance?” They documented that Ritalin is similar in its effects to amphetamine and cocaine:

“Like amphetamine and cocaine, abuse of MPH [Ritalin] can lead to marked tolerance and severe psychologic dependence. The pattern of abuse is characterized by escalation in dose, binge use followed by severe depression, and an overpowering desire to continue the use of the drug despite negative medical and social consequences. The abuser may alter the mode of administration from oral use to intranasal or intravenous use to intensify the effects of the drug.” (p. 35)

They described physical overstimulation, euphoria, and psychosis as consequences of Ritalin abuse. The two DEA officials wrote:

“In conclusion, animal studies have shown that MPH has an abuse liability similar to that of other Schedule II stimulants, including amphetamine, methamphetamine, and cocaine. Actual data on abuse indicate that the pattern of MPH abuse is similar to that of other potent psychostimulants and that MPH is diverted and abused to a similar extent as other pharmaceutical Schedule II substances. Taken collectively, the data indicate that MPH fits the profile of a Schedule II substance.”

All of the DEA’s observations run contrary to the Ritalin label as found in the Physicians’ Desk Reference (2007)[87], which continues to identify this potent, highly addictive drug as a “mild central nervous system (CNS) stimulant” (p. 2269), misleading doctors and consumers alike. Although the DEA and all responsible pharmacologists view Ritalin as essentially similar to amphetamine, the dependence warnings on the Ritalin label remain extremely weak in comparison to those on the Dexedrine and Adderall (amphetamine) labels.

Drugs that are addictive are especially brain disabling and spellbinding. The “overpowering desire to continue the use of the drug despite negative medical and social consequences” described by Sannerud and Feussner (2000)[96] is a central aspect of intoxication anosognosia or medication spellbinding. Addiction is caused by drug-induced brain dysfunction that comes to the surface as the dose wears off or is terminated. Addiction is an extreme form of spellbinding, rendering the individual wholly unable to appreciate the adverse psychiatric effects of the drug and often driving the victim to act in ways that would otherwise feel wholly alien and repulsive.

11.10 Nadine Lambert Studies

Studies published since the last edition of this book should have laid to rest the question of whether or not taking prescribed Ritalin predisposes a child to stimulant abuse as a young adult. Nadine Lambert (Lambert et al., 1998[65]; especially, Lambert, 2005[66]) conducted a 28-year prospective longitudinal study of ADHD children and normal controls identified from among 5,112 elementary school students. The participants were followed through childhood and adolescence and evaluated three times in young adulthood. The authors found that independent of the diagnosis of ADHD, “stimulant treatment
increased the odds of dependence on tobacco, cocaine, and cocaine/amphetamine”. By contrast, “ADHD and problem behavior did not increase the odds of either daily smoking or lifetime use of any of the substances”. It is not ADHD but the treatment for ADHD that puts children at risk for future drug abuse. This conclusion is entirely consistent with the fact that animals and humans cross addict to Ritalin, amphetamine, and cocaine and that exposure to Ritalin in young animals causes permanent changes in the brain.

11.11 The Brain-Disabling, Spellbinding Effects of Stimulants

Consistent with the brain-disabling principle and medication spellbinding, experts generally agree that Ritalin affects normal children in the same way it affects diagnosed children. Golden (1991) 49 observed, “The response to the drug cannot be used to validate the diagnosis. Normal boys as well as those with ADHD show similar changes when given a single dose of a psychostimulant” (p. 37).

Within an hour after taking a single dose of a stimulant drug, any child tends to become more obedient, narrower in focus, and more willing to concentrate on humdrum tasks and instructions. Parents in conflict with a little boy can hand him a pill, knowing he will soon be more docile.

It is commonly held that stimulants have a paradoxical effect on children compared to adults, but these drugs probably affect children and adults in the same way. At the doses usually prescribed by physicians, children and adults alike are spaced out, rendered less in touch with their real feelings, and hence more willing to concentrate on boring, repetitive, schoolroom tasks.

At higher doses, both children and adults become more obviously stimulated into excitability or hyperactivity. There is, however, great variability among individuals, and a number of children and adults will become more hyperactive and inattentive at the lower doses as well.

