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Psychostimulants in the treatment of children diagnosed with ADHD: Risks and mechanism of action *

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Abstract. Millions of children in North America are diagnosed with attention deficit/hyperactivity disorder and treated with psychostimulants such as methylphenidate, dextroamphetamine, and methamphetamine. These drugs produce a continuum of central nervous system toxicity that begins with increased energy, hyperalertness, and overfocusing on rote activities. It progresses toward obsessive/compulsive or perseverative activities, insomnia, agitation, hypomania, mania, and sometimes seizures. They also commonly result in apathy, social withdrawal, emotional depression, and docility. Psychostimulants also cause physical withdrawal, including rebound and dependence. They inhibit growth, and produce various cerebral dysfunctions, some of which can become irreversible.

The "therapeutic" effects of stimulants are a direct expression of their toxicity. Animal and human research indicates that these drugs often suppress spontaneous and social behaviors while promoting obsessive/compulsive behaviors. These adverse drug effects make the psychostimulants seemingly useful for controlling the behavior of children, especially in highly structured environments that do not attend to their genuine needs.

1. Introduction

The diagnosis of Attention Deficit/Hyperactivity Disorder (ADHD) in children, and the use of stimulant medication for behavioral control, has become very common in North America, and is spreading to Europe and Australia. In 1995, the International Narcotics Control Board (INCB) showed concern that "10 to 12 percent of all boys between the ages of 6 and 14 in the United States have been diagnosed as having ADD and are being treated with methylphenidate" (p. 2). Recently, the US Drug Enforcement Administration (DEA) announced an eight-fold increase in production quotas for methylphenidate (MPH) from 1,768 kg in 1990 to 14,442 kg in 1998 (Feussner, 1998). In addition, the use of stimulant medication has further escalated with the vigorous marketing of amphetamines. No official data are available, but probably 4–5 million children receive psychostimulants in the United States each year (Breggin, 1998a).

Drawing largely on double-blind placebo-controlled trials, this report examines adverse drug reactions (ADRs) associated with dextroamphetamine (AMPH) (Dexedrine®, Adderall®),[1] methamphetamine

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[1]Since the present paper is devoted almost exclusively to the situation in the United States, the trade names cited will be those most commonly used in that country.

(M-AMPH) (Desoxyn®, Gradumet®), and MPH (Ritalin®). Special attention will be given to ADRs affecting the central nervous system (CNS). The report also examines the mechanism of stimulant drug action. The behavioral or clinical effects of stimulants may be understood as a continuum of CNS toxicity. The drugs suppress spontaneous and social behaviors while promoting obsessive/compulsive or perseverative behaviors. These adverse drug effects make children more manageable in structured or controlled situations, especially those that lack sufficient adult supervision and attention. The effects are independent of any diagnosable disorder and occur in entirely normal animals and children.

2. Overview of stimulant-induced adverse drug reactions (ADR's)

2.1. The continuum of psychostimulant toxicity

Psychostimulants produce a continuum of toxicity based on generalized CNS excitation with direct effects on various neurotransmitter systems, including dopamine, norepinephrine, and serotonin. The continuum begins with feelings of increased energy, hyper-alertness, and an intensified focus on rote activities. It progresses toward insomnia, obsessive/compulsive or perseverative activities, agitation, hypomania, mania, and sometimes seizures.

Other psychostimulant ADRs – such as somnolence, fatigue, lethargy, social withdrawal, and mental depression – probably result from a combination of direct drug actions and the brain's compensatory reactions to these effects. Compensatory reactions became especially apparent during reductions in the blood concentration of the drug during withdrawal or between doses. Rebound is a worsening of symptoms above baseline as direct drug effects wear off and compensatory CNS reactions become more dominant.

Table 1 summarizes the ADRs caused by MPH and AMPH as compiled from several well-recognized sources. In addition to familiar psychiatric ADRs such as nervousness, irritability, anxiety, depression, and increased emotional sensitivity or easy crying, there are infrequently emphasized ADRs such as impaired cognitive performance, compulsions, decreased social interest, and, in the extreme, a "zombie-like" constriction of affect and spontaneity mentioned by name and described by Arnold and Jensen (1995), Swanson, Cantwell, Lerner, McBurnett, Pfiffner et al. (1992), and Fialkov and Hasley (1984).

3. ADRs in eight double-blind placebo-controlled clinical trials

The eight studies listed in Table 2 were double-blind and (with one partial exception) placebo-controlled, and were selected because they are relatively recent and make an attempt to evaluate ADRs (Table 2).

3.1. One recent study of ADRs in pre-school children

Firestone, Musten, Pisterman, Mercer, and Bennett (1998) found statistically significant MPH-induced ADRs in younger children across treatment conditions on the broad categories of "Somatic Complaints" and "Sociability", including inhibition or suppression of behavior such as Sad/unhappy, Drowsiness, Talks less with others, and Uninterested in others, as well as Nightmares, and Decreased appetite. Obsessive/compulsive ADRs were not included in the list of potential ADRs.

Table 1
Summary of adverse drug reactions (ADRs) caused by methylphenidate and amphetamines

Cardio-vascular	Central nervous system	Gastro-intestinal	Endocrine/ metabolic	Other	Withdrawal and rebound
Palpitations	Psychosis with hallucinations (skin crawling or visions) [psychotic depression and mania]	Anorexia	Pituitary dysfunction, including growth hormone and prolactin disruption	Blurred vision	Insomnia
Tachycardia		Nausea		Headache	Evening crash
Hypertension		Vomiting		Dizziness	Depression
Arrythmias		Stomach ache, cramps		Hypersensitivity reaction with rash, conjunctivitis, or hives	Overactivity and irritability
Chest pain	Excessive brain stimulation [convulsions]	Dry mouth			Rebound worsening of ADHD-like symptoms
[Cardiac arrest]	Drowsiness, "dopey", less alert	Constipation	Weight loss		
	Confusion	[Abnormal liver function tests]	Growth suppression	[Hair loss]***	
	Insomnia		Growth retardation	Exfoliative dermatitis***	
	Agitation, anxiety, irritability, nervousness	Bad taste****	Disturbed sexual function****	Anemia***	
	[Hostility]	Diarrhea****		Leukopenia***	
	Dysphoria			Enuresis***	
	Impaired cognitive test performance			Fever*** (unexplained)	
	Dyskinesias, tics, Tourette's			Joint pain***	
	Nervous habits (e.g., picking at skin, pulling hair)			Unusual sweating***	
	Stereotypy and compulsions				
	Depression, emotional oversensitivity, easy crying				
	Decreased social interest				
	Zombielike constriction of affect and spontaneity*				
	Amphetamine look (pinched, somber expression)**				

Note: Data drawn from Arnold and Jensen (1995, Table 38-5, p. 2306), Drug Enforcement Administration (1995, p. 23), Dulcan (1994, Table 35-6, p. 1217), and Maxman and Ward (1995, pp. 365–6). Additional material taken from the Food and Drug Administration (1997, March) and indicated by brackets. *Arnold and Jensen (1995, Table 38-5, p. 2306, Table 38-7, p. 2307, and column 2, p. 2307). **Arnold and Jensen (1995). ***For methylphenidate only. ****For dextroamphetamine only.

In comparing placebo to the higher dose there were striking findings in regard to ADRs that suppress behavior: "Talks less with others" increased from 21.9 to 50% with a rise in severe cases from 3.1 to 9.4%; "Uninterested in others" increased from 31.2 to 75% with a rise in severe cases from 0 to 12.5%; "Sad/unhappy" rose from 47 to 84% with a rise in severe cases from 9 to 19%; and "Drowsiness" increased from 12.5 to 66% with a rise in severe cases from 3.1 to 15.6%. "Nightmares" increased from 28 to 62% with an increase in severity from 0 to 6%. "Tics or nervous movements" increased from 3.1 to 12.5% with a rise in severe cases from 0 to 3.3%.

The authors also made a separate calculation of the percentage of children who "deteriorated" in regard to various symptoms when comparing the 0.5 mg/kg dose to placebo: Sad/unhappy – 69% ($p = 0.01$); Drowsiness – 62% ($p = 0.001$); Uninterested in others – 62% ($p = 0.0002$). In addition, there was a deterioration of appetite in 75% ($p = 0.001$) of the children on 0.5 mg/kg compared to placebo.

Four of 41 children (10%) withdrew from treatment (reasons unspecified in report). As a conservative estimate, at least 4 children had severe ADRs.

Table 2

Methylphenidate (MPH) and D-amphetamine (AMPH) adverse drug reactions (ADRs) in 8 double-blind placebo-controlled studies of children diagnosed with ADHD

Study	Group*	Dose mg/kg	Duration	Salient ADRs
1. Firestone et al. (1998)	41, age 4–6	MPH 0.3 and 0.5 BID	7–10 days	Marked deterioration from placebo to 0.5 mg in Sad/unhappy (69% of children), Drowsiness (62%), Uninterested in others (62%). Loss of appetite in 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%).
2. Mayes et al. (1994)**	69, age 2–13	MPH most commonly 0.3 TID	mean 8 days	6 discontinued because of ADRs. 13 "significantly worse" on drug. 5.8% increase or emergence of "stereotypical behaviors, including hand-wringing, arm-waving, teeth-grinding and foot-tapping". 7% severe reactions with one manic-like. 18.8% experience lethargy: "Children with lethargy were variously described by raters as tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive". 26% "irritability".
3. Barkley et al. (1990)	83, age 5–13	MPH 0.3 and 0.5 BID	14–20 days	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".
4. Schachar et al. (1997)	46, age 6–12	MPH approximately 0.5–0.6 BID	4 months	$>$10% drop out due to ADRs, 3 due to "sadness and behavioral deterioration, irritability, withdrawal, lethargy, violent behavior, or rash"; 1 due to "withdrawal and mild mania"; 1 due to "withdrawal and dysphoria". 45% experienced an increase in at least 1 ADR ($p < 0.005$). Increased severity of affective ADRs (mostly withdrawal, sadness, crying) ($p < 0.01$). Increased severity of physiological ADRs (mostly anorexia and stomachaches) ($p < 0.005$).
5. Gillberg et al. (1997)	62, age 6–11	AMPH varying doses	4–15 months	3 cases of hallucination, 1 with severe tics. 32% abdominal pain occasionally or often. 56% poor appetite.
6. Borcherding et al. (1990)	46 boys, age 6–12	Average weekly dose: MPH 0.5, 0.8, and 1.3 BID. AMPH 0.2, 0.5, and 0.7 BID	3 weeks	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 3.
7. Solanto and Wender (1989)	19, age 6–10	MPH 0.3, 0.6 and 1.0 QD	3 separate days	Studied cognitive functions. 42% "overaroused" with "cognitive perseveration" (overfocused, OCD reaction).
8. Castellanos et al. (1997)	20, age 6–13; all comorbid for Tourette's	AMPH means 0.2, 0.41, 0.64 BID. MPH means 0.43, 0.67, and 1.20 BID	3 weeks	25% develop obsessive ADRs on MPH. 3 stopped medication at completion due to increased tics. One third experienced worsened tics.

