

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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A much shorter, modified version of this paper (Breggin, 1998d, for the abstract) was given as a scientific presentation at the National Institutes of Health (1998) Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder and will be published in the proceedings of that conference.

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¹Since 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	Anorexia	Pituitary	Blurred vision	Insomnia
Tachycardia	(skin crawling or visions)	Nausea	dysfunction,	Headache	Evening crash
Hypertension	[psychotic depression and	Vomiting	including	Dizziness	Depression
Arrhythmias	mania]	Stomach	growth	Hypersensitivity	Overactivity
Chest pain	Excessive brain stimulation	ache,	hormone and	reaction with	and
[Cardiac arrest]	[convulsions]	cramps	prolactin	rash,	irritability
	Drowsiness, “dopey”, less alert	Dry mouth	disruption	conjunctivitis,	Rebound
	Confusion	Constipation	Weight loss	or hives	worsening
	Insomnia	[Abnormal	Growth	[Hair loss]***	of ADHD-
	Agitation, anxiety, irritability,	liver	suppression	Exfoliative	like
	nervousness	function	Growth	dermatitis***	symptoms
	[Hostility]	tests]	retardation	Anemia***	
	Dysphoria	Bad taste****	Disturbed sexual	Leukopenia***	
	Impaired cognitive test	Diarrhea****	function****	Enuresis***	
	performance			Fever***	
	Dyskinesias, tics, Tourette’s			(unexplained)	
	Nervous habits (e.g., picking			Joint pain***	
	at skin, pulling hair)			Unusual	
	Stereotypy and compulsions			sweating***	
	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. Borcharding 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× daily; TID = 3× 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, dozey, 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 Borcharding 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. Borcharding 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, Borcharding, 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), Borcharding 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.

²Solanto 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 System³**

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):

³The 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 Heischouer, 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, Eliopoulos 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, Ehrenkauf, 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 Kuczenski (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 Neuman (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.

⁴In 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 Mazzotta, 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

⁵My 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)	General dampening of social behavior (5)	Somber (19) Subdued (14)
Perseverative behavior (1, 4, 6, 9, 14)	Reduced social interactions, talking, or sociability (1*, 2*, 5, 8, 10**, 14)	Apathetic; lethargic: “tired, withdrawn, listless, depressed, dopey, dazed, subdued and inactive” (14; also 11, 16)
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) Diminished curiosity, surprise, or pleasure (15)
Over-focusing or excessive focusing (4, 9, 18)	Increased solitary play (8*, 17) Diminished play (1*)	Humorless, not smiling (15) Drowsiness (10) 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. Borcharding et al. (1990); 5. Buhrmester 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, Connors 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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Psychiatric drug-induced Chronic Brain Impairment (CBI): Implications for long-term treatment with psychiatric medication¹

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Abstract. Understanding the hazards associated with long-term exposure to psychiatric drugs is very important but rarely emphasized in the scientific literature and clinical practice. Drawing on the scientific literature and clinical experience, the author describes the syndrome of Chronic Brain Impairment (CBI) which can be caused by any trauma to the brain including Traumatic Brain Injury (TBI), electroconvulsive therapy (ECT), and long-term exposure to psychiatric medications. Knowledge of the syndrome should enable clinicians to more easily identify long-term adverse effects caused by psychiatric drugs while enabling researchers to approach the problem with a more comprehensive understanding of the common elements of brain injury as they are manifested after long-term exposure to psychiatric medications. Treatment options are also discussed.

Keywords: Psychiatric drugs, adverse effects of psychiatric drugs, cognitive dysfunction, dementia, chronic brain impairment (CBI)

1. Introduction

Every type of psychiatric medication initially produces effects that are specific to the particular drug's unique impact on neurotransmitters and other aspects of brain function. For example, the SSRI antidepressants block the removal of the neurotransmitter serotonin from the synapses; the antipsychotic drugs suppress and block dopamine neurotransmission; and the benzodiazepines amplify GABA neurotransmission which in turn suppresses overall brain function.

Although all psychiatric drugs have specific initial biochemical effects, over time other neurotransmitter systems react to the initial effects and broader changes begin to take place in the brain and in mental functioning.

2. Antipsychotic-induced brain damage and dysfunction from long-term exposure

As an example, the neurotoxicity of antipsychotic drugs has been studied and demonstrated for decades. Antipsychotic drugs produce Neuroleptic Malignant Syndrome with nearly identical brain pathology to that of a viral encephalitis (encephalitis lethargica or von Economo's disease), which was epidemic

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around World War I [1]. Clinical doses of haloperidol and olanzapine over 17–27 months duration in macaque monkeys have been shown to cause 8%–11% shrinkage in tissue weight (indicating cell death) throughout the brain [2]. The toxicity of the antipsychotic drugs on a cellular level includes the inhibition of most enzyme systems in mitochondria [3–5]. Kim et al. [5] observed that chronic blockage of dopamine neurotransmission by antipsychotic drugs “results in persistently enhanced release of glutamate, which kills striatal neurons”.

Dwyer et al. reviewed the “cytotoxic properties” of the older antipsychotics, which they describe as “well known” [6]. Their own studies of the atypical antipsychotic drugs found them cytotoxic as well, but less so than the older drugs. In defense of olanzapine, the researchers stated that olanzapine “actually stimulated proliferation of neuronal cells,” implying this is potentially beneficial. However, neurons very rarely proliferate and are only known to do so in response to injury. Second, many studies of drug-induced neuronal growth have found that the cells look grossly abnormal under the microscope [7].

Tardive dyskinesia, a potentially severe and usually irreversible movement disorder associated with antipsychotic treatment, is caused by damage to the basal ganglia where dopaminergic neurons are clustered. In response to the antipsychotic-induced blockade of dopamine neurons, the dopamine receptors grow in sensitivity and proliferate in number. This eventually leads to the production of abnormal movements. However, the basal ganglia are also involved in mental function, and tardive dyskinesia, as well as most or all other diseases of the basal ganglia (e.g. Huntington’s chorea), eventually lead to dementia. All neuropsychiatric studies of patients with tardive dyskinesia have revealed an associated impairment of cognitive and affective functioning [7–9].

A persistent withdrawal tardive psychosis has been identified, confirming long-term chronic changes in mental function [10]. Many patients develop Neuroleptic-Induced Deficit Syndrome (NIDS) with cognitive and affective losses [11]. One of the few studies to address the neuropsychiatric condition of a large group of individuals exposed to antipsychotic drugs found generalized cognitive dysfunction [12]. Two recent studies have shown atrophy of the brain attributable to the antipsychotic drugs in long-term treatment of patients diagnosed as schizophrenic [13, 14].

Studies of all classes of psychiatric drugs have yielded similar findings of mental dysfunction and atrophy of the brain in humans after long term exposure, as well as atrophy of the brain, abnormal proliferations of cells and persistent biochemical changes in animals [5]; for the benzodiazepines [15, 16], for lithium see [17] for antidepressants see [18–22].