Although drug companies are putting market pressure on them, thus far, the British have remained more cautious than Americans about using stimulants for children. Grahame-Smith and Aronson (1992) 51, authors of the Oxford Textbook of Clinical Psychopharmacology and Drug Therapy, suggested that stimulants may work in children in the same way they work in rats, by “inducing stereotyped behavior in animals, i.e., in reducing the number of behavioural responses” (p. 141). Stereotyped behavior is simple, repetitive, seemingly meaningless activity, often seen in brain damaged individuals. The textbook states somewhat suggestively, “It is beyond our scope to discuss whether or not such behavioural control is desirable” (p. 141).

The stereotypical behavior mentioned by Grahame-Smith and Aronson (1992) 51 has been carefully studied in the laboratory in regard to both amphetamine and methylphenidate, which produce identical results in animals. Randrup and Munkva (1970) 89 described the stereotypical behavior produced in rats by subcutaneous injections of amphetamine:

“It begins within one hour after the injection and lasts for an hour or two. The behavior consists of continuous sniffing, licking, or biting the cage floor or the animal’s own forelegs. The rat sits in a crouched posture and usually presses its body against the cage wall. Normal activities such as grooming, eating, rearing, and forward locomotion are absent; backward locomotion is seen occasionally.”

Randrup and Munkva (1970) 89 noted that the stereotypical behavior varies from species to species but always involves the suppression of normal behavior:

“The stereotyped activities are always performed continuously in the absence of normal activities, but the form of the stereotypy depends on the species. Rodents gnaw, lick, or sniff; cats move their head from side to side; and dogs run in circles or back and forth along a fixed route.
The monkeys perform various repetitious movements with their hands, limbs, body or head, and locomotion along a fixed route has been observed in a few cases."

The authors considered stereotypical behavior similar to certain obsessive and compulsive behaviors seen in humans taking stimulants. They cited Scher (1966)\textsuperscript{99}, who observed,

"One of the most peculiar phenomena which may occur in the course of the use of amphetamines, especially methamphetamine, is what is called 'being hung up'."

"An individual who is 'hung up' will literally get stuck in a repetitious thought or act for hours. He may sit in a tub all day long, clean up the house or a particular item, hold a note or phrase of music, or engage in nonejaculatory intercourse for extended periods. The danger of getting 'hung up' in this way seems to be peculiar to amphetamines."

Getting "hung up" is a manifestation of stimulant-induced compulsive behavior that includes overfocusing and stereotypical or repetitive behavior. Consistent with the brain-disabling principles, Kramer et al. (1970)\textsuperscript{62} identified these abnormal compulsive behavioral reactions as the sought-after effect in children and adults:

"They are no longer hyperresponsive to their environment and, for the first time, they focus on the object or task before them. For the first time in their lives they can accomplish a task like reading, which requires concentration, without responding to someone who's talking in the room. Some adults also take amphetamines before going to a party, because it cuts down on the peripheral distraction and the noisy background din ... Cats who are in this stereotypy mode cannot be distracted by stimuli in their periphery; you can wave your arms, etc., to no avail."

Because of its importance as a demonstration of the brain-disabling principles, I have previously reviewed at length the extensive scientific literature confirming the dual action of stimulant drugs on animals and children alike (a) reducing spontaneous behavior and (b) enforcing obsessive-compulsive behavior (Breggin, 1999a\textsuperscript{17}, 1999b\textsuperscript{18}, 1999c\textsuperscript{19}). The animal literature dramatically illustrates how stimulant drugs reduce spontaneity, exploratory behavior, and social behavior, while inducing compulsive behavior (e.g., Arakawa, 1994\textsuperscript{3}, Bell et al., 1982\textsuperscript{10}; Hughes, 1972\textsuperscript{55}; Randrup et al., 1967\textsuperscript{90}; Rebec et al., 1997\textsuperscript{91}; Schiöring, 1979\textsuperscript{100}; Wallach, 1974\textsuperscript{117}). Exactly as these drugs turn normal monkeys into passive, obsessive monkeys, they turn normal children into compliant classroom children.
### TABLE 11.5 - Harmful Stimulant Effects Commonly Misidentified as Therapeutic or Beneficial for Children Diagnosed With ADHD