Note: QD = once daily; BID = 2$\times$ daily; TID = 3$\times$ daily; *Placebo subjects were not included in totals; **Only the preschoolers were double-blind placebo-controlled.

The authors raised the possibility that observers might unintentionally consider the social dampening ADRs as improvements in the children's behaviors. However, they also noted: "This social dampening effect reported by parents is of some concern, especially considering claims that methylphenidate is used as a 'chemical billy club' or 'straightjacket' " (p. 20). These findings, indicating severe ADRs among very young children, are consistent with an earlier study by Schleifer, Weiss, Cohen, Elman, Crejic et al. (1975) who reported "less social behavior and interaction", as well as "sadness, irritability, excessive hugging and clinging, and increased solitary play, as well as the more usual side effects of poor appetite and difficulty getting to sleep. . ." (p. 49). The treating physician and the parents discontinued treatment in 25 of 28 children because of ADRs.

3.2. Four recent studies that evaluate a spectrum of psychiatric ADRs

Mayes, Crites, Bixler, Humphrey, and Mattison (1994) conducted double-blind placebo-controlled MPH trials involving preschoolers but trials involving older children were single blind. There was a substantial rate of behavior-suppressing ADRs: 18.8% of the children suffered from lethargy. "Children with lethargy were variously described by raters as tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive" (p. 1104). In 5.8% there was an increase or emergence of "stereotypical behaviors, including hand-wringing, arm-waving, teeth-grinding and foot-tapping" (p. 1104). Obsessive-compulsive activities (stereotypy) were also observed.

Mayes et al. reported that 26.1% of the children suffered from "irritability" during treatment. Five children (7%) displayed disturbing ADRs, including one manic-like reaction with "incessant talking", one "wild" and "out of control", and one "aggressive behavior" (p. 1105). Two of these five also developed abnormal movements. Mayes et al. also described more typical MPH adverse effects, including insomnia (13%); stomachache, nausea or vomiting (11.6%); loss of appetite (20.3%); and headache (4.3%).

Allowing for overlapping reports of more than one ADR per child in study, probably more than 50% of the children suffered from lethargy and other adverse CNS reactions. Six were discontinued due to ADRs and that number will be used to make a conservative estimate of severe ADRs.

Schachar, Tannock, Cunningham and Corkum (1997) found that 5 of 46 children ($>$10%) dropped out due to ADRs in a 24-week long MPH study. These 5 children will be used to calculate the number of severe ADRs. Their drug-induced symptoms included behavioral aberrations such as "sadness and behavioral deterioration, irritability, withdrawal, lethargy, violent behavior", "withdrawal and mild mania", and "withdrawal and dysphoria" (p. 760). Parental ratings by phone indicated a statistically significant overall increase in physiological symptoms (commonly, anorexia and stomachaches) and affective symptoms (commonly, withdrawal, sadness, and crying).

The authors concluded, "Affective symptoms were significantly associated with MPH, but they tended to develop later in the course of treatment" (p. 761). *These delayed ADRs will be missed in typical drug studies which last only a few weeks.*

Barkley, McMurray, Edelbrock, and Robbins (1990) studied ADRs associated with MPH by using a predetermined list of 17 potential ADRs. The list did not include obsessive/compulsive and perseverative symptoms. There were significant differences between MPH and placebo in decreased appetite, insomnia, stomachaches (all $p < 0.01$), and headaches ($p < 0.05$). The first two were rated as "serious" in 13% and 18% of children on the two MPH doses compared to 1% and 7% on placebo.

Barkley et al. also found that "the percentage of children experiencing proneness to crying also increased by at least 10% during the low-dose condition" ($p < 0.05$) and that "the percentage reporting tics/nervous movements increased by 10% at the high dose of medication" ($p < 0.05$) (p. 187). Finally,

Barkley et al. reported that three children (3.6%) "were unable to complete the protocol because of serious adverse reactions to medication... One child had a nervous facial tic, dizziness, and headache; a second had dizziness, headache, and increased hyperactivity; and the third had excessive speech and disjointed thinking" (p. 186). Even in this brief, relatively low dose study, one child developed manic-like symptoms with "excessive speech and disjointed thinking". Again choosing a relatively conservative estimate, Barkley et al. study had three children with severe ADRs.

Gillberg, Melander, von Knorring, Janols, Thernlund et al. (1997) reported that three children developed hallucinations on routine doses of AMPH. Two subsided on discontinuation of the drug and one on reduction. The total number of subjects in the pool is unclear but did not exceed 62 (minimum rate of 4.8%). Overall, the study does not appear to be well-focused on ADRs.

3.3. Three studies that focus on obsessive/compulsive ADRs

Borcherding, Keysor, Rapoport, Elia, and Amass (1990) focused on perseverative, obsessive-compulsive or overfocused ADRs (for details, see Table 3). The treatment included both MPH and AMPH. Observations were made on the day hospital ward, in school, and by the families. This close scrutiny probably accounts for the "extraordinarily high rate of obsessive-compulsive behaviors, movement abnormalities, or both" (p. 92). Most of these ADRs "were seen only by staff sensitive to these possible effects" (p. 92).

Borcherding et al. found a strong connection between abnormal movements and obsessive/compulsive behaviors in association with MPH ($p = 0.009$). Tics, overfocusing, and other compulsive behaviors were observed in 34 (76%) of the 45 participants who completed the study, plus one subject with severe tics who was dropped. Abnormal movements were observed in 26 of 45 children (58%). Obsessive/compulsive or perseverative ADRs (summarized in Table 3) were observed in 23 of 45 children (51%). The authors reported, "When compared to placebo, both drugs increased the likelihood ($p < 0.01$) of repetitious, perfectionistic, overfocused behaviors" (p. 90). Of these 23 children, 14 (60.8%) suffered *one or more* of the following abnormal movements: orofacial, stereotypy, or other tics. Twelve of the 23 had orofacial tics and 6 had stereotypy, including 4 who had both. At least three children developed severe drug-induced obsessive/compulsive symptoms (one on MPH, two on AMPH), including a child who played Legos for a 36-hour period without breaking to eat or sleep and another who "became compulsive about raking leaves and did so for 7 consecutive hours, after which he still felt compelled to rake individual leaves as they fell" (p. 87).

One child had to stop the trial "due to both the severity of the tic he developed during his initial treatment phase (AMPH) and exacerbated symptoms of separation anxiety. This child also lost 2 pounds during treatment" (p. 85). At one point the tics "increased to occur over 10 times per hour" (p. 87). The tics did not fully clear. Conservatively, at least 4 children in this trial had severe ADRs.

Solanto and Wender (1989) studied cognitive function using one daily dose of MPH for 3 days. They found that 42% of the children became "overaroused" with "cognitive perseveration". Compulsive, perseverative behaviors thus begin with the first doses of stimulant medication, accounting for its immediate "therapeutic" effect.

Castellanos, Giedd, Elia, Marsh, Ritchie et al. (1997) studied the effects of AMPH and MPH on children comorbid for ADHD and Tourette's syndrome. While the investigators focused on tics rather than on perseverative/obsessive ADRs, they reported: "Largely transient obsessive-compulsive symptoms were also noted ($n = 5$ on MPH, 1 on AMPH) including retracing letters, excessive erasing, rearranging and collecting compulsions, and obsessional sexual thoughts" (p. 593). The rate of obsessive ADRs for MPH was 25% during a three-week exposure.

Table 3

Obsessive-compulsive adverse drug reactions in 23 of 45 hyperactive boys treated with methylphenidate (MPH) and dextroamphetamine (AMPH)

Subject	Age	Perseverative/compulsive behaviors	
		MPH	AMPH
1	6		Perseverative drawing and writing at home; counting puzzle pieces
2	6		Perseverative play with Legos and puzzles
3	6	Perseverative playing of piano	
4	6		Perseverative speech
5	7		Rewriting work; overerasing; repetitive checking of work; overly neat and organized at home
6	7	Rewriting work	Compulsively lining up crayons
7	8	Overly detail oriented	
8	8	Coloring over and over the same area	Repetitive checking of work; frantically goal-directed; solitary activities
9	8	Perseverative playing of video games	Cleaning room compulsively; buttoning and then folding dirty laundry
10	8		Repetitive checking of work: perseverative with work in school
11	8	Overerasing; redrawing; excessive pressure on pencil	Overerasing
12	8	Markedly detail oriented in drawings	
13	9		Overerasing; making lists (TV shows, model cars)
14	9		Cleaning room compulsively; overly orderly at home
15	9		Perseverative at school
16	9	Overerasing; rewriting; excessive pressure on pencil and crayons; perseverative speech	Overly meticulous; inability to terminate school and play activities; perseverative speech
17	9	Inability to terminate school and play activities; repetitive erasing and redoing projects; overly detail oriented	
18	10		Cleaning room compulsively; folding dirty laundry
19	10		Repetitive checking behavior; lining things up; excessive pressure on pencil; repetitive erasing and rewriting
20	11		Overly meticulous work; overly neat and organized; cleaning room compulsively; raking leaves as they fall individually
21	11		Lining up crayons; repetitive erasing and redrawing
22	11	Repetitive erasing; “perfectionist”; excessive pressure on pencil	
23	12		Overly detail oriented; excessive pressure on pencil and crayons

Note: Adapted from Borcherding et al. (1990, pp. 88–89).