3. The syndrome of Chronic Brain Impairment (CBI)

The clinical effect of chronic exposure to psychoactive substances, including psychiatric drugs, produces effects very similar to those of close-head injury due to traumatic brain injury (TBI) [23] or the Postconcussive Syndrome [24]. Generalized or global harm to the brain from any cause produces very similar mental effects. The brain and its associated mental processes respond in a very similar fashion to injuries from causes as diverse as electroshock treatment [25] closed head injury from repeated sports-induced concussions or TBI in wartime, chronic abuse of alcohol and street drugs, long-term exposure to psychiatric polydrug treatment, and long-term exposure to particular classes of psychiatric drugs including stimulants, benzodiazepines, lithium and antipsychotic drugs.

Global or generalized brain impairments – those that involve the whole brain – look so much alike in their mental symptoms because the injured brain has only a limited repertoire of reactions. The healthy brain seems almost infinite in its capacity to create, so that the mental life of individuals with normal brains is very complex, rich and varied, and always unique. The wounded brain, and its associated mental

malfunctions, is much more limited and pedestrian. Its remaining richness and complexity depend on the existence of sufficient remaining brain function to allow for unique self-expression.

Based on these observations I have proposed the syndrome and diagnosis of Chronic Brain Impairment (CBI).² The specific cause of the CBI is added as a prefix, as in Alprazolam CBI, Antipsychotic Drug CBI, or Poly Psychiatric Drug CBI.³ Other examples are ECT CBI, Polydrug Abuse CBI, and Concussive CBI.

3.1. Symptoms and characteristics of CBI

Knowledge about CBI can help the clinician to identify the more subtle but potentially disabling effects of long-term exposure to psychiatric drugs and aid the clinician in determining the need to reduce or terminate drug treatment. CBI is the most frequent reason families become concerned about taking a family member off psychiatric drugs. CBI also leads individual patients to seek psychiatric help for themselves, but often they do not attribute their worsening condition to drug effects. Instead, they attribute it to “mental illness”.

Psychiatric Drug CBI, like all CBI, is associated with generalized brain dysfunction and therefore manifests itself in an overall compromise of mental function. To help in identifying these deficits in clinical practice, the CBI syndrome can be divided into four symptom complexes which commonly present together:

- (1) Cognitive dysfunctions which manifest in the early stages as short-term memory dysfunction and impaired new learning, inattention and difficulty concentrating.
- (2) Apathy or loss of energy and vitality, often manifesting as indifference (“not caring”) and fatigue. The individual commonly loses interest in creative activities, as well as other endeavors requiring higher mental processes, sensitivity to others, and spontaneity. The loss of empathy seen in these patients is probably an aspect of apathy as well as an aspect of the overall affective worsening.
- (3) Emotional worsening (affective dysregulation) including loss of empathy, increased impatience, irritability, and anger, as well as frequent mood changes with depression and anxiety. This deterioration usually has a gradual onset over months or years so that it seems “normal” or becomes attributed to “stress,” “mental illness,” or “getting old”.
- (4) Anosognosia – lack of self-awareness of these symptoms of brain dysfunction. Whether it involves TBI, Alzheimer’s disease, drug-induced tardive dyskinesia, or psychiatry drug CBI – patients commonly fail to identify their mental symptoms of brain dysfunction. Often someone other than the patient notices these changes. This is an aspect of anosognosia or the inability to recognize brain dysfunction in oneself [23].

As a result of these deficits, there is an associated reduction in the quality of life.

4. Comparison to dementia and Organic Brain Syndrome (OBS)

The cognitive criteria for CBI are less severe than those for dementia [26]. Only the most severe CBI patients will develop dementia symptoms such as apraxia, aphasia and agnosia; and any disturbances

²The phrase “chronic brain impairment” appears in various places in the literature on psychoactive drugs; but it has not been used as an overarching concept for a generic brain condition caused by multiple physical stressors, including long-term exposure to psychiatric drugs.

³Psychiatric Drug CBI and ECT-Induced CBI ([7], pp. 233–234) are aspects of the brain-disabling principle of biopsychiatric treatment ([7], Chapter 1).

of executive functioning would likely be very subtle. From a clinical standpoint, patients suffering from CBI are rarely diagnosed with dementia, even if they meet the criteria, because clinicians miss the subtle signs. Also, clinicians tend to think of dementia as a very severe and disabling disorder. In addition, clinicians are reluctant to diagnose dementia when it caused by psychiatric drug treatment.

Also in contrast to the diagnosis of dementia, the clinical criteria for CBI are more consistent with the actual clinical phenomenon associated with more subtle aspects of generalized or global brain dysfunction, including subtle cognitive deficits, apathy, affective dysregulation, and anosognosia. If a case of CBI becomes very severe, it would qualify as dementia. Because CBI is a specific syndrome, the severe condition should be diagnosed as CBI with dementia.

The concept of CBI also resembles the concept of organic brain syndrome (OBS). However, OBS is no longer used in the diagnostic system or in clinical practice [26]. When used in the past [27], it was not defined as a specific syndrome or a specific diagnosis with defined criteria. OBS was used to subsume a class of disorders that included specific diagnoses such as dementia or organic personality disorder. It did not have the nuance and broad spectrum of effects associated with CBI. It was not viewed as a unitary syndrome resulting from any physical harm to the brain.

4.1. Confounding factors

When a patient has been exposed to years of psychiatric medication, other factors can cause or exacerbate Psychiatric Drug Induced CBI. The long-term impact of the individual's original psychological and emotional problems can induce apathy and emotional instability, and some degree of psychological denial that could be easily confused with anosognosia. However, there is no convincing evidence that primary psychiatric disorders, such as bipolar disorder or schizophrenia, can cause cognitive disorders or generalized brain dysfunction. In addition, CBI usually develops specifically in relationship to the persistent use of psychiatric drugs and can often be seen to worsen as doses are increased. Furthermore, CBI will usually begin to improve when the psychiatric drug dose is reduced. In contrast, pathology caused by a primary psychiatric disorder would be expected to worsen as the medication is reduced. After a syndrome consistent with CBI is identified, improvement with drug withdrawal is probably the most useful diagnostic criterion in distinguishing Psychiatric Drug Induced CBI from other disorders. The symptoms are partially or entirely relieved, and the quality of life improves.

Another potential confounding factor is exposure to other psychoactive substances. Many individuals who are exposed to long-term psychiatric medication will also be taking other prescribed medications that have psychoactive potential, including antihypertensive agents, pain medications, and anticonvulsants. Others will be exposed to psychoactive herbal remedies, alcohol or illegal drugs. A detailed clinical history is required to disentangle these drug effects. Again, improvement during psychiatric drug withdrawal is important diagnostically.

Many people in long-term psychiatric treatment, especially combat veterans, will also suffer from closed head injury. Also, any accompanying Post Traumatic Stress Disorder could become confused with CBI, since the symptoms overlap. Except for improvement on withdrawal from the psychiatric medications, CBI can be difficult to distinguish from closed head injury, with or without accompanying PTSD.