<table>
<thead>
<tr>
<th>Obsessive-Compulsive Effects</th>
<th>Social Withdrawal Effects</th>
<th>Behaviorally Suppressive Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compulsive persistence at meaningless activities (called stereotypical or perseverative behavior)</td>
<td>Socially withdrawn and isolated</td>
<td>Compliant in structured environments; socially inhibited, passive, and submissive</td>
</tr>
<tr>
<td>Increased obsessive-compulsive behavior (e.g., repeating chores endlessly and ineffectively)</td>
<td>General dampened social behavior</td>
<td>Somber; subdued, apathetic, lethargic, drowsy, dopey, dazed, and tired</td>
</tr>
<tr>
<td>Mental rigidity (called cognitive perseveration)</td>
<td>Reduced communicating or socializing</td>
<td></td>
</tr>
<tr>
<td>Inflexible thinking</td>
<td>Decreased responsiveness to parents and other children</td>
<td>Bland; emotionally flat; humorless; not smiling; depressed and sad, with frequent crying</td>
</tr>
<tr>
<td>Overly narrow or excessive focusing</td>
<td>Increased solitary play and diminished overall play</td>
<td>Lacking in initiative or spontaneity, curiosity, surprise, or pleasure</td>
</tr>
</tbody>
</table>

Note: Modified from Breggin (1999b [17]). Reprinted with permission of Springer Publis, Company. References to 20 clinical trials provided in Breggin (1999b [18], 1999c [19]).

Table 11.5 provides descriptions of stimulant adverse reactions from the clinical and research literature that are consistent with the brain-disabling principle. A broad array of stimulant side effects in fact provides the primary effects of the drug.

Stimulant drugs very commonly cause obsessive-compulsive reactions in children, but teachers, who too often value these traits in children, almost never interpret them as negative drug effects. The imaginative child easily becomes distracted by her own thoughts or imaginings, but on stimulants becomes compulsively overfocused, dutifully writing down everything the teacher says. The energetic youngster who cannot sit still all day long becomes drained of spontaneity and now flops into his chair for the duration of the school day. The social butterfly who wants to chat with her classmates, especially when class gets boring, loses her social interest and now sits through every lesson as if she had no friends in class. Similarly, parents who have grown weary of their child’s need for attention and resistance to homework or chores find a relief in the child’s drug-induced compulsive attention to homework or endless preoccupation with playing computer games. These quieter, preoccupied children provide a respite for their parents and even seem to be doing “better” when in fact they are suffering from stimulant drug toxicity.

I could find only one study that specifically looked for obsessive compulsive symptoms in children taking stimulants (Borcherding et al., 1990 [11]), and these reactions were identified in 23 of 45 children taking stimulants. That is, more than 50% of the children taking methylphenidate or amphetamine displayed symptoms of drug-induced compulsivity. I have summarized the 23 cases in Table 11.6.

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11.12 Brain Damage and Dysfunction Caused By Stimulants

The following sections examine studies of underlying stimulant-induced abnormalities in various brain functions that in part account for the broad range of adverse drug reactions related to brain dysfunction. We begin with some of the most disturbing data concerning atrophy induced by methylphenidate.

11.12.1 Brain Atrophy Caused By Methylphenidate

Nasrallah et al. (1986) [81] found a small but measurable degree of atrophy of the brain in more than half of 24 young adults with prior stimulant-treated hyperactivity during childhood. The authors suggested, “Cortical atrophy may be a long-term adverse effect of [stimulant] treatment” (p.245).

Several brain scan studies have claimed to demonstrate brain abnormalities associated with ADHD (Giedd et al., 1994 [47]; Hynd et al., 1991 [56]; Lou et al., 1984 [70]). Most of the studies have found relatively small brain structures in various parts of the frontal lobes and basal ganglia in children diagnosed with ADHD. The differences were based on comparisons between groups of normals and groups of children labeled ADHD. The findings are not perceptible on a case-by-case basis and cannot be used for diagnostic purposes.

TABLE 11.6 - Obsessive-Compulsive Adverse Drug Reactions to Methylphenidate (MPH) and Amphetamine (AMPH) in 23 of 45 Children (51%)

1. 6 AMPH: Perseverative drawing and writing at home; counting puzzle pieces
2. 6 AMPH: Perseverative play with Legos and puzzles (36 hours with Legos with no breaks to eat or sleep)
3. 6 MPH: Perseverative playing of piano
4. 6 AMPH: Perseverative speech
5. 7 AMPH: Rewriting work; overwriting; repetitive erasing of work; overly neat and organized at home
6. 7 MPH: Rewriting work
   AMPH: Compulsively lining up crayons
7. 8 MPH: Overly detail oriented
8. 8 MPH: Coloring over and over the same are a
   AMPH: Repetitive erasing of work; frantically goal directed; solitary activities
9. 8 MPH: Perseverative playing of video games
   AMPH: Cleaning room compulsively, buttoning and then folding dirty laundry
10. 8 AMPH: Repetitive erasing of work; perseverative with work in school
11. 8 MPH: Overerasing; redrawing; excessive pressure on pencil
    AMPH: Overerasing
12. 8 MPH: Markedly detail oriented in drawings
13. 9 AMPH: Overerasing; making lists (TV shows, model ears)
14. 9 AMPH: Cleaning room compulsively; overly orderly at home