Castellanos et al. (1997) reported that one child on AMPH dropped out due to vomiting and another due to worsened behavior. Three more had “greater tic severity scores on all doses of both stimulants than at baseline” and were discontinued from stimulants at the conclusion of the study. This leads to a conservative estimate of 5 severe ADRs.

Stimulant-induced obsessions and compulsions have been reported as long as 4 years after the beginning of drug treatment (Kouris, 1998). Therefore, even the high rates found in these studies are likely to underestimate these ADRs for long-term treatment.

3.4. Stimulant-induced abnormal movements

Firestone et al. found an increase in "Tics or nervous movements" from 3.1% on placebo to 12.5% on 0.5 mg/kg MPH, with an increase in severe cases from 0% on placebo to 3.1% on 0.5 mg/kg. Borcherding et al. (1990), as noted, reported the appearance of abnormal movements in approximately 58% of their children, including one seemingly irreversible case. Barkley et al. (1990) found a 10% increase in tics in children treated with the higher dose of MPH. With both MPH and AMPH, Castellanos et al. (1997) found a dose-dependent worsening of tics in a "substantial minority" of patients comorbid for ADHD and Tourette's syndrome. As already noted, three discontinued medication at the conclusion of the trials due to increased tic severity on both MPH and Amph. They observed, "a substantial proportion of our small sample (one third) continued to have stimulant-associated exacerbations of their tic disorder which outweighed the clinical benefits of stimulants" (p. 594).

Lipkin, Goldstein and Adesman (1994) (not 1 of the 8 controlled trials) found a 9% rate of abnormal movements in a retrospective evaluation of 122 children diagnosed with ADHD currently or recently treated with stimulants. One child developed a very severe and *irreversible* Tourette's syndrome involving "facial twitching, head turning, lip smacking, forehead wiping, and vocalizations". Other tics and dyskinesias found in the study included mouth movements; eye blinking, rolling, or deviation; throat clearing or vocalizations; eye "bugging"; neck turning; and face rubbing. Five of the children had more than one type of dyskinesia. There were no differences in rates on MPH and AMPH. Children developed the tics or dyskinesias with drug exposures varying from less than 1 week to 23 months.

Schmidt, Kruesi, Elia, Borcherding, Elin et al. (1994) recorded changes in calcium and magnesium concentrations in the blood during treatment with MPH and AMPH that they believe may contribute to the abnormal movements.

Tics can be stigmatizing, embarrassing, and even disfiguring. Many children would probably prefer to suffer from "ADHD-like" symptoms rather than endure tics.

3.5. Summary of findings in clinical trials

Even though most of these clinical trials were short-term and low dose (Table 2), many serious ADRs were reported.[2] The total estimated number of *severe* ADRs is 30 out of 359 children (8%). Using broader criteria, the rate rises to probably between 10–20%.

If clinically observable, potentially significant ADRs are included, the rate is much higher, in the 20–50% (or more) range. For example, in the three studies that examined obsessive/compulsive ADRs (including overfocusing or perseveration), these ADRs were extraordinarily common – 25, 42, and 51%, respectively, for Castellanos et al. (1997), Borcherding et al. (1990) and Solanto and Wender (1989).

Despite such high rates for serious, severe ADRs, the rates and severity of ADRs should be expected to be much higher under routine clinical conditions. These conditions include much longer exposures to stimulants (months or even years instead of the 1–3 weeks in most of the controlled trials), often higher doses (more than the 0.3–0.6 mg/kg MPH in most of the controlled trials), polypharmacy, less adequate medical evaluations and supervision, and parents and teachers who are not educated to identify ADRs and to terminate treatment before they worsen.

[2]Solanto and Wender (1989) are not included since the children received only one dose per day for three days and overall ADRs were not listed.

3.6. Lessons from stimulant-induced psychosis

Many studies have compared stimulant-induced psychoses to the symptoms of schizophrenia (Ellinwood and Tong, 1996; Murray, 1998; Rebec and Bashore, 1984; Segal, Weinberger, Cahill, and McCunney, 1980). MPH is used experimentally to produce or worsen psychotic symptoms in adults diagnosed schizophrenic (Koreen, Lieberman, Alvir, and Chakos, 1997; Lieberman, Kane, and Alvir, 1987). Stimulant abuse is also known to cause a disorder that may remain chronic and become indistinguishable from schizophrenia (Flaum and Schultz, 1996).

3.7. Effects of selective serotonin reuptake inhibitors (SSRI's) in children

Psychoactive drugs will probably tend to produce mental disorders, including psychosis, at a higher rate in children than adults. For example, the rate for mania/hypomania induced by the SSRI-type antidepressant fluoxetine (Prozac) in all US clinical trials with adults was 0.7% (Physicians' Desk Reference, 1998, p. 860). In many of the short placebo-controlled clinical trials, it was even less (range of 0–0.8%). However, in a recent placebo-controlled clinical trial of fluoxetine in children and adolescents (Emslie, Rush, Weinberg, Kowatch, Hughes et al., 1997), three out of 48 children dropped out due to "manic symptoms" (6.2%).

King, Riddle, Chappell, Hardin, Anderson et al. (1991) described the "Emergence of self-destructive phenomena in children and adolescents, ages 10 to 17, during fluoxetine treatment". They found "self-injurious ideation or behavior appeared de novo or intensified" in 6 of 47 patients being treated with fluoxetine for obsessive-compulsive disorder. Four of the cases required hospitalization and three required "restraints, seclusion, or one-to-one nursing care". Riddle, King, Hardin, Scahill, Ort et al., 1990/1991) found that 12 of 24 children and adolescents, ages 8 to 16, developed two or more behavioral side effects in reaction to fluoxetine. Most of the youngsters were being treated for obsessive compulsive symptoms. The drug-induced effects included motor restlessness sufficient to cause concern to parents or teachers, insomnia, social disinhibition manifested by garrulousness or subtle impulsivity, and a subjective sense of discomfort due to restlessness, agitation, or excessive energy. The group included three children with attention deficit-hyperactivity disorder (ADHD), all of whom became worse. The behavioral abnormalities remained stable for weeks until the fluoxetine was reduced or stopped, and were easily confused with the children's original emotional problems. The seven children on placebo developed no such effects.

4. ADR Reports from the FDA Spontaneous Reporting System[3]

A review of the 2,821 reports of adverse drug events to the Spontaneous Reporting System for MPH (1985–March 3, 1997) revealed some potential often ignored ADRs (Food and Drug Administration, 1997). Here are some highlights (analyzed by Breggin, 1998b; methodology of analysis discussed in Breggin, 1998c; Kessler, 1993; Leber, 1992):

[3]The FDA lists criteria that can be used for "assessing" the "causal relationship" between a drug and adverse drug events that are reported to occur in association with it (Food and Drug Administration, 1996, p. 6; Breggin, 1997, 1998c). Spontaneous reports sent to the agency play a major role in driving FDA decisions concerning medications, including removal from the marketplace (General Accounting Office, 1990). Clinical trials are typically too small, too brief, too narrow in population, and often too biased toward positive medication effects to demonstrate relatively common but serious adverse effects (Breggin, 1997, 1998c; Leber, 1992).

(1) *More than 150 reports of liver abnormalities, mostly abnormal liver function tests*. This signal becomes especially important in the light of recent disclosures of liver tumors in mice (Dunnick and Hailey, 1995; National Toxicology Program, 1995).
(2) *Sixty-nine reports of convulsions, including 18 specified as grand mal*. The convulsive properties of stimulants are important but seldom mentioned in reviews.
(3) *Eighty-seven reports of drug dependency and addiction, and 30 reports of drug withdrawal*.
(4) *Two hundred fifty reports of hair loss*.
(5) *More than 50 reports of leukopenia* (abnormally low white blood cell count).
(6) *Hundreds of psychiatric ADRs*, including agitation (55), hostility (50), depression (48) and psychotic depression (11), abnormal thinking (44), hallucinations (43), psychosis (38), and emotional lability (33). There were more than 50 reports in the combined categories of overdose, overdose intentional, and suicide attempt.

5. Cardiovascular problems associated with MPH

Ellinwood and Tong (1996) summarized case reports of arrhythmias, shock, and cardiac muscle pathology (p. 20). The FDA's (1997) Spontaneous Reporting System collected 121 reports of cardiovascular problems (excluding hypertension). Most were arrhythmias and conduction problems, as well as 9 cardiac arrests and 4 heart failures.

AMPH, M-AMPH, and MPH are known to overstimulate the sympathetic nervous system. Several studies have now confirmed that they have a direct cardiotoxic effect (Karch, 1996, pp. 213–215).

In an electronmicroscopy study of mice and rats, Henderson and Fischer (1994) found that MPH has cardiotoxic effects in "minimum dosages (7.5 mg/kg/week in mice, 6.0 mg/kg/week in rats)" that "fell within the range of therapeutic dosage prescribed for patients with attention deficit disorder" (p. 77). Changes first appeared as early as 3 weeks and worsened over 14 weeks. Pathology (including various membrane abnormalities) was still apparent in the myocardium 12 weeks after terminating the injections. The injections produced similar results to those found by the authors in unpublished data of oral doses in animals. Henderson and Fisher believe that humans treated with routine clinical doses are at-risk for the development of cardiac pathology.