5. Patient awareness of CBI

Many patients desire to come off psychiatric drugs because they have some awareness of their deteriorating mental function. However, they almost never fully grasp how impaired they have become. This

lack of self-awareness of impaired brain function stems from two sources – psychological denial and neurologically-induced anosognosia. Psychological denial occurs when the individual has enough intact brain function to recognize symptoms of brain dysfunction but psychologically rejects this awareness and utilizes denial. Anosognosia is physically caused when brain injury impairs the capacity for this aspect of self-awareness [8, 9, 23]. Obviously, the two phenomena can be difficult to separate.

Drug-induced anosognosia when severe can become intoxication anosognosia or medication spellbinding in which an individual can develop dangerous behavioral patterns, including suicide and violence, that would not otherwise have occurred [7, 28]. This risk must be taken into account by the prescriber, the therapy team, the patient and the patient's support network, especially during dose changes and withdrawal.

5.1. Frequency of CBI

Psychiatric Drug CBI was relatively rare in the early decades of my career in psychiatry (I graduated medical school in 1962) when far fewer children and teens were treated with psychiatric drugs, when polydrug treatment was looked upon much more critically, when doctors rarely encouraged patients to stay on psychiatric drugs for the remainder of their lives, and when potent antipsychotic drugs were not given out so freely to patients with no signs whatsoever of psychosis. Undoubtedly, the widespread use of alcohol and illegal drugs, often taken in combination with prescription drugs, has helped turn CBI into an epidemic.

It is difficult to estimate what percentage of patients will develop CBI after years of exposure to psychiatric drugs. In my clinical experience, nearly all patients who remain on these chemical agents for many years will develop some symptoms of CBI. If the patient is taking multiple psychiatric drugs for years at time, in my experience CBI is always marked.

The most noticeable effects are short-term memory dysfunction and a loss of interest in daily activities, hobbies, creative endeavors, and sometimes family and friends. The clinician can inquire about creative activities requiring higher mental function, sensitivity to others, and spontaneity – such as art work, writing, music, close friendships, and sexual relations. Individuals exposed long-term to psychiatric drugs will commonly report a loss of interest, intensity or satisfying engagement in these activities. Sometimes they will deny their losses which are nonetheless confirmed by family members and loved ones.

5.2. Recovery from CBI

Recovery from CBI usually begins early in the withdrawal process and can continue for some time, even years, after stopping all psychiatric medication. As the number of drugs and their dosages are reduced, patients show improvements in memory, engagement in activities, and mood stability. Because of anosognosia, the patient may not recognize the improvements as quickly or thoroughly as the prescriber, therapist, or family; but it would be unusual if the patient fails to notice or acknowledge any positive changes early in the drug withdrawal process.

If the patient does not begin displaying significant improvement in CBI symptoms during the drug withdrawal process, the clinician should suspect the presence of another underlying medical disorder, and take appropriate steps to ensure adequate medical evaluation. Psychiatric Drug CBI can be confused with or worsened by any additional disorders that impair brain function. The covert use of alcohol or illegal drugs can impair the withdrawal process.

While further medical evaluation is conducted, the medication withdrawal should be continued, if possible, in order to clarify the clinical diagnosis and provide optimum conditions for healing any underlying physical disorder. Many underlying disorders, including neurological disorders that impair brain function, are apt to be significantly worsened by continued exposure to psychoactive substances, including psychiatric drugs.

Young children and teenagers often seem to experience full recovery from CBI despite years of exposure. It is imperative to prevent the long-term exposure of children and youth to psychiatric medications, all of which can impede learning and emotional development, and injure the brain. In my clinical experience, children and teenagers are especially resilient after removal from the offending agents.

Adult patients are more likely to experience continued subtle CBI difficulties with memory, attention or concentration after withdrawal from years of exposure to psychiatric medication; but even in the presence of residual symptoms, they can lead fulfilling lives.

Of course, there is also a risk of psychiatric relapse. However, even if this occurs, improvement in the patient's CBI may be worth it to the patient and the family. In addition, these "relapses" are often due to delayed withdrawal reactions manifested, for example, as the return of depression a few weeks after antidepressant withdrawal or the return of manic symptoms within weeks after withdrawal from lithium. In this case, instead of reinstating a starting dose of medication, it may be sufficient to provide drug-free psychotherapy or to extend the withdrawal somewhat longer with small doses of the medication.

Persistent multi-drug exposure, high drug doses, length of exposure, and older age can contribute to the risk and severity of CBI. The best way to prevent CBI is to use psychiatric medications sparingly and to limit exposure to the shortest possible length of time.

5.3. Treatments for CBI

The initial and only effective treatment for CBI is complete withdrawal from all psychiatric drugs as well as all other psychoactive substances. During the withdrawal process, it is important to establish healthy living practices in regard to good nutrition (no special diets), moderate exercise, and sufficient rest and sleep.

Patients should be discouraged from turning to additional psychoactive substances, including herbs or natural remedies. They can worsen the CBI and interfere with a successful withdrawal process. The covert use of alcohol and illegal drugs will also impair withdrawal.

Close monitoring of the patient during drug withdrawal is required. In addition, the drug withdrawal process should be accompanied by supportive psychotherapy for both the patient and significant others who can provide support during the sometimes difficult process. Couples or family therapy is potentially the most effective. It can help the uninjured partner understand the struggle to triumph over brain dysfunction and strengthen the relationship in supportive ways for both partners. Cognitive-behavioral Therapy (CBT) can be useful in promoting better ways to think of responsibility and self-determination but nothing is more important than supportive relationships when brain function is impaired.

The patient's subjective experience is the best gauge for pacing the withdrawal process. Utilizing a person-centered approach [29], it is best to start with a small dose reduction, and then to step-by-step make reductions dependent upon how the patient is responding. To reduce fear and anxiety, patients must feel in charge of the rate of the withdrawal process.

Any therapy that can produce emotional stress, such as insight therapy that explores childhood trauma, or couples therapy that deals with severe conflicts, should be delayed until the patient is able, willing and eager to take on these challenges.

Programs for cognitive rehabilitation are probably less effective than encouraging the individual to engage in useful, pleasurable and stimulating physical and mental activities. Encourage individuals with CBI to rediscover activities that they once loved. Frequently, they have given them up.

A recurrence or worsening of the individual's psychiatric disorders is a major concern during withdrawal, especially in regard to individuals who have been made vulnerable by CBI. In my own experience, however, judiciously and slowly removing long-term psychiatric drugs – along with appropriate psychotherapy – usually helps in recovery from psychiatric disorders.

After medication withdrawal, patients often declare, "I've gotten my life back. I'm myself again!" Family members often feel that they have regained the husband, wife or child that they used to know and love before the adverse medication effects set in. The work of psychiatric drug withdrawal, while sometimes difficult and hazardous, can be very gratifying to the clinician and extremely empowering to the patient and family.

6. Conclusion

By learning to recognize Psychiatric Drug-Induced Chronic Brain Impairment (CBI), clinicians can enhance their ability to identify patients who need to be withdrawn from long-term psychiatric drug treatment. CBI symptoms are the main reason why patients and their families seek professional help in withdrawing from psychiatric medications.