15. 9 AMPH: Perseverative at school

16. 9 MPH: Overerasing; rewriting; excessive pressure on pencil and erasers; perseverative speech
   AMPH: Overly meticulous; inability to terminate school and play activities; perseverative speech

17. 9 MPH: Inability to terminate school and play activities; repetitive erasing and redoing projects;
   overly detail oriented

18. 10 AMPH: Cleaning room compulsively; folding dirty laundry

19. 10 AMPH: Repetitive checking behavior; lining things up; excessive pressure on pencil; repetitive
   erasing and rewriting

20. 11 AMPH: Overly meticulous work; overly neat and organized; cleaning room compulsively;
   raking leaves (7 hours) and then as they fall individually

21. 11 AMPH: Lining up erasers; repetitive erasing and redrawing

22. 11 MPH: Repetitive erasing; perfectionistic; excessive pressure of speech

23. 12 AMPH: Overly detail oriented; excessive pressure on pencil and era

Note. From B. Borcherding et al. (1990) (p. 87) [11]. Double-blind placebo-controlled overstudy. Both drugs increased likelihood of “repetitious, perfectionistic, overfocused behaviors” (p < .01). MPH associated with combination of abnormal movements and ADRs (p = .009). Fourteen
of the 23 (60.8%) suffered from “orofacial” tics at stereot Twelve of the 23 had orofacial tics and
6 had stereotypy, including 4 who had both. Similarity to animal studies in the combination of
perseveration and abnormal movements.

The differences found between normal brains and those of children diagnosed with ADHD in reality
are due to medication effects. At the 1998 NIH Consensus Development Conference on ADHD [82],
Swanson presented a paper reviewing the range of genetic and brain scan studies purporting to show
biological bases of ADHD (Swanson et al., 1998 [108]). A number of the studies involved Swanson’s
coauthor, Castellanos (Castellanos et al., 1998 [30]; Giedd et al., 1994 [47]). My own review (Breggin,
1998a [16]) indicated that some of the studies failed to mention prior drug treatment, while drawing
on populations, such as the NIH clinics, where the diagnosed children have extensive prior drug
exposure (e.g., Giedd et al., 1994 [47]). Other studies alluded to previous drug treatment without
attempting to correlate it with the brain changes (Hynd et al., 1991 [56]).

In the unpublished public discussion following Swanson’s presentation, neurologist Frederick Baugh-
man Jr. asked Swanson if any of the studies in his review involved children without a history of drug
treatment. Swanson could not name a single study based on untreated patients and offered the
abundant and untrue explanation that untreated children diagnosed with ADHD are difficult to obtain
in the United States. On the basis of Swanson’s confession that all the children had been exposed to
stimulant drugs, I suggested in my presentation that Swanson’s report be incorporated into mine
as additional evidence of the brain-damaging effects of stimulants.

After hearing all the scientific presentations and discussions, the Consensus Conference panel
concluded that “there are no data to indicate that ADHD is due to a brain malfunction” (National
Institutes of Health, 1998a, p. 2 [82]). This important conclusion has a sound basis but was removed
from later editions by NIH authorities after the consensus panel had been disbanded (1998b [83]).
As previously described, psychostimulants have demonstrable toxic effects on both gross and biochemical functions of the brain, including the frontal lobes and basal ganglia. In sharp contrast to all the data confirming toxic effects of stimulants, any association between ADHD and brain pathology remains speculative and extremely unlikely. No valid ADHD syndrome has been demonstrated, and no neurological or other physical findings have been found in association with it (see subsequent discussion). Brain structural abnormalities found in children diagnosed with ADHD and treated with stimulants - to the extent that they are valid findings - are almost certainly due to the stimulants and other psychiatric medications to which they have been exposed. These studies add to the accumulating evidence that psychostimulants cause irreversible brain damage.