Ishiguro and Morgan (1997) in a study of ferret papillary (ventricular) muscles found that MPH at concentrations consistent with clinical usage produces a negative effect on muscle contractibility (direct negative inotropic effect or NIEs).

Psychostimulants also raise the blood pressure of children, adding further stress to the cardiovascular system. In adults, elevated blood pressure is considered a major health risk for stroke and heart attack.

African American youngsters are at higher risk for adult hypertensive disorders, including life-threatening kidney failure. Brown and Sexson (1988) conducted a placebo-controlled study of 11 black male adolescent boys taking 6 weeks of MPH (0.15, 0.30, and 0.5 mg/kg). They found a significant rise in blood pressure (placebo mean, 69 diastolic; drug mean, 83 at the higher doses). They recommended closer monitoring of the blood pressure of adolescent boys.

6. Stimulant-induced rebound, withdrawal, and dependence

According to Feussner (1998) of the U.S. Drug Enforcement Administration, "An extensive scientific literature spanning more than 30 years of research unequivocally indicates that MPH has a high abuse

liability. . . In clinical studies, MPH produces behavioral, psychological, subjective, and reinforcing effects similar to d-amphetamine and cocaine" (p. 202; also see American Psychiatric Association, 1994, pp. 204–12; Drug Enforcement Administration, 1995; Ellinwood and Cohen, 1972; Ellinwood and Tong, 1996; International Narcotics Control Board, 1995, 1997; Karch, 1996; Spotts and Spotts, 1980).

The existence of rebound confirms that stimulants transform brain function, making the brain physiologically dependent. Scahill and Lynch (1994) reported that behavioral rebound typically takes place as long as 5–10 hours after the last stimulant dose and includes excitability, insomnia, hyperactivity, and garrulousness.

A double-blind placebo-controlled study by Rapoport, Buchsbaum, Zahn, Weingartner, Ludlow et al. (1978) gave normal children age 6 to 12 years a single 0.5 mg/kg dose of AMPH. They found "a marked behavioral rebound" in 10 of 14 children starting approximately 5 hours after each dose. It consisted of "excitability, talkativeness, and, for three children, apparent euphoria" (p. 562).

Porrino, Rapoport, Behar, Ismond, and Bunney (1983), in another double-blind placebo controlled study, used portable activity monitors attached to hyperactive children to measure rebound hyperactivity from single doses of AMPH ranging from 0.23–0.75 mg/kg. The rebound began early in the evening and continued throughout the night during sleep. The hyperactivity "occurred at a time that might be particularly disruptive in terms of homework, mealtime, and bedtime" (p. 692). Rapoport et al. (1978) and Porrino et al. (1983) confirmed that rebound is probably a significant problem for most children who take psychostimulants.

The US Drug Enforcement Administration (1995, 1996) and the International Narcotics Control Board (1995, 1997) have warned about the risk of dependence and abuse among children who have previously been prescribed stimulants. Although few published clinical reports indicate that children become addicted to MPH or AMPH during routine use, abuse experts have observed a tendency for prescription drug use to lead to subsequent non-medical use (e.g., MacKenzie and Heischober, 1997; also see Murray, 1998). Recently, Lambert (1998; also see Lambert and Hartsough, in press) reported on a long-term prospective study indicating that the use of prescribed methylphenidate in children "is significantly and pervasively implicated. . . in cocaine dependence, and in lifetime use of cocaine and stimulants" (p. 198).

The DEA and INCB have warned that the escalating widespread availability of these drugs is increasing their abuse among youth in general. One DEA survey found that about 30–50% of adolescents in treatment centers reported the "nonmedical" use of MPH (Drug Enforcement Administration, 1996; Feussner, 1998). The freedom with which these drugs are prescribed to children makes them readily available and also encourages older youngsters to believe it is safe to experiment with them (Drug Enforcement Administration, 1995, 1996; Feussner, 1998). Accurate epidemiological data on such use were collected perhaps for the first time by the annual student survey of the Indiana Prevention Resource Center (1998):

> "Non-medical use of this drug has been noted in several Indiana communities. Our survey shows that about seven percent of Indiana high school students have used Ritalin® non-medically at least once, and that about 2.5% of high school students use it on a monthly or more frequent basis" (p. 2).

7. Growth suppression and inhibition

Klein, Landa, Mattes, and Klein (1988) measured rebound growth in height and weight in children during two summers of withdrawal from MPH. In the first summer, the drug-free children gained 0.9 kg more than the control group but height was unaffected. After the second summer, the drug-free group

grew an additional 1.5 cm. The rebound corresponded with Klein and Mannuzza's (1988) estimated 1.8 cm decrement in growth for children averaging 9.2 years of age after two years of continuous treatment with MPH. Safer, Allen, and Barr (1975) found that MPH reduced the expected monthly weight gain by 25%. When MPH was stopped, the rebound produced a weight gain of 68% per month above the expected. This indicates drastic abnormalities in growth rate during and after the drug exposure. Height rebound was also significant but less dramatic.

It is very misleading to view growth reduction followed by growth escalation as normal. Both processes are abnormal. There is no guarantee that the rebound growth returns the child to a normal state of brain or body functioning. Recapturing lost growth will depend on how long the children remain on the drug and then how long they are off the drug. It will also depend on age. Increasing numbers of children are being continued on stimulant medication into young adulthood and even later. Under such circumstances, there will be no significant rebound.

A study by Spencer, Biederman, Harding, O'Donnell, Faraone et al. (1996) attempted to show that growth deficits are related to ADHD rather than to MPH. However, the study has numerous flaws. The control group was one year older (mean of 15.5 vs. 14.5 years old; $p = 0.03$, Table 1, p. 1463) than the ADHD group. Since age is the most significant confounding factor for height and weight, this invalidates the control group. Speculative statistical manipulations were required to compensate for this difference. Also, the control group was skewed toward young adults over age eighteen compared to the ADHD group (38/109 [34%] vs. 25/124 [20%], note to Table 2, p. 1464). Yet there were more children under age twelve in the control group (25 of 109 [23%] vs. 17 of 124 [14%]). Indeed, there were so few children under age twelve in the ADHD group as to cast doubt on the entire study. Furthermore, Spencer et al.'s entire data for "growth" consisted of one height and weight measurement for each child: "Growth measures were obtained only at the 4-year follow-up assessment" (p. 1462). This is therefore not a "growth" measure, but one measure of height and weight at one time in the child's life. It required considerable speculation to justify the value of these limited data. For unknown reasons, readily available earlier measurements for most children were not used to make the study longitudinal. Meanwhile, studies that Spencer et al. attempted to supersede – such as Klein et al. (1988) and Safer et al. (1975) – utilized multiple longitudinal growth measurements over a period of time with the children on and off the drugs to observe growth suppression and rebound.

7.1. Mechanism of growth suppression

While the anorectic effect of stimulants causes some growth inhibition, the major effect probably results from disruption of the hypothalamic-pituitary axis with disruption of the growth hormone cycle (Brown and Williams, 1976; Joyce, Donald, Nicholls, Livesey, and Abbott, 1986; Shaywitz, Hunt, Jatlow, Cohen, Young et al., 1985; reviewed in Dulcan, 1994, and Jacobvitz, Sroufe, Stewart, and Leffert, 1990). A substantial amount (20–40%) of growth hormone release takes place during 60–90 minutes after sleep, and this part of the cycle is suppressed by stimulants (Barter and Kammer, 1978; Aarskog Fevang, Klove, Stoa, and Thorsen, 1977). It is probably due to drug-induced changes in dopaminergic neurotransmission in the hypothalamic-pituitary axis. Citing the literature, Jacobvitz and her colleagues (1990) observed that "disturbances in the normal release of growth hormone may not only influence height velocity but may also impact on other critical aspects of physical development such as sexual maturation" (pp. 683–684). Stimulants also disrupt the production of prolactin, a hormone that in part controls sexual development.

8. 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 CNS ADRs.

8.1. Gross brain dysfunction caused by stimulants

Volkow, Wang, Fowler, Logan, Angrist et al. (1997) in a PET (photon emission tomography) study of normal adults given MPH found a reduced relative metabolic rate in the basal ganglia and other changes correlating with the distribution of dopamine receptors. Wang, Volkow, Fowler, Ferrieri, Schlyer et al. (1994), using the PET in normal adults, measured the effect of MPH (0.5 mg/kg IV) and found that MPH decreased the overall flow of blood by 23–30% into all areas of the brain. The decrement was maintained when last tested (30 minutes after the final dose). The researchers warned that these effects "should be considered when prescribing this drug chronically" (p. 143).

Bell, Alexander, Schwartzman, and Yu (1982), using rat brain tissue, found that MPH reduced glucose metabolic rates in the motor cortex and increased in the substantia nigra and other deep structures. Porrino and Lucignani (1987), using MPH (1.25 to 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. PETs also reveal that normal adults exposed to an injection of 0.15 mg/kg of AMPH will undergo increased glucose metabolism throughout most of the brain (Ernst, Zametkin, Matochik, Schmidt, Jons et al., 1997). These studies demonstrate the effect of stimulant drugs on brain of normal animals or persons.

8.2. Abnormalities of brain chemistry caused by stimulants

Studies show that MPH and AMPH bind to receptors throughout most of the forebrain, including the basal ganglia and frontal cortex (Unis, Dawson, Gehlert, and Wamsley, 1985). Many studies confirm AMPH-induced persistent abnormalities in biochemical structure and function (Robinson and Badiani, 1998).