The symptoms of this syndrome include (1) Cognitive deficits, often first noticed as short-term memory dysfunction and impaired new learning, and difficulty with attention and concentration; (2) Apathy, indifference or an overall loss of enjoyment and interest in life activities; (3) Affective dysregulation, including emotional lability, loss of empathy and increased irritability; (4) Anosognosia or a lack of self-awareness about these changes in mental function and behavior.

Most patients begin to recover from CBI early in the withdrawal process. Many patients, especially children and teenagers, will experience complete recovery. Others may recover over a period of years. Even when recovery is incomplete, or psychiatric relapses occur off the medication, most patients remain grateful for their improved CBI, and wish to remain on reduced medication or none at all.

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Brain-Disabling Treatments in Psychiatry

**DRUGS, ELECTROSHOCK, AND
THE ROLE OF THE FDA**

Peter R. Breggin, MD

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Neuroleptic Malignant Syndrome, Tardive Dyskinesia, Tardive Dystonia, and Tardive Akathisia

This chapter focuses on two well-known neurological disorders caused by the neuroleptics—tardive dyskinesia (TD) and neuroleptic malignant syndrome (NMS), with emphasis on their frequency and their destructive impact on the physical and emotional life of the individual. It also discusses neuroleptic withdrawal syndrome. The next chapter will explore irreversible damage to the brain that primarily affects mental functioning, including tardive psychosis and tardive dementia. However, as products of neuroleptic neurotoxicity, all these drug-induced abnormalities are clinically and neurologically interrelated.

TARDIVE DYSKINESIA

Within a few years after the development of the first neuroleptic, it became obvious that many patients were not recovering from their drug-induced neurologic disorders even after termination of the therapy. Reports were made in the late 1950s. Delay and Deniker (1968) date their awareness

of irreversible neurological syndromes to 1959. By 1968 they were able to provide a vivid review of several varieties, including buccolingual, truncal, and variable choreic movements. In 1964 Faurbye (Faurbye, Rasch, Petersen, & Brandborg, 1964) named the disorder tardive dyskinesia.

As if governed by one mind, psychiatry as a profession refused to give any official recognition to this potential tragedy. Then Crane made it a personal crusade to gain the profession's recognition of the problem (1973). The American College of Neuropsychopharmacology/Food and Drug Administration Task Force (1973) described the syndrome in a special report. Following 1973, everyone in the profession should have been alerted to the dangers of TD; but too many psychiatrists have continued to act as if it hardly exists.

In 1980, the American Psychiatric Association (APA) published a task force report on TD. In 1985 the FDA took the unusual step of setting specifically worded requirements for a class warning in association with all neuroleptic labeling and advertising ("Neuroleptics," 1985). In a wholly unprecedented move, in the same year the APA sent out a warning letter about the dangers of tardive dyskinesia to its entire membership (see chapter 11 for further discussion of the FDA's role).

TD often begins with uncontrolled movements of the face, including the eyes (blinking), tongue, lips, mouth, and cheeks; but it can start with almost any group of muscles. The most common early sign is a quivering or curling of the tongue. Tongue protrusions and chewing movements are also common, and can become serious enough to harm teeth and impair chewing and swallowing. The hands and feet, arms and legs, neck, back, and torso can be involved.

The movements displayed are highly variable, and include writhing contortions, tics, spasms, and tremors. The person's gait can be badly impaired. More subtle functions can be affected and are easily overlooked: respiration (involving the diaphragm), swallowing (involving the pharyngeal and esophageal musculature), the gag reflex, and speech (Yassa & Jones, 1985).

The movements usually disappear during sleep, although I have seen exceptions. They sometimes can be partially suppressed by willpower; frequently are made worse by anxiety; and can vary from time to time (see below).

Many cases of TD appear to be relatively mild, often limited to movements of the tongue, mouth, jaw, face, or eyelids. Nonetheless, they are

frequently disfiguring and often embarrassing. Patients have been known to commit suicide (Yassa & Jones, 1985).

The abnormal movements can sometimes become totally disabling. Turner (1971) describes patients who cannot eat and must have their teeth removed in order to facilitate the entry of food into their mouths. He also describes patients who cannot keep shoes on their feet because they wear them out while sitting with the constant foot-shuffling activity. I have evaluated a number of cases in which the tardive dyskinesia was wholly disabling, including massive distortions of the position of the neck or body, rocking and swaying, shoulder shrugging, and rotary or thrusting movements of the pelvis, as well as disturbances of respiration, such as periodic rapid breathing, irregular breathing, and grunting.

Ironically, the disease makes the patient look “very crazy” because of the seemingly bizarre facial and bodily movements. Tragically, this has often led to patients being treated more vigorously with neuroleptics, ultimately worsening their TD.

As in other neurological disorders, the patient may attempt to hide the disorder by adding voluntary movements to the involuntary ones in order to disguise them. For example, to cover up a tendency to move the arms continually, the patient may make grooming movements around the face and hair. This can make it seem as if the individual suffers from a psychological compulsion instead of a neurological disorder. Or the patient may clasp his arms together in order to control the movements, making it seem as if he is trying to psychologically “hold onto himself.”

All the neuroleptics (see chapter 2 for a list) can cause tardive dyskinesia, including the atypical neuroleptics clozapine (Weller & Kornhuber, 1993) and risperidone (Addington, Toews, & Addington, 1995). The overall adverse effects of the atypical neuroleptics are summarized in chapter 5.

Masking the Symptoms of TD with Continued Neuroleptic Treatment

The symptoms of tardive dyskinesia are masked or suppressed by these drugs, so that the disease symptoms do not fully appear until the patient has been removed from the treatment. For this reason, in addition to using the smallest possible dose for the shortest possible time, whenever possible patients should periodically be removed from their neuroleptics, if only

for a short period, to determine if they are developing tardive dyskinesia. Permanent removal from the neuroleptics is a more difficult matter, often requiring many months of gradual withdrawal for the brain to adjust to the drug-free environment.

Harold Klawans has discussed the dangerousness of trying to control or treat TD with the causative agent. He asserts (in the discussion following Goetz et al., 1980): "Treatment of tardive dyskinesia with neuroleptics themselves is clearly treatment with the presumed offending agent and should be avoided." He calls it "short-sighted" to use the neuroleptics in the treatment of tardive dyskinesia, and concludes that the therapy "serves to aggravate its pathogenesis." Unhappily, Klawans himself in the same article too readily recommends reserpine as a helpful agent in the treatment of TD, when it too can cause the disorder.

Nonetheless, I have seen cases of TD that were so disabling that the only recourse seemed to be treatment with a neuroleptic. But two points must be borne in mind about these cases. First, in each instance, the case became so severe because physicians failed to detect the disorder when it first appeared and continued neuroleptic treatment long after it should have been terminated. This has been true in nearly all the most disabling cases I have examined. Second, the individuals in question were overcome with suffering and rendered wholly unable to function by the TD. They and their families made informed decisions to continue the offending agent because the TD was making life unbearable for the patient.