11.12.2 Gross Brain Dysfunction Caused By Methylphenidate and Amphetamine

Volkow et al. (1997) [114], in a PET study of normal adults given methylphenidate, found a reduced relative metabolic rate in the basal ganglia and other changes correlating with the distribution of dopamine receptors. Wang et al. (1994) [118], using the PET scan in normal adults, measured the effect of methylphenidate (0.5 mg/kg IV) and found that methylphenidate decreased the overall flow of blood by 23% to 30% into all areas of the brain. The decrement was maintained when last tested (30 min after the final dose). The researchers warned that these effects “should be considered when prescribing this drug chronically” (p. 143). Bell et al. (1982) [10], using rat brain tissue, found that methylphenidate reduced glucose metabolic rates in the motor cortex and increased in the substantia nigra and other deep structures. Porrino and Lucignani (1987) [88], using methylphenidate (1.25-15.0 mg/kg) in conscious rats, found “significant dose-dependent alterations in metabolic activity” in numerous areas of the brain, even at the lowest dosage.

PET scans also reveal that normal adults exposed to an injection of 0.15 mg/kg of amphetamine will undergo increased glucose metabolism throughout most of the brain (Ernst et al., 1997 [41]). These studies demonstrate the effect of stimulant drugs on the brains of normal animals persons or persons.

Stimulant-induced reduced metabolic rate and reduced blood flow in the brain make a mockery of the concept that the medications are treating a disorder of the brain. Consistent with the brain-disabling principles of biopsychiatric treatment, the stimulants cause gross malfunctions in the brain that are then mistaken for improvement.

11.12.3 Abnormalities of Brain Chemistry and Microscopic Pathology Caused By Stimulants

Studies show that methylphenidate and amphetamine bind to receptors throughout most of the forebrain, including the basal ganglia and frontal cortex (Unis et al., 1985 [112]). Many studies confirm amphetamine-induced persistent abnormalities in biochemical structure and function (Robinson et al., 1998 [94]).

11.12.3.1 Methamphetamine

Because it is a common drug of abuse that is almost always obtained illegally, there is more research exploring methamphetamine-induced brain abnormalities than the other stimulants that are obtained by prescription and promoted by clinicians and pharmaceutical companies. While methamphetamine is FDA approved for the treatment of behavioral disorders in children, thankfully I have never seen it prescribed.
The capacity of methamphetamine to cause neurotoxicity—including the destruction of brain cells—has long been demonstrated in animals. Chronic exposure to methamphetamine can produce irreversible loss of receptors for dopamine and/or the death of dopaminergic and other neurons in the brain (Melega et al., 1997b [78]; Schmued et al., 1997 [102]; Sheng et al., 1996 [104]; Sonsalla et al., 1996 [106]; Wagner et al., 1980 [116]; Zaczek et al., 1989 [123]). Melega et al. (1997b) [78], for example, found persistent neurotoxic changes in dopamine function (dopamine depletions of 55% to 85%) in vervet monkeys at 10-12 weeks with doses that were relatively small and acute (two doses of 2 mg/kg 4 hours apart).

After subjecting mice to methamphetamine, Sonsalla et al. (1996) [106] also demonstrated dopaminergic cell loss of 40% to 50% in the substantia nigra. The doses were large but acute (four injections of 10 mg/kg spaced at 2-hour intervals). Battaglia et al. (1987) [9] found that large chronic doses of methamphetamine also cause the death of serotonergic nerves in animals. The changes were described as “long-lasting neurotoxic effects with respect to both the functional and structural integrity of serotonergic neurons in brain” (p. 911). Brain levels of norepinephrine are also depleted in the frontal cortex for at least 6 months or more, indicating irreversible damage to that system as well (Wagner et al., 1980 [116]). Thus methamphetamine causes destructive changes in all three of the neurotransmitter systems that are stimulated by the drug (see also Zaczek et al., 1989 [123]).

Methamphetamine has been demonstrated to be irreversibly neurotoxic. Given the biochemical and clinical similarities to amphetamine and methylphenidate, this gives cause for grave concern.

11.12.3.2 Amphetamine

Dextroamphetamine, or simply amphetamine (Dexedrine, Adderall), is another FDA-approved drug for treating behavioral problems in children. Yet the existence of amphetamine neurotoxicity has also been documented for more than 30 years (Huang et al., 1997 [54]).

Wagner et al. (1980) [116] found that treating rhesus monkeys with amphetamine leads to a long-lasting loss of dopamine and dopamine uptake sites (receptors). Juan et al. (1997) [58] confirmed that amphetamine produces a depletion of striatal dopamine that is measurable on autopsy of mice at 5 days and 2 weeks (the final experiment). The animals were administered four doses of 10 mg/kg spaced 2 hours apart.