8.3. Methamphetamine

M-AMPH is FDA-approved for the treatment of behavioral disorders in children. However, its capacity to cause neurotoxicity – including the destruction of brain cells – has long been demonstrated in animals. Chronic exposure to M-AMPH can produce irreversible loss of receptors for dopamine and/or the death of dopaminergic and other neurons in the brain (Melega, Raleigh, Stout, Lacan, Huang et al., 1997b; Schmued and Bowyer, 1997; Sheng, Ladenheim, Moran, Wang X.-B., and Cadet, 1996; Sonsalla, Jochnowitz, Zeevalk, Oostveen, and Hall, 1996; Wagner, Ricaurte, Johanson, Schuster, and Seiden, 1980; Zaczek, Battaglia, Contrera, Culp, and De Souza, 1989). Melega et al. (1997b), for example, found persistent "neurotoxic" changes in dopamine function (dopamine depletions of 55–85%) in vervet monkeys at 10–12 weeks with doses that were relatively small and acute (2 doses of 2 mg/kg 4 hours apart).

After subjecting mice to M-AMPH, Sonsalla et al. (1997) also demonstrated dopaminergic cell loss of 40–50% in the substantia nigra. The doses were large but acute (4 injections at 10 mg/kg) at two-hour intervals. Battaglia et al. (1987) found that large chronic doses of M-AMPH cause the death of serotonergic nerves in animals. The changes are 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 six months or more, indicating irreversible damage to that system as well (Wagner et al., 1980). Thus M-AMPH causes destructive changes in all three of the neurotransmitter systems that are stimulated by the drug (also see Zaczek et al., 1989).

M-AMPH has been demonstrated to be irreversibly neurotoxic. *On this basis alone, it should no longer be prescribed to children.*

8.4. Brain atrophy caused by methylphenidate

Nasrallah, Loney, Olson, McCalley-Whitters, Kramer et al. (1986) 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 that "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, Castellanos, Casey, Kozuch, King et al., 1994; Hynd, Semrud-Clikeman, Lorys, Novey, Eliopulos et al., 1991; Lou, Henriksen, and Bruhn, 1984). 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.

The differences found between normal brains and those of children diagnosed with ADHD are probably due to medication effects. At the recent NIH Consensus Development Conference on Attention Deficit Hyperactivity Disorder and Its Treatment, Swanson presented a paper reviewing the range of genetic and brain scan studies purporting to show "Biological Bases of ADHD" (Swanson and Castellanos, 1998). A number of the studies involved Swanson's coauthor, Castellanos (Castellanos, Giedd, Marsh, Hamburger, Vaituzis et al., 1997; Giedd et al., 1994). My own review (Breggin, 1998a) indicates that some of the studies fail to mention prior drug treatment while drawing on populations, such as the NIH clinics, where the children are likely to have extensive prior drug exposure (e.g., Giedd et al., 1994). Other studies allude to previous drug treatment without attempting to correlate it with the brain changes (Hynd et al., 1991).

In the unpublished public discussion following Swanson's presentation, neurologist Frederick Baughman, 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 explained that untreated children are difficult to obtain in the United States.

After hearing all the scientific presentations and discussions, the consensus conference panel concluded "there are no data to indicate that ADHD is due to a brain malfunction" (National Institutes of Health, 1998, p. 2). This important conclusion has a sound basis. 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 addition, stimulants are known to disrupt growth hormone which could affect brain development. By contrast, any association between ADHD and brain pathology remains speculative and unlikely. No valid ADHD syndrome has been demonstrated and no neurological or other physical findings have been found in association with it (see below). *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.*

8.5. Dextroamphetamine

AMPH (Dexedrine, Adderall) is another FDA-approved drug for treating behavioral problems in children. Yet the existence of AMPH neurotoxicity has also been documented for more than thirty years and the mechanism continues to be refined (Huang, Wan, Tseng, and Tung, 1997).

Wagner et al. (1980) found that treating rhesus monkeys with AMPH leads to a long-lasting loss of dopamine and dopamine uptake sites (receptors). Juan, McCann, and Ricaurte (1997) confirmed that AMPH 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 4 doses of 10 mg/kg spaced 2 hours apart.

Robinson and Kolb (1997) treated rats with AMPH twice a day for 5 days a week for a total of 5 weeks with a dose that was gradually increased from 1 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 their spines. In a microdialysis study, Weiss, Hechtman, Milroy, and Perlman (1997) treated rats with AMPH (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, DeJonghe, and Robinson (1997) administered a rising dose of AMPH (1 to 10 mg/kg over 10 days) to rats and then withdrew the animals for 1 to 30 days. Using in vivo microdialysis, they found changes lasting 1 month in norepinephrine concentrations in the hippocampus as well as altered responses to AMPH challenge. They concluded that AMPH produces biochemical adaptations that far outlast the acute drug effects and may account for both transient and more persistent discontinuation effects in humans.

Melega et al. (1997b) used PET in vervet monkeys to determine presynaptic striatal dopamine function following the administration of AMPH 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 AMPH-treated animal at 32 weeks. Biochemical analysis showed decreased striatal dopamine concentrations of 55% at 10–12 weeks. They concluded that acute AMPH doses produce long-lasting "neurotoxicity". In another study using larger, more chronic doses (4–18 mg/kg over 10 days), Melega, Raleigh, Stout, Huang, and Phelps (1997a) found a gradual recovery from neurotoxicity in the striatum over a two-year period after termination of treatment.

Addressing the use of stimulants for the treatment of children, Ellinwood and Tong (1996) concluded: "Drug levels in children on a mg/kg basis are sometimes as high as those reported to produce chronic CNS changes in animal studies" (p. 14). Juan et al. (1997) warned that when psychostimulants are indicated as in ADHD, "it would seem prudent to prescribe methylphenidate rather than AMPH, since methylphenidate appears to lack the DA neurotoxic potential that has been well documented for amphetamine" (p. 174).

AMPH, like M-AMPH, has been demonstrated to be irreversibly neurotoxic and, on this basis alone, should not be prescribed for children.

8.6. Methylphenidate

Mach, Nader, Ehrenkaufer, Line, Smith et al. (1997) used PET in Rhesus monkeys to confirm the similarity of effects among MPH, AMPH, M-AMPH, and cocaine on dopamine release in the basal ganglia. It should therefore be expected that MPH will produce the same neurotoxic effects as other psychostimulants.

Barnett and Kuczenksi (1986) found downregulation of dopamine receptors after MPH administration to animals but did not test for recovery. Mathieu, Ferron, Dewar, and Reader (1989) found reduction of the density of the norepinephrine receptors after treatment with MPH. Lacroix and Ferron (1988) after 7 days of MPH 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) found dopamine depletion in the mouse striatum 5 days after terminating treatment with MPH but not two weeks after.

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

8.7. SSRIs

The selective serotonin reuptake inhibitors (e.g., fluoxetine, paroxetine and sertraline) cause downregulation – a compensatory reaction to over-stimulation characterized by a loss of serotonin receptor sensitivity and/or number. The loss of serotonin receptors begins within days of the initiation of treatment in animals (Wamsley, Byerley, McCabe, McConnell, Dawson et al., 1987; Wong and Bymaster, 1981; Wong, Reid, Bymaster, and Threlkeld, 1985; reviewed in Breggin, 1997; Breggin and Breggin, 1994). At lower doses, both increases and decreases in receptor density are reported to take place in various areas of the brain (Wamsley et al., 1987; also see Fuller, Perry, and Molloy, 1974). Up to 60% of some classes of serotonin receptors can disappear. The downregulation is widespread, involving the frontal lobes and cortex.

These are ominous findings in regard to the brain function of children and adults. Yet, no studies have attempted to demonstrate whether or not recovery takes place.

9. Long-term adverse clinical effects

There have been few long-term follow-up studies. However, Castellanos et al. (1997) provide valuable data in their long-term follow up of a series of clinical trials for MPH and AMPH conducted at NIH on children who were comorbid for Tourette's syndrome.

Of 22 original enrolled subjects, two dropped out due to probable ADRs ("severe exacerbation of tics" and "excessively disruptive" behavior) (p. 591) and one dropped out due to "vomiting, which subsided when the medication was discontinued" (p. 593). Three more discontinued medication at the end of the trials due to increased tic severity on both drugs. This constitutes a 23% drop-out rate due to ADRs.

Of 16 completers, 13 were followed for 6–36 months. No information is given about the fate of the three other children in the high dose cohort. Of the eight children prescribed MPH at the end of the study, six were eventually put on additional psychiatric drugs, including one on haloperidol. Of the five put on AMPH, the total put on other drugs is not mentioned, but three of the children were prescribed haloperidol for a time. Thus, four of 13 children required treatment with haloperidol, a drug that causes severe and sometimes irreversible ADRs, including tardive dyskinesia. One of the children on haloperidol was also hospitalized and then placed in residential treatment.

A telephone follow-up was conducted for 21 of the original 22 children 1–4 years after study entry. A total of six subjects had been discontinued from stimulants due to "deleterious effects on tics" (p. 593).

Fifteen children remained on stimulants, "most" on additional psychiatric drugs as well (p. 594). The study has limits (small size, limited to children comorbid with Tourette's); however, in terms of long-term follow up, the children clearly continued to have severe problems despite, or because of, their medication treatment. Many had worsening of their tics due to medication. Others had worsening of obsessive-compulsive symptoms that may have been due to medication as well.

Some authors of follow up studies have concluded that children diagnosed with ADHD grow up to do poorly as young adults. These conclusions have been used to justify early drug interventions. However, the subjects who did poorly were young adults who had been diagnosed and treated with stimulants as children (Mannuzza, Klein, Bessler, Malloy, and LaPadula, 1993; Weiss, Hechtman, Milroy, and Perlman, 1985).