The anticholinergic drugs typically used to ameliorate the symptoms of drug-induced parkinsonism also may aggravate the symptoms of TD (Yassa et al., 1992). They include benztropine (Cogentin), biperiden (Akineton), and trihexyphenidyl (Artane, Tremin). These agents are known to worsen similar symptoms in Huntington's chorea (Hunter, Blackwood, Smith, & Cumings, 1968; Klawans, 1973). At present the role of these drugs in the development or exacerbation of tardive dyskinesia is controversial and undetermined, but caution is required in giving them to patients on neuroleptics. Their adverse effects are discussed in chapter 2. These agents are often used to treat acute extrapyramidal symptoms and may be mistakenly prescribed for TD.

Rates of TD

In 1980 the APA produced a detailed analysis of the disease in its *Task Force Report: Tardive Dyskinesia*. It made clear that TD is a serious,

usually irreversible, untreatable, and highly prevalent disease resulting from therapy with the neuroleptics. The task force estimated the prevalence rate for TD in routine treatment (several months to 2 years) as *at least 10%–20%* for *more than minimal* disease. For long-term exposure to neuroleptics, the rate was at least 40% for more than minimal disease.

Even after the publication of the 1980 task force report and a mountain of confirmatory evidence, some biologically oriented psychiatrists, such as Nancy Andreasen (1984), in *The Broken Brain: The Biological Revolution in Psychiatry*, continued to misinform the public that tardive dyskinesia is “infrequent” (p. 210) and occurs in “a few patients” (p. 211).

The more recent APA task force (1992) report cites a rate of 5% per year, cumulative over the first several years of treatment. Jeste and Caligiuri (1993) estimate the annual incidence rate among young adults at 4%–5%.

In a recent prospective project emanating from Yale, Glazer, Morgestern, and Doucette (1993) reported a long-term evaluation of 362 outpatient psychiatric patients who were free of TD at baseline and who were being maintained on neuroleptics. For patients who are starting neuroleptics, according to projections from their data, the risk of tardive dyskinesia will be 31.8% after 5 years of exposure—a rate of slightly over 6% per year. The risk is 49.4% after 10 years, 56.7% after 15 years, 64.7% after 20 years, and 68.4% after 25 years.

Chouinard, Annable, Mercier, & Ross-Chouinard (1986) followed a group of 136 persons who had already been receiving neuroleptics but had not yet manifested TD. Over 5 years, 35%—a rate of 7% per year—developed the disorder.

Overall, in relatively young and healthy patients, the cumulative risk of contracting TD when exposed to neuroleptics ranges from 4%–7% per year during the first several years of treatment. Approximately one-third of the patients will develop this largely irreversible disorder within the first five years of treatment. This represents an astronomical risk for patients and should become part of the awareness of all mental health professionals, their patients, and their patients' families. Furthermore, we shall find that TD brings with it the additional risk of irreversible cognitive dysfunction and dementia (chapter 5).

There is evidence that rates for tardive dyskinesia are increasing. It may be caused by the growing tendency to use drugs with seemingly more toxic effects on the extrapyramidal system, such as Haldol and Prolixin (see Jeste & Wyatt, 1981). These drugs also come in long-acting

intramuscular preparations that do not permit patients to independently lower their own dosages by taking fewer pills than prescribed.

It is unusual for TD to develop in less than 3–6 months' treatment and standard texts suggest that TD which develops earlier requires special investigation. However, it is not possible to place too much emphasis on one point that has been mentioned by Tepper and Haas (1979) and others (for example, Hollister, 1976): tardive dyskinesia can develop in low-dose, short-term treatment. DeVeugh-Geiss (1979) has seen cases develop in a matter of weeks. I have seen several cases develop at around 3 months of treatment. One patient developed tardive dyskinesia after 1 month of recent exposure, with a history of 2 months' prior exposure several years earlier. One case which developed in 3 months of constant exposure had a probable history of prior head injury from childhood. In the elderly, many cases may develop within a few weeks (see below).

THE ELDERLY AND OTHER VULNERABLE POPULATIONS

It is important to remember that medications in general are more likely to cause dysfunction in the elderly (Nolan & O'Malley, 1988). Nowhere is this demonstrated more tragically than in regard to TD.

A study of elderly nursing home patients by Yassa, Nastase, Camille, and Belzile (1988) found that 41% developed tardive dyskinesia over a period of only 24 months and that none fully recovered. While long-term studies have found a spontaneous dyskinesia prevalence of 1%–5% in the elderly, none of the non-drug-treated controls developed spontaneous dyskinesias during the 2 years. Yassa, Iskander, and Ally (1988) found TD in 45% of an outpatient clinic population with a mean age of 60.

In a more recent study, Yassa, Nastase, Dupont, and Thibeau (1992) followed up patients from a geriatric psychiatric unit who had received neuroleptics for the first time during the hospitalization. Out of 99 patients, 35 (35.4%) had developed TD after a mean exposure of 20.7 months. Of these 35, 21 had moderate TD and 3 had severe. Some had tardive dystonia (see below).

Saltz and his colleagues (1991) found the incidence of TD was 31% following 43 weeks of cumulative neuroleptic treatment in the elderly. The incidence was higher among patients who had previous electroshock

treatment. Patients with early signs of parkinsonism developed TD at a faster rate. Of great importance, in this older population, the mean cumulative time while taking neuroleptics was very brief, a mere 22.7 weeks. One patient developed TD at 2 weeks.

Jeste, Lacro, Gilbert, Kline, and Kline (1993), in an ongoing prospective study, found that 26% of middle-aged and elderly patients developed TD after 12 months. The authors also reviewed the literature on neuroleptic withdrawal and found “that almost 60 percent of the patients withdrawn from neuroleptics did not relapse over a mean period of 6 months.” They concluded, “it seems feasible to discontinue neuroleptic medication from a select population of older schizophrenic patients, if it is done carefully with adequate monitoring and follow up.” They also experimented with brief 2-week placebo-substituted withdrawal in their own group of patients, both younger and older subjects, and found it relatively benign: none relapsed or required resumption of neuroleptics. They concluded, “Given the heightened risk of TD in older patients, it seems that a trial of neuroleptic withdrawal is warranted in this population.”

Jeste et al. (1993) emphasize that “The potential seriousness of neuroleptic-induced TD warrants obtaining competent, informed consent to treatment from patients or guardians.” They recommended that consent be periodically renewed and cited other sources to confirm their position.

In addition to age, prior brain damage probably increases the risk of TD (Breggin, 1983; Chouinard, Annable, Ross-Chouinard, & Nestoros, 1979), although studies are contradictory and not conclusive. McKeith, Fairbairn, Perry, Thompson, and Perry (1992) found that 13 of 16 patients with Lewy body type dementia showed deterioration on neuroleptics, including the development of extrapyramidal features. The authors conclude, “Severe, and often fatal, neuroleptic sensitivity may occur in elderly patients with confusion, dementia, or behavioral disturbance. Its occurrence may indicate senile dementia of the Lewy body type . . .” Pourcher, Cohen, Cohen, Baruch, and Bouchard (1993) found a correlation between TD and prior organic brain disorder.