Robinson and Kolb (1997) [93] treated rats with amphetamine twice a day for 5 days a week for a total of 5 weeks with a dose that was gradually increased from 1 mg/kg to 8 mg/kg. Thirty-eight days later, they found lasting structural modifications in the nucleus accumbens and prefrontal cortex neurons, including increased length of dendrites and density of spines. In a microdialysis study, Weiss et al. (1997) [120] treated rats with amphetamine (1.5 mg/kg injected twice a day for 14 days). Seven days after withdrawal, the animals continued to show a reduced dopamine release in the ventral striatum in response to stress.

Camp et al. (1997) [28] administered a rising dose of amphetamine (1-10 mg/kg over 10 days) to rats and then withdrew the animals for 1-30 days. Using in vivo microdialysis, they found changes lasting 1 month in norepinephrine concentrations in the hippocampus as well as altered responses to amphetamine challenge. They concluded that amphetamine produces biochemical adaptations that far outlast the acute drug effects and may account for both transient and more persistent discontinuation effects in humans.

As previously noted, Melega et al. (1997b) [78] used PET in vervet monkeys to determine presynaptic striatal dopamine function following the administration of amphetamine with small acute doses. The animals were given two doses of 2 mg/kg 4 hours apart. These doses produced marked decreases in dopamine synthesis (25% at 10-12 weeks) with a 16% reduction in one amphetamine-
treated animal at 32 weeks. Biochemical analysis showed decreased striatal dopamine concentrations of 55% at 10-12 weeks. The authors concluded that acute amphetamine doses produce long-lasting neurotoxicity. In another study using larger, more chronic doses (4-18 mg/kg over 10 days), Melega et al. (1997a) [79] found a gradual recovery from neurotoxicity in the striatum over a 2-year period after termination of treatment.

Addressing the use of stimulants for the treatment of children, Ellinwood and Tong (1996) [39] concluded, “Drug levels in children on a mg/kg basis are some times as high as those reported to produce chronic CNS changes in animal studies” (p. 14). Juan et al. (1997) [58] warned that when psychostimulants are indicated, as in ADHD, “it would seem prudent to prescribe methylphenidate rather than amphetamine, since methylphenidate appears to lack the DA [dopamine] neurotoxic potential that has been well documented for amphetamine” (p. 174). However, amphetamine has become increasingly popular among clinicians.

11.12.3.3 Methylphenidate

Mach et al. (1997) [71] used PET in rhesus monkeys to confirm the similarity of effects among methylphenidate, amphetamine, methamphetamine, an cocaine on dopamine release in the basal ganglia. It is inevitable that methylphenidate will produce similar neurotoxic effects as other psychostimulants.

Barnett and Kuczenski (1986) [8] found down-regulation of dopamine receptors after methylphenidate administration to animals but did not test for recovery. Mathieu et al. (1989) [73] found reduction of the density of the norepinephrine receptors after treatment with methylphenidate. Lacroix and Ferron (1988) [64], after 7 days of methylphenidate treatment in rats, found that “the efficacy of cortical NA [noradrenergic] neurotransmission is markedly reduced following methylphenidate treatment” (p. 277). Neurons became less responsive to various forms of stimulation, indicating desensitization. The changes persisted at the last testing, 18 hours after drug exposure. Juan et al. (1997) [58] found dopamine depletion in the mouse striatum 5 days after terminating treatment with methylphenidate, but not 2 weeks after.

The few studies that have tested for longer-term dopamine depletion from methylphenidate have failed to document it (Wagner et al., 1980 [116]; Yuan et al., 1997 [122]; Zaczek et al., 1989 [123]). However, this does not rule out irreversible neurotoxicity. Given the findings of short-term abnormalities, and the lessons from amphetamine and methamphetamine, suspicion must remain high that irreversible changes are also caused by methylphenidate.

11.13 The Latest Ominous News About Ritalin

In 2005, a study appeared in Cancer Letters that would have evoked widespread media coverage if it had been about an illegal drug, rather than about a pharmaceutical company product (El-Zein, 2005 [40]). Researchers from the University of Texas examined 12 children treated with therapeutic effects of Ritalin to determine “whether this central nervous system stimulant produces cytogenetic abnormalities in pediatric patients at therapeutic doses”. Using peripheral blood lymphocytes taken from the children, they found a 2.4-fold increase in chromosome aberrations and similar defects. They concluded, “These findings warrant further investigations of the possible health effects of methylphenidate in humans, especially in view of the well-documented relationship between elevated frequencies of chromosome aberrations and increased cancer risk”.