Mannuzza, Klein, Bessler, Malloy, and LaPadula (1998) recently conducted a study with a proband group that consisted of "clinically diagnosed, white boys of average intelligence who were referred by teachers to a psychiatric research clinic at an average age of 7.3 years" and then evaluated at a mean age of 24.1 years. They found a significantly higher prevalence of antisocial personality disorder and nonalcohol substance abuse. The study did not take into account the possibility that the development of antisocial personality disorder and drug abuse is an untoward effect of diagnosis and treatment. Furthermore, the study group was from a significantly lower SES than the control group. Every symptom of antisocial personality disorder is associated with low SES (Breggin and Breggin, 1998).[4]

Furthermore, the study undermined the concept that ADHD is a chronic disorder. In a group of children diagnosed with relatively severe ADHD, only 4% retained the diagnosis at the average age of 24. If the ADHD behaviors do not persist into young adulthood, how do they become transformed into antisocial behaviors and nonalcoholic drug abuse in young adulthood? These negative outcomes were probably not caused by "ADHD" but by a combination of drug treatment, psychiatric stigmatization, and lower SES. These studies indicate that treatment for ADHD probably contributes to a negative iatrogenic outcome, including nonalcoholic drug abuse.

10. Psychological responses to stimulant medication

Diagnosing and medicating children teaches them to shift responsibility and the locus of control from within themselves to outside sources, including "the pill" (Breggin, 1998a; Jensen, Bain, and Josephson, 1989; Sroufe and Stewart, 1973).

Early in the history of psychostimulants, Sroufe and Stewart (1973) observed that children who take stimulants have a tendency to think that they are not responsible for their behavior. These findings were confirmed by Sleator, Ullmann, and von Neuwman (1982) who found that most children reported adverse psychological reactions to unspecified stimulant medications. Forty-two percent "disliked" or "hated" the drug. Six children reported feelings of "depression" in reaction to the drug, such as "I don't want to play", "It makes me sad. . ." and "I wouldn't smile or anything". Seven reported a "drugged feeling", including being "spaced out", "It numbed me", and "It takes over of me; it takes control". Ten reported negative changes in self-perceptions, such as "It makes me feel like a baby" and "Don't feel like myself". One reported rebound, stating he was "wild" after the medication wore off.

[4]In abbreviated form, the criteria for antisocial personal disorder from the *DSM-IV* (American Psychiatric Association, 1994) are (1) unlawful behavior and arrests, (2) conning, lying, etc., (3) impulsivity and failure to plan ahead, (4) fights and assaults, (5) reckless disregard for safety of self and others, (6) poor work behavior or financial responsibility, and (7) lack of remorse about harmful actions. The frequency of these characteristics is of course increased by growing up in urban poverty.

The researchers were troubled by an intensive "pervasive dislike among hyperactive children for taking stimulants" (p. 478). Only 29% of the children could be rated "positive" or "mildly positive" toward taking the drug. While only four children said so openly, the researchers believed that 16 of them felt that "taking medication was a source of embarrassment to them" (p. 477).

Sleator et al. found that many children lied to their doctors to feign medication compliance and enthusiasm for the drug. The main tendency of the children was to "overstate their enthusiasm for drug treatment and their adherence to the prescribed regimen" (p. 478). For a various reasons, children will almost always tell authority figures what they imagine they want to hear. Drug-induced compliance and apathy would tend to reinforce this tendency.

When told what they want to hear by children, adults too often will accept it as the truth. Sleator et al. found that "Of 23 interviews proven totally or partially unreliable, 21 were coded by raters as having good credibility" (p. 476). The children, while distorting the truth, came across as "sincere and believable" to the doctor and two other raters. An "Editors' Note" cites a reviewer who raised the possibility that a "great many" children are "thought to be improved because of their medication but are failing to take it" (p. 474).

Jensen et al. (1989) studied "Why Johnny Can't Sit Still: Kids's Ideas On Why They Take Stimulants". The completed study has remained unpublished but was briefly summarized in *Science News* (Bauer, 1989). Using interviews, child psychiatric rating scales, and a projective test entitled "Draw a Person Taking the Pill", Jensen et al. systematically evaluated twenty children given MPH by their primary care physicians. The authors found that taking MPH produced the following negative psychological, moral, and social effects: (1) "defective superego formation" manifested by "disowning responsibility for their provocative behavior"; (2) "impaired self-esteem development"; (3) "lack of resolution of critical family events which preceded the emergence of the child's hyperactive behavior"; and (4) displacement of "family difficulties onto the child".

Many of the children concluded that they were "bad" and that they were taking the pill to "control them". They often ascribed their negative conduct to outside forces, such as eating sugar or failing to take their pill, and not to themselves or their own actions. Jensen et al. warned that the use of stimulant medication "has significant effects on the psychological development of the child". They found the use of medication distracts parents, teachers, and doctors from paying needed attention to problems in the child's environment.

In a four week low-dose double-blind study, Efron, Jarman, and Barker (1998) investigated the perceptions of children (average age 9 years and 3 months) taking stimulants and their parents. Although a majority of the children viewed the drug favorably, "there was a relatively large number of subjects who reported negative feelings toward the medication" (p. 290). The percentage of children feeling worse or more worse while taking medication was 18.8% for AMPH and 12.7% for MPH. One quarter of the time, parents thought the children were improved when the children did not think so. The authors recognized that the children may have pretended to like the treatment in order to please the adults.

The paucity of studies on how children feel about stimulants reflects on the nature of the diagnosis itself which is oriented to behaviors that cause difficulty for adults rather than to the suffering or the needs of the children.

11. Mistaking ADRs for mental disorders requiring further drug treatment

Clinicians and even researchers seem to frequently confuse stimulant-induced ADRs with evolving mental disorders in the children. Stimulants, for example, very frequently cause symptoms of depression

(including apathy and lethargy) and obsessive/compulsive disorder. Less frequently, they cause mania. Based on my clinical practice and on anecdotal reports to the International Center for the Study of Psychiatry and Psychology (1998), physicians often fail to identify stimulant-induced ADRs that affect mental function. They mistakenly attribute them to newly emerging psychiatric disorders in the children. Instead of stopping the stimulants, new psychiatric medications are added. The increasing diagnosis of depression, obsessive/compulsive disorder, and mania in children may be due in part to unrecognized stimulant adverse effects.

12. Developmental toxicity: the dangers of exposing the child's growing brain to psychoactive medications

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 (Chugani, Phelps, and Mazziotta, 1987; Huttenlocher, 1990; for discussion, see Vitiello, 1998). In 1995 the National Institute of Mental Health (NIMH) and the Food and Drug Administration held a conference on the future testing and use of psychiatric drugs for children. In his remarks at the Conference, Vitiello made a critical disclosure:

> "Now, 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 to environmental input (Koslow, 1995). The brain creates new brain cell synapses and prunes old ones in response to experience (Greenough and Black, 1992; Weiler, Hawrylak, and Greenough, 1995). 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.

13. Psychostimulant mechanism of action on behavior

Stimulant-induced social inhibition and obsessive/compulsive or perseverative behaviors (Tables 1–4) seem indistinguishable, except at times in degree, from the sought-after clinical effects (behavioral changes) in children diagnosed with ADHD and given stimulants. Animal literature points to the nature of these basic behavioral effects.

13.1. Psychostimulant behavioral effects on animals

Innumerable research studies demonstrate that psychostimulants consistently cause two specific, closely related ADRs in animals:

First, *stimulants suppress normal spontaneous or self-generated activity, including socialization* (Arakawa, 1994; Hughes, 1972; Randrup and Munkvad, 1967; Sams-Dodd and Newman, 1997; Schiorring, 1979, 1981; Wallach, 1974). Exploration, novelty seeking, curiosity, purposeful locomotion, and escape behaviors are diminished. Inhibitions in socialization are demonstrated by reductions in approach

behavior, interactions, mutual grooming, and vocalizations. There may be avoidance of contact with the cage mate, obliviousness to other animals, and increased fearfulness.

Second, *stimulants promote stereotyped, obsessive/compulsive, overfocused behaviors that are often repetitive and meaningless* (Bhattacharyya, Ghosh, Aulakh, and Pradhan, 1980; Conti et al., 1997; Costall and Naylor, 1974; Hughes, 1972; Koek and Colpaert, 1993; Kuczenski and Segal, 1997; Melega et al., 1997a; Mueller, 1993; Randrup and Munkvad, 1967; Rebec and Bashore, 1984; Rebec and Segal, 1980; Rebec, White and Puotz, 1997; Sams-Dodd and Newman, 1997; Segal, 1975; Segal et al., 1980; many early studies reviewed in Wallach, 1974, and Schiorring, 1979). The effects may be demonstrated by limited or constricted pacing, reduced or localized self-grooming, staring out the cage, staring at small objects, repetitive head movements, and other compulsive behaviors, such as picking, scratching, gnawing, or licking limited areas of the body or objects.

These dual effects can occur in rats at doses as low as 0.63 mg/kg MPH (Koek and Colpaert, 1993) or 0.3 mg/kg AMPH (Rebec and Bashore, 1984). Sometimes all normal behaviors cease (Randrup and Munkvad, 1967; Wallach, 1974). Some behavioral changes may persist long after withdrawal from stimulants. Melega et al. (1997a) found that ten days of AMPH treatment in vervet monkeys resulted in a six month reduction in affiliation or social behavior.

While stimulants sometimes seem to increase activity, "Amphetamine-induced locomotion is stereotyped because rather than occurring across the entire periphery of the cage, as in non-drugged rats, it is expressed as perseverative running back and forth along a cage wall" (Rebec and Bashore, 1984, p. 154). In other words, *the quality of the activity is diminished from that of normal spontaneous, exploratory, or social behaviors, to compulsive, narrowly focused behaviors*.[5]

As an aspect of drug-induced stereotypical or compulsive behavior, animals become less aware of routine environmental stimuli and hence less distractible by loud noises, quick movements, or other animals (Sams-Dodd and Newman, 1997).

13.2. Psychostimulant behavioral effects on humans

Drawing on data from controlled clinical trials, Table 4 provides a list of stimulant ADRs that are easily misdiagnosed as improvements in the behavior of children diagnosed with ADHD. That is, they can potentially be misinterpreted as "beneficial". Many of these ADRs parallel the effects reported in animal studies. Overall, spontaneous and social behaviors are suppressed, and obsessive, perseverative behaviors are caused or increased. The abnormal movements seen in the animals are also seen in stimulant-treated children, including rhythmic head movements, picking or rubbing the body, and lip movements (Borcherding et al., 1990) (Table 3).