Relapse, Exacerbation, and Delayed Onset after Termination

TD typically waxes and wanes, both in the course of a day and in the course of weeks or months. Especially in the elderly, both partial remissions and relapses are common (Lacro et al., 1994).

As in many neurological disorders, the manifestations of TD can worsen during stress and can be somewhat calmed with sedation (Jeste & Caligiuri, 1993). In my experience, anxiety, exhaustion, and other general stresses to the mind and body can temporarily exacerbate the symptoms, while relaxation, when possible, can temporarily reduce them.

With great effort, patients can sometimes suppress some of their symptoms for a short time. They can also integrate their movements into more natural-looking actions, such as grooming or smiling, in order to disguise them. One patient with whom I consulted would hide her involuntary facial grimaces by trying to smile. The effect was to make her look even more strange to the casual observer.

Neither the fact that TD waxes and wanes, sometimes in response to stress, nor the patient's ability to partially suppress it with an exertion of will, should mislead observers into believing that it is psychological or emotional in origin. Too often the early signs of TD are overlooked, denied, or dismissed by physicians on these mistaken grounds.

Christensen, Moller, and Faurbye (1970) have documented that a significant percentage of TD cases may not show up at all until many months or even several years after discontinuation of the treatment. They believe that the symptoms are brought on by the interaction between the damage caused by the drugs and by the aging process. If this is true, then a tragic reality may develop as we observe the evolution of TD in aging populations. I have on occasion seen cases that did not become apparent until several months or more after termination of treatment.

Reversibility Is Rare

In the vast majority of cases, TD is irreversible and there is no effective treatment. One report indicates that among patients with persistent TD, followed for a period of 5 years, 82% showed no overall significant change, 11% improved, and 7% became worse (Bergen et al., 1989).

Another study followed 49 outpatient tardive dyskinesia cases for a mean of 40 weeks (range 1–59 months) after discontinuation of medication (Glazer, Morgenstern, Schooler, Berkman, & Moore, 1990). Many patients showed noticeable improvement in their movements within the first year after stopping neuroleptics, but only 2% showed complete and persistent recovery. The authors conclude, "A major finding of this study is that complete reversal of TD following neuroleptic discontinuation in chronically treated patients was rare."

underestimated. I therefore reviewed the subject in detail. Fortunately, this is no longer necessary, since it is now well-recognized that children are susceptible to TD at rates no less than adults, and that the disorder is often more virulent in children, because it frequently affects the torso, including posture and locomotion (Breggin, 1983a; Gualtieri & Barnhill, 1988; Gualtieri, Quade, Hicks, Mayo, & Schroeder, 1984; Gualtieri, Schroeder, Hicks, & Quade, 1986). A high percentage of neuroleptic-treated children also develop a permanent worsening of their emotional and behavioral problems, psychoses, or dementia (see chapter 5). Physicians should not use neuroleptics for behavioral control in children.

TARDIVE DYSTONIA

It is now apparent that there are at least two related variants of TD, tardive dystonia and tardive akathisia. In a 1988 review of tardive dystonia, Burke and Kang found 21 reports describing 131 patients (for reviews, also see Greenberg & Gujavarty, 1985, and Kane & Lieberman, 1992).

Tardive dystonia involves “sustained involuntary twisting movements, generally slow, which may affect the limbs, trunk, neck, or face” (Burke et al., 1982, p. 1335). The face and neck are by far the most frequently affected areas of the body. Severe deformities of the neck (torticollis) can cause extreme pain and disability. I have seen several cases affecting the orbital muscles of the eyes (blepharospasm) to the degree that the individual’s vision was impaired, requiring botulin injections to paralyze the muscles. I’ve also seen respiratory and abdominal muscles affected in a painful and debilitating manner.

Tardive dystonia can produce cramplike, painful spasms that temporarily prevent the individual from carrying out normal activities. Sometimes the spasms are so continuous that the individual is largely disabled. Damage to the joint and skeleton system, including fractures, can occur (Burke & Kang, 1988). The pain and muscle tension, as well as the effort to compensate for the spasms, can be exhausting and demoralizing.

The torsions can be worsened by other bodily movements, such as attempts to write or to walk. Sometimes they can be relieved by particular movements, such as touching the chin to relieve torticollis or touching the brow to relieve blepharospasm.

Physician and Patient Denial of TD

Physicians understandably find it painful to face the damaging effects of their treatments. Sometimes it is difficult for them to confront the damage done to patients by other physicians as well. In addition, physicians may consciously seek to protect themselves or their colleagues by failing to acknowledge or to record obvious symptoms of tardive dyskinesia. I have seen many hospital and outpatient records in which obvious, severe cases of tardive dyskinesia have gone either unrecognized or undocumented, sometimes by several physicians in succession. For example, the nurse's notes may make clear that the patient is in constant motion, yet the doctor's physical examination or progress notes will give no indication of the disorder. Even official discharge summaries may fail to record TD in patients who have been demonstrating the disorder throughout the period of hospital or clinic treatment. This denial of the obvious is mirrored within the profession itself, which has been very remiss in recognizing or emphasizing the seriousness of the problem (for an analysis of this history, see Breggin, 1983a; Brown & Funk, 1986; Cohen & McCubbin, 1990; Wolf & Brown, 1987).

Psychiatrists sometimes accuse patients of exaggerating their tardive dyskinesia. In reality, most patients tend to deny the existence or severity of their TD. As discussed in detail in chapter 5, patient denial is caused in part by neuroleptic-induced lobotomy effects and in part by denial associated with brain damage. The mutual denial of TD by physician and patient is an aspect of iatrogenic helplessness and denial—the use of brain-disabling treatments in psychiatry to enforce the patient's denial of both his personal problems and his iatrogenic brain dysfunction and damage (chapter 1).

The Size of the Epidemic

It is difficult to determine the total number of TD cases. Van Putten (see Lund, 1989) estimated 400,000–1,000,000 in the United States. My own earlier estimate is higher, ranging in the several millions (Breggin, 1983). It is no exaggeration to call tardive dyskinesia a widespread epidemic and possibly the worst medically induced catastrophe in history.

Children and TD

When I reviewed the subject in 1983, I was among the first to state that the rate and severity of tardive dyskinesia in children was being vastly

As Burke and Kang (1988) point out, tardive dystonia can be mistakenly dismissed as a manifestation of hysteria, psychological in origin: "In this regard it is important to realize that dystonia, like many other neurological disorders, can be influenced transiently by suggestion, placebo, or sedation (e.g., during an amobarbital interview) and such maneuvers cannot exclude a true dystonia." Also, like many other neurological disorders, it can sometimes be partially controlled by extreme exertions of will.