More recent studies of the effect of methylphenidate on the growing animal brain have produced even more ominous results with direct connections to emotional and behavioral development. Car-
lezon and Konradi (2004)\textsuperscript{[29]}, from Harvard’s Department of Psychiatry, observed that some children are being treated with psychiatric drugs as early as age 2. They summarized their research:

“When we exposed rats to the prescription stimulant methylphenidate during early adolescence, we discovered long-lasting behavioral and molecular alterations that were consistent with dramatic changes in the function of the brain reward systems.”

In a presentation at the annual meeting of the American College of Neuropsychopharmacology (ACNP) in late 2004\textsuperscript{[29]}, William Carlezon and his collaborator, Susan Andersen, explained that following exposure to methylphenidate when young, the animals’ behavior became abnormal in adulthood. According to the reporter (“New Study Shows,” 2004 \textsuperscript{[39]},

“The animals had a reduced ability to experience pleasure and reward, particularly when it was measured by sensitivity to cocaine. In addition, they found that the animals exposed to Ritalin during pre-adolescence were more prone to express despair-like behaviors in stressful situations (such as swim tests) as adults. Overall, the animals showed more evidence of dysfunctional brain reward systems and depressive-like behaviors in adulthood.”

In 2005 \textsuperscript{[72]}, Mague et al. published more on their research, again finding that methylphenidate caused changes in the young rat’s brain that persist into adulthood. They concluded, “Reduced sensitivity to these various types of reward may reflect general dysfunctions of brain reward systems”. None of this is good news for children and adolescents who have been treated with Ritalin products.

Nonetheless, the ACNP, an organization of experts beholden to the drug companies, came out spinning on this study, invoking the antiquated, unscientific myth that methylphenidate is specific for ADHD. Unconscionably, they claimed in a press release that the rat study only had implications for normal children and that properly diagnosed ADHD children would not suffer adverse consequences (Lobliner, 2004 \textsuperscript{[69]}).

In an editorial in Ethical Human Psychology and Psychiatry, Leo (2005)\textsuperscript{[67]} ridiculed the ACNP’s conclusions, which are based on the premise that the rats have normal brains but ADHD children, with abnormal brains, will be fixed by the drugs. Not only is this a bizarrely self-serving stretch of credulity on the part of these drug advocates, but it also flies in the face of the scientific reality that stimulant drugs have the same effects on normal individuals as children labeled ADHD, and in fact have been used by everyone from U.S. Army pilots to professional athletes and untold numbers of college students to focus more obsessivel for brief spans of time. Moreover, as we have seen, the drugs even affect the behavior of normal animals in the same negative way that they affect children.

11.14 Developmental Neurotoxicity

The development of the human brain continues long after birth and infancy, with significant changes taking place in the number and organization of brain cells into adolescence. When the NIMH (1995)\textsuperscript{[84]} and the FDA held a conference on the future testing and use of psychiatric drugs for children, Vitiello (1998)\textsuperscript{[113]} made a critical disclosure:

“But, we know from work in animals that if we interfere with these neurotransmitter systems at some crucial times, like the prenatal or the perinatal or neonatal phase of their lives, we can change in these animals the destiny of the neurotransmitters forever. We can cause permanent changes.” (p. 29)
The term plasticity has been used to emphasize the brain's responsiveness and ability to adapt to changing environmental input. The brain creates new brain cell synapses and prunes old ones in response to experience (Greenough et al., 1992\cite{52}; Weiler et al., 1995\cite{119}). Caged animals with limited opportunities for spontaneous activity will not develop as many neuronal interconnections as more free-ranging animals. It is doubtful that the brains of children would be any less responsive to the environment than those of rats. If environmental influences, such as the frequency and quality of communication, can influence brain development, chronic drug exposure should be viewed as potentially dangerous. In addition, the stimulants make children less spontaneous, reducing their interactions with the environment and hence their brain development.