Just as stimulant-induced behavioral changes occur in healthy mammals, stimulant effects on human behavior are independent of any psychiatric diagnosis or disorder. They represent a specific drug effect on all children (Dulcan, 1994; Dulcan and Popper, 1991; Rapoport et al., 1978, 1980; Swanson (circa 1993); Swanson et al., 1992; Taylor, 1994). Whether or not children seem to be overactive, impulsive, or distractible, psychostimulants will subdue these behaviors.

A number of investigators have noted the parallels between stimulant effects in animals and in humans (e.g., Schiorring, 1981). Robbins and Sahakian (1979) suggested that stimulant effects on children may result from the two basic behavior effects seen in animals: the reduction in "social interaction" and the

[5]My own earliest scientific publications reported the subduing effect on the exploratory behavior of rats caused by long-acting doses (intramuscular in oil) of the endogenous stimulant epinephrine (Breggin, 1964, 1965).

promotion of "over-focusing" or "cognitive inflexibility" (stereotypy). They also suggested that the drug-induced reduction in socializing, combined with the tendency to play alone with objects, make medicated children seem more "compliant" (p. 946).

Rebec and Bashore (1984) summarized the vast literature on the behavioral effects of AMPH on both animals and humans: "This syndrome consisted of repetitive, apparently meaningless behaviors, behaviors that collectively were called stereotyped behaviors" (p. 153).

Rie, Rie, Stewart, and Ambuel (1976) referred to "the typical suppressive behavioral effects" of the drug. In their double-blind placebo-controlled study, MPH-treated children became:

> ". . . distinctly more bland or "flat" emotionally, lacking both the age-typical variety and frequency of emotional expression. They responded less, exhibited little or no initiative and spontaneity, offered little indication of either interest or aversion, showed virtually no curiosity, surprise, or pleasure, and seemed devoid of humor. Jocular comments and humorous situations passed unnoticed. In short, while on active drug treatment, the children were relatively but unmistakably affectless, humorless, and apathetic" (p. 258).

Buhrmester, Whalen, Henker, MacDonald, and Hinshaw (1992) conducted a double-blind placebo-controlled study with 0.6 mg/kg of MPH administered for one week to 19 hyperactive boys age 7–12 who were acting as leaders for groups of small, unfamiliar children. They found that MPH caused mild dysphoria and suppressed social behavior: "Medication had a general dampening effect on hyperactive children's social behavior" (p. 116). The boys were "less responsive" to other children, displaying less "prosocial" behavior and less "social engagement". At one point in their article they described this as a "normalization" (p. 112) but more frequently as an ADR. Ellinwood (in Kramer, Lipton, Ellinwood, and Sulser, 1970) pointed out that humans sometimes use stimulants to decrease their reactivity in social groups.

Panksepp (in press) pointed out that stimulant drugs are "powerful play-reducing agents". He warned that "this fact has not penetrated either the popular or professional imaginations". Stimulants reduce the natural rambunctious and impulsive play of children (Panksepp, Normansell, Cox, Crepeau, and Sacks, 1987). The suppression of play – a basic maturational process – may have profound (if immeasurable) consequences for the growing child and later adult.

13.3. Extreme expressions of the sought-after clinical effect

Schiorring (1981) compared the effects of psychostimulants on the behavior of animals, addicts, and children. He describes how stimulant addicts develop an abnormally narrow range of focus so that they are unaffected by strong stimuli, including crying and aggression, in the same room. Schiorring observed: "Social isolation, social withdrawal or 'autism' are behavioral states that are found in both animals and man after amphetamine administration" (p. 116).

Swanson et al. (1992) reviewed "cognitive toxicity" caused by MPH:

> "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 "somber", "quiet", and "still" may produce social isolation by increasing "time spent alone" and decreasing "time spent in positive interaction" on the playground" (p. 15).

Arnold and Jensen (1995) also comment on the "zombie" effect caused by stimulants:

> "The amphetamine look, a pinched, somber expression, is harmless in itself but worrisome to parents, who can be reassured. If it becomes too serious, a different stimulant may be more tolerable.
> The behavioral equivalent, the "zombie" constriction of affect and spontaneity, may respond to a reduction of dosage, but sometimes necessitates a change of drug" (p. 2307).

These effects are simply exaggerations of the behavior routinely observed in children and animals subjected to clinical doses of psychostimulants. These ADRs, even when exaggerated, are likely to be considered improvements by those who seek to impose greater control over children.

13.4. Causing obsessive/compulsive overfocused behavioral abnormalities

The twin effects of the stimulants – the suppression of spontaneous behavior and the enforcement of obsessive behavior – often expresses itself as drug-induced asocial overfocused behavior in children. Dyme, Sahakian, Golinko, and Rabe (1982) studied "perseveration induced by methylphenidate" in hyperactive children who were thought to be doing well on treatment. Using a single dose of 1.0 mg/kg, they found that 4 out of 5 children "worsened in a measure of flexibility of thinking". Teachers and parents continued to rate their behavior improved, even when the children displayed "excessive focusing of attention".

Dyme et al. concluded, "Our results suggest that with psychomotor stimulants, improved focusing of attention may be accompanied by increased perseveration (difficulty in changing mental set from one idea to another)" (p. 272). They warned, "Clinicians should be aware that psychomotor stimulant drugs may produce over-focusing of attention or perseveration in hyperactive children" (p. 272).

As described earlier, Solanto and Wender (1989) found that one dose of MPH caused ineffective, persistent, compulsive "cognitive perseveration" in 8 of 19 children:

> "As the children continued, the quality of the response appeared to decline, with an increase in the number of responses that did not make sense, were vague, tangential, or repetitive. This phenomenon was observed to occur at all dosages" (p. 900).

Borcherding et al. (1990), as already noted, observed obsessive/compulsive perseverative behaviors in 51% of children (descriptions in Table 3). In regard to their most serious ADR, a child who was dropped from the study after developing tics and anxiety, the authors remarked: "It is important to note, however, that while this subject had a severe adverse effect of amphetamine, his behavior and performance in school did improve" (p. 92). The "repetitious, perfectionistic, overfocused behaviors" (p. 90) produced by the stimulants certainly can cause a child to focus on rote educational tasks. These children received only 9 weeks of stimulant treatments, but obsessions have been reported to develop several months to 7 years after the beginning of treatment (Koizumi, 1985).

In their concluding statement, Borcherding et al. (1990) confirmed the principle of *continuum of toxicity*: "Overfocused and compulsive behaviors may seem to be positive signs in some cases, and teachers and parents may thus overlook them or not report them unless specifically asked to do so" (p. 93).

13.5. Confusing ADRs with improvement (Table 4)

The previous observations and discussion suggest that the "therapeutic" effect of stimulants in children is an early sign of the basic toxic effect. The sought-after effect – reduced spontaneous behavior and increased "focus" – is actually a manifestation of toxicity.

Table 4
Stimulant adverse drug reactions (ADRs) potentially misidentified as "therapeutic" or "beneficial" for children diagnosed ADHD. Data from 20 controlled clinical trials

Obsessive compulsive ADRs	Social withdrawal ADRs	Behaviorally suppressive ADRs
Stereotypical activities (4, 14)	Social withdrawal and isolation (13, 14, 16)	Compliance, especially in structured environments (2*, 7*, 8*, 17*)
		Reduced curiosity (18)
Obsessive-compulsive behavior (4, 6, 14, 18)		Somber (19)
	General dampening of social behavior (5)	Subdued (14)
Perseverative behavior (1, 4, 6, 9, 14)		Apathetic; lethargic: "tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive" (14; also 11, 16)
	Reduced social interactions, talking, or sociability (1*, 2*, 5, 8, 10**, 14)	
Cognitive perseveration (4, 18)		Bland, emotionally flat, affectless (15, 20)
		Depressed, sad, easy/frequent crying (3, 10**, 11, 14, 16, 17)
Inflexibility of thinking (9, 18)	Decreased responsiveness to parents and other children (2*, 5, 10**)	Little or no initiative or spontaneity (15)
Over-focusing or excessive focusing (4, 9, 18)		Diminished curiosity, surprise, or pleasure (15)
		Humorless, not smiling (15)
	Increased solitary play (8*, 17)	Drowsiness (10)
	Diminished play (1*)	Social inhibition with passive and submissive behaviors (12)

Note: *Considered positive or therapeutic by the source; **Considered possibly positive or therapeutic by source; 1. Barkley and Cunningham (1979); 2. Barkley et al. (1985); 3. Barkley et al. (1990); 4. Borcherding et al. (1990); 5. Buhrmestar et al. (1992); 6. Castellanos et al. (1997); 7. Cotton and Rothberg (1988); 8. Cunningham and Barkley (1978); 9. Dyme et al. (1992); 10. Firestone et. al. (1998); 11. Gittelman-Klein et al. (1976); 12. Granger et al. (1993); 13. Handen et al. (1990); 14. Mayes et al. (1994); 15. Rie et al. (1976a); 16. Schachar et al. (1997); 17. Schleifer et al. (1975); 18. Solanto and Wender (1989); 19. Tannock et al. (1989); 20. Whalen et al. (1989).

Table 4 (also see Tables 1–3) compiles ADRs – drawn from controlled clinical trials – that are mistakenly seen as "improvements". The first column, "Obsessive Compulsive ADRs", lists behaviors directly related to the increased willingness of children to do school work and chores that they would ordinarily find boring, meaningless, or frustrating. By struggling compulsively over their work, they may seem to be learning, even when they are not. The second column, "Social Withdrawal ADRs", describes drug reactions that render children more quiet, less seemingly needy, and less troublesome. The third column, "Behaviorally Suppressive ADRs", includes behaviors related to enforced compliance, submissiveness, and apathy. If the children are "out of control" due to improper discipline, boredom, or other psychological and social problems, their behavior will nonetheless be suppressed so that they appear "more normal". In reality, the drugs are suppressing normal spontaneous behavior and enforcing abnormal obsessive/compulsive behavior.