Tardive dystonia can make an individual appear unsympathetic or bizarre, especially to the uninformed observer who equates the facial grimaces or neck distortions with being "crazy." As in all the drug-induced dyskinesias, the individual may try to cover up for the disorder with additional movements that make the disorder seem voluntary, and therefore not a product of mental illness. The result can be very confusing or distressing to the observer.

TARDIVE AKATHISIA

Tardive akathisia involves a feeling of inner tension or anxiety that drives the individual into restless activity, such as pacing (see chapter 3 for details). The first report of tardive akathisia I have located in the literature was published by Walter Kruse in 1960. He described three cases of muscular restlessness that persisted at least 3 months after discontinuation of treatment with fluphenazine and triflupromazine. The "akathistic syndrome . . . consisted of inability to sit still, pacing the floor all day, jerky movements of arms and shoulders." Once again Delay and Deniker (1968) were also among the first clinicians to notice the disorder. In discussing "syndromes persisting after cessation of medication," they mention "hyperkinetic" ones. As early as 1977, Simpson more definitively made an association between tardive dyskinesia and akathisia that would not respond to treatment.

Gualtieri and Sovner (1989) reviewed the subject of tardive akathisia, cited studies with prevalence rates of 13%–18%, and called it "a significant public health issue." Nonetheless, the drug companies have ignored it in the labeling of their products.

The anguish associated with akathisia should not be minimized. Consider Van Putten's (1974) description of a mild, temporary akathisia or hyperkinesia: "Patient feels 'all nerved up,' 'squirmy inside,' 'uptight,'

‘nervous,’ ‘tense,’ ‘uncomfortable,’ ‘impatient’. . . . Subjective feeling of ill-being may be accompanied by restless changes in posture.’”

One reason that so little attention has been given to the mental disruption associated with the dyskinesias is the tendency to blame the mental component on the mental illness of the patient. Indeed, it has been commonplace to blame the obvious motor disturbances on the mental illness as well, often resulting in increased treatment, and a worsening of the symptoms, until immobility sets in, masking the entire process.

It takes no great imagination to grasp the suffering of a patient condemned to a relatively mild tardive akathisia for a lifetime. I have seen cases of this kind that were previously mistaken for severe anxiety or agitated depression. Chapter 3 reviewed research indicating that acute akathisia can drive a patient into psychosis, and to violence and/or suicide. Considering the millions of patients subjected to this torment, the problem takes on epidemic proportions.

Tardive akathisia can be subtle. A woman in her mid-sixties consulted me because of seemingly bizarre feelings that other doctors attributed to her depression and to somatic delusions or hallucinations. She had a feeling of “electricity” going in periodic bursts throughout her body. Although she sat quietly in the office, she spoke of feeling fidgety and driven to move about.

Her hospital and clinic charts disclosed that 2 years earlier she had been treated for approximately 6 months with neuroleptics. The sensation she was describing had first been noted while she was taking the medication. I concluded that she probably had tardive akathisia, a subtle case that did not actually force her to move about. However, because she didn’t show external signs of the disorder, other physicians were reluctant to make the diagnosis. The patient felt “driven to distraction” and even to suicide by the disorder; but after my probable diagnosis, she actually felt somewhat relieved. At least she was being taken seriously.

In 1993, Gualtieri wrote:

In terms of clinical treatment and the public health, however, TDAK [tardive akathisia] is a fact, not a question. It is one more serious side effect of neuroleptic treatment, like TD and the Neuroleptic Malignant Syndrome. Taken together, they define neuroleptic treatment as a necessary evil, a treatment that should be administered with care and caution, and reserved for patients who have no other recourse.

RESPONSES TO TARDIVE DISORDERS

Physical Exhaustion

Fatigue to the point of exhaustion almost always accompanies tardive disorders of any severity. The patient can be exhausted by the movements themselves, by the effort to hide them, and by increased effort required to carry out daily activities. The primary impact on the brain itself may also produce fatigue. Although the disorders tend to disappear in sleep, they can make it difficult to fall asleep, adding to the exhaustion. Having to contend with the physical pain associated with tardive akathisia (inner torment) and with tardive dystonia (muscle spasms) can also wear a person down.

Psychological Suffering

Commonly, patients experience shame and humiliation, often leading to social withdrawal. Even a seemingly mild dyskinesia that affects facial expression can be sufficiently humiliating to cause a person to withdraw from society. So can a speech abnormality that makes a person seem to “talk funny.”

The experience of constant pain from dystonia or inner torture from akathisia can drive a person to suicidal despair. The physical disabilities associated with disorders can also become very depressing to patients.

In a clinical report from the Mayo Clinic by Rosenbaum (1979), depression was found closely linked to tardive dyskinesia. Rosenbaum states, “Almost all patients in our series had depressive symptoms accompanying the onset of tardive dyskinesia,” and he cites other studies confirming his observation.

Tardive dyskinesia patients often feel very betrayed by the doctors who prescribed the medication or who later failed to detect the disorder or to tell the patient about it. Too frequently, perhaps in a self-protective stance toward their colleagues, several psychiatrists in a row will fail to inform the patient or family about the obvious iatrogenic disorder. This can leave patients feeling that they cannot trust psychiatrists. In the extreme, it can create an understandable distrust of doctors in general.

Even a slight or minimal degree of tardive disorder can end up seriously impairing an individual’s quality of life.

NEUROLEPTIC WITHDRAWAL SYNDROME

Withdrawal frequently causes a worsening mental state, including tension and anxiety. With those drugs that produce potent anticholinergic effects, such as Thorazine and Mellaril, a cholinergic withdrawal syndrome (cholinergic rebound) may develop that mimics the flu, including emotional upset, insomnia, nausea and vomiting, diarrhea, anorexia and weight loss, and muscle aches.

Withdrawal symptoms can also include a temporary worsening of dyskinetic effects, both painful and frightening.

While classic addiction to these substances has not been demonstrated, the drugs should be considered addictive in the sense that withdrawal symptoms can make it impossible for patients to stop taking them. For this reason, I have suggested viewing these drugs as addictive (Breggin, 1989a, 1989b).

Because of the withdrawal symptoms, it is often necessary to reduce these drugs at a very slow rate. Sometimes withdrawal seems to be impossible. I have described the principles of withdrawing from psychiatric drugs in *Talking Back to Prozac*.

NEUROLEPTIC-INDUCED PSYCHOSIS AND DEMENTIA

The following chapter will describe irreversible psychosis and dementia associated with the neuroleptics. These may first become obvious as withdrawal effects that make it seemingly impossible to stop the drug therapy.

OTHER NEUROLEPTIC-INDUCED NEUROLOGICAL IMPAIRMENTS

The neuroleptics can produce a variety of other symptoms of central nervous system dysfunction, including abnormal electroencephalogram (EEG) findings, an increased frequency of seizures, respiratory depression, and disturbances of body temperature control (Davis, 1980; Davis & Cole,

1975). Endocrine disorders, especially in females, may also be of central nervous system origin (Davis, 1980). There is some evidence that autonomic dysfunction can become irreversible (tardive autonomic disorders).