Reviewing the literature (see also Breggin, 1999a\cite{17}, 1999b\cite{18}, 1999c\cite{19}, 2001a\cite{21}, 2002c\cite{24}) produces a wide variety of brain dysfunctions induced by stimulants, including the following:

- reduced blood flow
- reduced oxygen supply
- persistence biochemical imbalances
- persistent sensitization (increased reactivity to stimulants)
- permanent distortion of brain cell structure and function
- brain cell death and tissue shrinkage
- cytotoxicity with chromosomal abnormalities
- dependence, tolerance, and withdrawal symptoms

### 11.15 Growth Suppression Caused By Stimulants

For many years in many books and articles, I have made the point that the stimulants cause a persistent suppression of height and weight (e.g., Breggin, 1997a\cite{15}, 1999c\cite{17}, 2001c\cite{23}, 2002b\cite{25}), and for an equal number of years, medication advocates have rejected the evidence. Despite resistance from stimulant advocates, scientific research long ago demonstrated these inhibiting effects on height and weight (for example, see Klein et al., 1988a&b\cite{60} &\cite{61}).

As a result of professional resistance to the facts about stimulant-induced growth suppression, very few young patients and their parents have been informed in advance that stimulant drugs will shorten the height and reduce the weight of the children.

The growth-suppression effects of stimulants are not due primarily to loss of appetite, as many doctors have proposed. Instead, it has been known for decades that stimulants impact on the brain and pituitary gland to disrupt growth hormone production (Aarskog et al., 1977\cite{1}; studies evaluated in Breggin, 1991c\cite{14}, 2001c\cite{23}).

Despite its extreme promedication bias, the MTA study settled the question, once again, when it found consistent suppression of height and weight in children taking stimulants (Swanson et al., 2007a\cite{110}; also see MTA Cooperative Group, 2004\cite{80}). Children with no previous exposure to stimulant drugs were treated with the medications for 14 to 36 months. Compared to the control group, the medicated children showed a 2-cm (0.8-inch) reduction in height, as well as a 2.7-kg (5.9-pound) reduction in weight.

Suppression of height, rather than merely weight, is a more serious finding because it indicates a stunting of the growth processes that cannot be accounted for by reduced appetite. The FDA-approved label for methylphenidate products such as Ritalin now includes a section titled “Long-Term Suppression of Growth” that confirms a suppression of height and weight during treatment with the
medication over periods of 14 to 36 months (Physicians' Desk Reference, 2007 [87]). There was no evidence “growth rebound” (p. 2270) or recovery. The FDA-approved labels also note that it is “likely” that amphetamine stimulants will have the same effect.

When a drug is generally toxic to the brain and also produces a specific dysfunction in the regulation of growth hormone, it should be assumed that brain growth is also being inhibited and distorted, if not stunted. If it were not for the power of the psychopharmaceutical complex, the suppression of growth by stimulant drugs would, by itself, contraindicate and ultimately stop their use in children.

11.16 Conclusion

Stimulants cause permanent abnormalities in brain chemistry and anatomy. Even after only one or two doses, they impair metabolism and blood flow in the brain. By disrupting the production of growth hormone, they suppress height and weight. They are addictive and predispose children to abuse cocaine in young adulthood.

Not only do the stimulants damage and disable the brain, but scientific research has also demonstrated how these physical disabilities are manifest in behavior changes. The stimulants impair behavior by crushing spontaneity and inducing compulsive behaviors. The less spontaneous, more compulsive children are seen as “improved” when in fact they are biologically and mentally impaired. The effect of the stimulants provides a clear-cut illustration of the brain-disabling principles described in chapter 1.

Meanwhile, the stimulants have no proven therapeutic effect beyond the first few weeks of behavioral suppression with enforced docility and compulsivity. Furthermore, they have no positive impact on learning, academic progress, or socialization. Instead, they disrupt learning by causing abnormal overfocusing, and they often induce obsessive-compulsive behavior, depression, and social withdrawal.

It is difficult to find strong enough language to communicate the folly - indeed, the tragedy - of using drugs to control and improve the behavior of millions of children. Children need parents, teachers, coaches, religious leaders, counselors, and other adults in their lives - not brain-disabling drugs. Children need the support of families, schools, and community organizations - not drugs in their brains. Children need healthy brains, not drug-drenched brains.

Ultimately, children grow up by learning to take control of their actions - by learning to be responsible and self-determined - something that diagnoses and drugs ultimately discourage. When they have difficulty growing up, children need increased attention from adults who are properly equipped to guide and to educate them in improving their self-control and academic skills. In my clinical experience, when we provide these children the needed psychological, social, and educational guidance, they thrive without drugs.
Bibliography