13.6. The importance of spontaneous activities in the young

From puppies and young chimpanzees to children, healthy young creatures spend much of their waking time in active, spontaneous activities described by researchers as socializing, play, mastery, self-determination, exploration, discovery, novelty-seeking, and curiosity. The young of most species often harass and stress their parents by vigorously expressing needs that range from hunger and security to play. High energy – *and especially the capacity to make powerful demands upon parents and other significant adults* – is part of survival. High energy in a child becomes destructive to the child only when adults cannot or will not take the necessary steps to teach the child to channel it into creative outlets.

In pre-industrial times, cultures did not expect children to sit still for hours at a time in confined spaces indoors in supervised groups as their primary method of preparing for adult life. Even today, the conditions imposed on children in school do not correspond to the requirements of the adult work place which more often rewards independent, spontaneous activity.

Recent animal research using electronmicroscopy demonstrates that the full development of the mammalian brain, as measured by numbers of synaptic connections, depends upon the opportunity for these spontaneous activities (Greenough and Black, 1992; Weiler et al., 1995). The lessons for our children seem obvious: any drug-induced suppression of their spontaneous activities will also suppress the development of the brain.

14. Physical mechanisms of drug effect on behavior

The dopaminergic effects of the stimulants, including disruption of basal ganglia function, probably play a major role in the production of the whole spectrum of CNS ADRs, especially the complex involving perseverative and obsessive/compulsive behavior, stereotypical behavior, and abnormal movements (Bell, Alexander, Schwartzman, and Yu, 1982; Conti, Segal, and Kuczenski, 1997; Mueller, 1994; Rebec, White, and Puotz, 1997). Spontaneous activity is often suppressed by drugs such as the neuroleptics, as well as by disorders such as Parkinson's disease, that disrupt dopaminergic and basal ganglia function (Breggin, 1990, 1993). MPH, for example, induces a significant reduction in metabolism in the basal ganglia (Volkow et al., 1997).

15. ADHD-like behaviors and the mechanism of stimulant action

The use of psychostimulants is usually based on the conviction that ADHD is a valid disorder or syndrome, yet considerable controversy surrounds the diagnosis, including its validity (Armstrong, 1995; Barbarin and Soler, 1993; Breggin, 1998a; Breggin and Breggin, 1996; Carey, 1998; McGuinness, 1989; National Institutes of Health, 1998; Schneider and Tan, 1997). The first and therefore most "powerful" behavioral items under the categories of hyperactivity, impulsivity, and inattention in the *Diagnostic and Statistical Manual of Mental Disorders, IV (DSM-IV*) (American Psychiatric Association, 1994) are the following: "Often fidgets with hands or feet or squirms in seat", "Often blurts out answers before questions have been completed", and "Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities". This is little more than a list of behaviors that make it difficult for teachers to manage children with a minimum of effective attention. Suppressing these behaviors enforces a quiet, easily managed classroom or household.

The ADHD diagnosis contains no "symptoms" that specifically pertain to any emotional suffering in the child. The focus is entirely on child-like behaviors that can at times cause inconvenience or frustration in adults. This confirms that the ADHD diagnosis is intended to facilitate behavioral control and suppression – a goal that turns out to be well tailored for psychostimulant drug interventions.

ADHD-like behaviors can be caused by innumerable factors in a child's life (reviewed in Breggin, 1998a). Among the causative factors are "family relational problems, and emotional or psychological difficulties" (Schneider and Tan, 1997, p. 238), as well as economic and social stresses on the family (Baldwin, Brown, and Milan, 1995; Barbarin and Soler, 1993).

The *DSM-IV* itself acknowledges that ADHD-like behaviors tend to disappear when the child is consistently disciplined, properly entertained, or engaged in a one-to-one relationship, and that the behaviors often constitute rebellion against boring, monotonous tasks:

> "Symptoms typically worsen in situations that require sustained attention or mental effort or that lack intrinsic appeal or novelty (e.g., listening to classroom teachers, doing class assignments, listening to or reading lengthy materials, or working on monotonous repetitive tasks)" (p. 79).

These observations relate directly to the dual mechanism of action of psychostimulants in suppressing the child's spontaneous behaviors and inducing compulsive, repetitive, monotonous ones.

The same paragraph continues:

> "Signs of the disorder may be minimal or absent when the person is under strict control, is in a novel setting, is engaged in especially interesting activities, is in a one-to-one situation (e.g., the clinician's office), or while the person experiences frequent rewards for appropriate behavior" (p. 79).

Thus, ADHD-like behaviors commonly disappear when the child is allowed to express his or her natural spontaneity, creativity, and energy, or when the child is provided with rational discipline, unconditional love, an interesting and playful environment, and inspiring educational opportunities. This extraordinary admission indicates that ADHD is a "disorder" quite unlike other disorders. It disappears when the child gets proper attention. Multiple sclerosis, cerebral palsy, genetic mental retardation, and other genuine neurological disorders would not so readily *disappear* under improved environmental circumstances. Exaggerated ADHD-like behaviors are often caused by situations in which unrealistic expectations are placed on children. Frequently the children are simply bored and frustrated, or in conflict with authorities, such as classroom teachers or parents. When a child's ADHD-like behaviors become highly exaggerated, extremely disruptive, or persistent in all settings – they can be caused by an infinite number of factors, including anxiety, inadequate teaching or parenting, an endless variety of emotional problems, or a simple developmental lag which the child will eventually overcome.

In my clinical experience, most children diagnosed as having ADHD are normal children forced to stay in trying circumstances, such as classrooms or homes that fail to meet their individual needs. A few of the children are suffering from real physical disorders, such as head injury or hypothyroid disorder, but these often go undiagnosed in the rush to diagnose ADHD. A child whose behavior is hyperactive, inattentive, or impulsive needs improved attention, including rational discipline and effective educational strategies. The child is not helped by drugs that suppress his or her signals of distress or conflict with adults.

16. The risk/benefit ratio for stimulants

Although conducted by medication advocates, most reviews of the literature have reached a surprisingly consistent consensus: short-term (defined by Swanson, below, as 7–18 weeks) there are no demonstrated improvements in academic performance or learning and long-term there are no demonstrated positive effects of any kind. In the most comprehensive "review of reviews" published, Swanson (1993) concluded:

> "Long-term beneficial effects have not been verified by research.
>
> Short-term effects of stimulants should not be considered a permanent solution to chronic ADD symptoms.

Stimulant medication may improve learning in some cases but impair learning in others.

In practice, prescribed doses of stimulants may be too high for optimal effects on learning (to be achieved) and the length of action of most stimulants is viewed as too short to affect academic achievement" (p. 44).

Swanson (1993) also summarized that there were:

"*No large effects on skills or higher order processes* – Teachers and parents should not expect significantly improved reading or athletic skills, positive social skills, or learning of new concepts.
No improvement in long-term adjustment – Teachers and parents should not expect long-term improvement in academic achievement or reduced antisocial behavior" [italics in original] (p. 46).

Swanson is not unique in finding limited short-term benefits and no long-term benefits from stimulant drugs. Popper and Steingard (1994) state that:

"Stimulants do not produce lasting improvements in aggressivity, conduct disorder, criminality, education achievement, job functioning, marital relationships, or long-term adjustment" (p. 745).

A team of medication advocates assembled by NIMH (Richters, Arnold, Jensen, Abikoff, Conners et al., 1995) came to a similar conclusion: "the long-term efficacy of stimulant medication has not been demonstrated for *any* domain of child functioning" (italics in original, p. 991). An earlier NIMH report by Regier and Leshner (1991) confirmed that short-term effects are limited to behavioral control such as reducing "class room disturbance" and improving "compliance and sustained attention", and that stimulants 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" (p. 4).

Whalen and Henker (1997) could document no "long-term advantage" to taking MPH. They observe that:

"It is often disheartening to observe how rapidly behavior deteriorates when medication is discontinued. Apparently, whether a child is medicated for 5 days, 5 months, or 5 years, many problems return the day after the last pill is taken" (p. 327).

Recently, the National Institutes of Health consensus development conference on ADHD and its treatment (1998) found that psychostimulants produce "little improvement in academic achievement or social skills" and that there are "no data on the treatment of ADHD, Inattentive type" (p. 21). While endorsing the short-term use of stimulants, it concluded "there is no information on long-term treatment" (p. 21), including efficacy and adverse effects.

17. Conclusions

The recent (1988) National Institutes of Health Consensus Development Conference on the Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder raised serious questions about the validity of the ADHD diagnosis and about stimulant treatment. The conference, at which I was a scientific presenter (Breggin, 1998d), encouraged what hopefully will become a more thorough critique of the use of stimulants to modify the behavior of children.

One of the gravest risks is that the psychostimulant will have its intended effect upon the child – that it will suppress autonomous, spontaneous, social, playful behavior and bring about compliance, docility,

and overly-focused obsessive and rote behavior. The widespread use of stimulants enables adults to subdue and control children without improving their own parenting or teaching, and without improving society's family structure and educational systems. It would be far better to meet the genuine needs of children for more effective, enlightened, and caring attention in the home, school, and community.

The limited, questionable, and controversial benefit of stimulant drugs seems to pale beside their suppressive mental effects and many adverse reactions, including persistent brain dysfunction and potentially irreversible CNS damage. Pharmacological interventions in the brain to suppress spontaneous behavior and to promote obsessive ones is wrong in principle. Enough is already known about the lack of benefit and the negative impact of stimulants to stop prescribing them for "ADHD" or for the control of any symptoms or behaviors in children.

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