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

This devastating disorder was seemingly so bizarre, unexpected, and inexplicable that physicians for years literally refused to believe their eyes. Seven years after the introduction of the drugs into North America, Leo Hollister (1961) reviewed their side effects for "Medical Intelligence" in the *New England Journal of Medicine*. In two separate places, he referred to syndromes that probably were NMS. He described a "bizarre" dystonic syndrome that can be "confused with hysteria, tetanus, encephalitis or other acute nervous-system disorders; a rare fatality may occur." Later he mentioned that "other clinical syndromes attributed to central-nervous-system effects of these drugs have resembled acute encephalitis, myasthenia gravis, bulbar palsy or pseudotabes."

Although NMS was identified in an English-language publication by Delay and Deniker as early as 1968, physicians continued to be reluctant to recognize the syndrome. Delay and Deniker declared it was caused by the neuroleptics, specifically including haloperidol (Haldol) and fluphenazine (Prolixin). Any neuroleptic can cause NMS. However, clinicians have found an increased danger with long-acting injectable neuroleptics.

Delay and Deniker were already able to identify many of the components of NMS, including pallor, hyperthermia, a severe psychomotor syndrome with akinesia and stupor or hypertonicity with varying dyskinesias. They warn that, at the first suspicion, "one must stop medication *immediately and completely*." They were already aware of fatalities. That the syndrome was named and definitively identified in English in 1968 is most remarkable in light of the failure of drug companies to give it formal recognition until compelled to do so by the FDA almost 20 years later (see chapter 11 for further discussion).

Neuroleptic malignant syndrome is characterized by "such symptoms as severe dyskinesia or akinesia, temperature elevation, tachycardia, blood pressure fluctuations, diaphoresis, dyspnea, dysphagia, and urinary incontinence" (Coons, Hillman, & Marshall, 1982). If unrecognized, as too often happens, it can be fatal in more than 20% of cases. The syndrome

frequently leaves the patient with permanent dyskinesias and dementia (see chapter 5).

Most cases develop within the first few weeks of treatment (even within 45 minutes!), but some develop after months or years, or after increased dosage (Gratz, Levinson, & Simpson, 1992).

Estimates for rates of neuroleptic malignant syndrome vary widely but studies indicate that they are very high. Pope, Keck, and McElroy (1986) surveyed 500 patients admitted during a 1-year period to a large psychiatric hospital and found a rate of 1.4%. The cumulative rate for patients would be much higher. Addonizio, Susman, and Roth (1986) carried out a retrospective review of 82 charts of male inpatients and found that prevalence for the diagnosed syndrome was 2.4%. Again, the cumulative rate over repeated hospitalizations or years of treatment would be much higher.

Although it is sometimes called "rare," NMS should be described as common or frequent (1/100 is common by FDA standards).

The rates for neuroleptic malignant syndrome, as well as its potential severity and lethality, make it an extreme risk for patients receiving antipsychotic drugs. A risk of this size would probably result in most drugs in general medicine being removed from the market.

I have reviewed cases in which several physicians at a time missed making the correct diagnosis in what seemed, from my retrospective analysis, like an obvious case of NMS. The failure to stop the neuroleptic and to institute proper treatment resulted in severe, permanent impairments, or death. The mistaken idea that NMS is rare may contribute to these errors in judgment.

After reviewing episodes of NMS in 20 patients, Rosebush and Stewart (1989) found that most cases fit the following cluster of symptoms: delirium, a high fever with diaphoresis, unstable cardiovascular signs, an elevated respiratory rate, and an array of dyskinesias, including tremors, rigidity, dystonia, and chorea.

Patients spoke little during the acute illness and later reported that they had found themselves unable to express their anxiety and feelings of doom. Almost all patients were agitated shortly before developing NMS, suggesting to the authors that they were undergoing akathisia. The white blood cell count was elevated in all cases, dehydration was common, and lab tests showed a broad spectrum of enzymatic abnormalities, including indications of muscle breakdown.

There is little or nothing about acute NMS to distinguish it from an acute, severe episode of encephalitis, especially lethargic encephalitis

(also called von Economo's disease), except for the fact of exposure to neuroleptic therapy. I have previously compared neuroleptic toxicity and lethargic encephalitis in detail (Breggin, 1993; also see chapter 5).

Although Rosebush and Stewart provide insufficient data to draw exact parallels, their NMS patients also suffered chronic impairments similar to those reported in lethargic encephalitis patients. Of the 20 patients, 14 continued to have "extrapyramidal symptoms or mild abnormalities of vitals signs and muscle enzymes at the time of discharge" (p. 721); but we are not told how many of the 14 specifically had persistent extrapyramidal signs. In a striking parallel with lethargic encephalitis, three patients displayed persistent parkinsonian symptoms until they were lost to follow-up. One patient, who had mild cognitive impairment prior to NMS, developed a persistent worsening of her dementia.

Neuroleptic malignant syndrome has also been reported with the atypical neuroleptics, clozapine (Anderson & Powers, 1991; DasGupta & Young, 1991) and risperidone (Dave, 1995; Mahendra, 1995; Raitasuo, Vataja, & Elomaa, 1994; Singer, Colette, & Boland, 1995).

NEUROLOGICAL MECHANISMS OF PARKINSONISM AND TD

Drug-induced parkinsonism apparently develops in part, but not wholly, from blockade of dopamine receptors in the basal ganglia, specifically the striatal region or striatum (the caudate and putamen), producing motor retardation, rigidity, and other symptoms. Damage and degeneration in the pigmented neurons of the substantia nigra play a key role. These neurons terminate in the striatum, where, when they are functioning normally, they release dopamine to act on striatal dopamine receptors.

Tardive dyskinesia is a more delayed reaction, probably based on the development of reactive supersensitivity or hyperactivity in these same striatal dopamine receptors following continuous blockade (see American Psychiatric Association, 1980; Fann, Smith, Davis, & Domino, 1980; Klawans, 1973; and chapter 5 in this volume). This supersensitivity of the dopamine receptors becomes most obvious when the drug is reduced or eliminated, terminating the blockade. The overactive, unblocked receptors produce the tardive dyskinesia symptoms. Undoubtedly a great deal more must be learned about the neuropathology of both these drug-induced

diseases, which probably involve multiple neurotransmitter system abnormalities.

CONCLUSION

The widespread use of neuroleptics has unleashed an epidemic of neurologic disease on the world. Even if tardive dyskinesia were the only permanent disability produced by these drugs, this would be among the worst medically induced disasters in history. Meltzer (1995) has urged that attempts be made to remove long-term patients from neuroleptics and has attempted to demonstrate its feasibility. Gualtieri (1993), warning about the extreme dangers, has suggested neuroleptics be viewed as a therapy of last resort. I believe the profession should make every possible effort to avoid prescribing them. Although beyond the scope of this book, it is worth ending with a reminder that there is strong evidence that psychosocial alternatives can be more effective in the treatment of both acute and chronic patients labeled schizophrenic (Breggin, 1991a; Breggin & Stern, 1996; Karon & Vandenbos, 1981; McCready, 1995; Mosher & Burti, 1989).