THE TRUTH ABOUT STIMULANTS

A COMPILATION OF FACTS

Presented by Grace E. Jackson, MD
Board Certified Psychiatrist
Winterville, NC 28590
gracejackson@ncfreedom.net

Includes Dr. Jackson's presentation to the FDA hearings on March 22 and 23, 2006
and
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FACT SHEET: Stimulants

Grace E. Jackson, MD
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What is a stimulant ?

A stimulant is any substance which increases or quickens a vital process. *Within* the central nervous system (brain and spinal cord), stimulants increase alertness, relieve fatigue, reverse cataplexy (muscle weakness), and/or induce euphoria.
Outside the brain and spinal cord, stimulants frequently activate the sympathetic nervous system. Stimulation of this nerve highway prepares the body for "fight or flight" by dilating the pupils, increasing heart rate, and raising blood pressure.

How are drugs classified as stimulants ?

The World Health Organization characterizes pharmaceutical substances on the basis of three properties: chemical, pharmacological, and therapeutic. The *chemical properties* of a drug include molecular composition (of what atoms is it composed ?) and spatial conformation (how are its atoms arranged ?). Chemical properties can provide an important clue about what a drug will do within the body, because the shape of a molecule has profound implications for a compound's net effect upon cellular processes (like a key fitting a lock).

Pharmacological properties refer to a drug's effects upon discrete chemical systems, cell receptors, and intracellular processes. For example, many stimulants have direct effects upon dopamine and norepinephrine (catecholamines). Other stimulants, such as caffeine and nicotine, influence dopamine indirectly. The pharmacological features of stimulants include their effects upon the central and peripheral (autonomic) nervous systems.

The *therapeutic (behavioral) properties* of stimulants refer to heightened arousal, enhanced stamina (decreased need for sleep), feelings of well-being, and appetite suppression. Other common behavioral effects include nervousness, insomnia, agitation, mania, paranoia, hallucinations, and movement abnormalities (tics, dyskinesias).

What is the difference between stimulation and addiction ?

During the development of new drug products, chemicals are screened for potential addictiveness using non-human models (typically, mice and rats). An *addictive* compound refers to a chemical which rodents will self-administer – usually with increasing frequency, and sometimes to the point of starvation, sleeplessness, or death. This animal model is presumed to reflect the capacity of a substance to stimulate the "reward" centers of the brain, resulting in increased drug liking or wanting (craving).

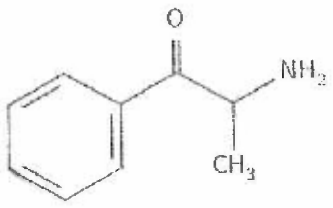
Under the Controlled Substances Act of 1970, addictive chemicals are designated by the Drug Enforcement Agency as "controlled" substances and ranked on one of five schedules (I through V) according to their relative propensity to induce compulsive use. It is possible for a pharmaceutical product to fulfill the criteria of a *stimulant* without meeting the DEA's criteria for chemical addictiveness.

Despite marketing claims to the contrary, atomoxetine (Strattera) and bupropion (Wellbutrin, Zyban) are *non-controlled stimulants.* They have been marketed as **non-stimulants,** in order to avoid negative reactions by consumers who might otherwise reject their use because of the assumption that all stimulants are powerfully addictive.

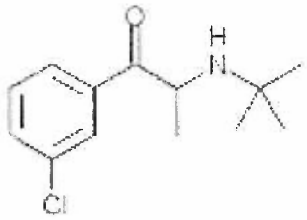
Examples of Stimulants That Have Been Marketed as Non-Stimulants

Bupropion (Wellbutrin) & Atomoxetine (Strattera)

Bupropion (Wellbutrin, Zyban) is *chemically* related to cathinone, the amphetamine ingredient of the botanical stimulant known as Khat or qat. As a substituted beta-keto-amphetamine, bupropion may trigger positive results on urine screens for illicit drug use.



chemical structure of cathinone

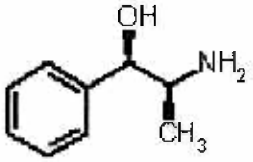


chemical structure of bupropion

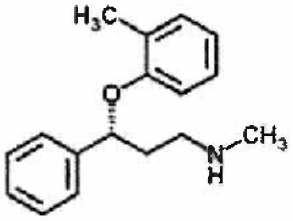
Buproprion's *pharmacological* effects include stimulation of the sympathetic nervous system (increase in heart rate and blood pressure), presumably via the modulation of catecholamines. Its usefulness in smoking cessation has historically been attributed to dopamine. However, more recent research has suggested a role for bupropion in blocking or antagonizing specific subtypes of cholinergic, nicotinic receptors on neurons.

Like other amphetamine compounds, bupropion's *behavioral effects* include anorexia, insomnia, arousal, agitation, mania, and psychosis.

Atomoxetine (Strattera) is a derivative of the stimulant *phenylpropanolamine,* or *PPA.* On November 6, 2000, the Food and Drug Administration issued a public health advisory about PPA, calling for its removal from over-the-counter cold remedies and other products due to its risk of hemorrhagic stroke (bleeding into the brain or surrounding tissues). It remains to be seen if atomoxetine will prove to have similarly dire effects upon the cerebrovascular system.



chemical structure of phenylpropanolamine



chemical structure of atomoxetine

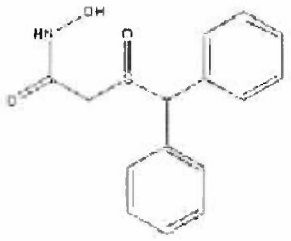
The direct *pharmacological effects* of atomoxetine involve the selective inhibition of the norepinephrine (adrenaline) reuptake transporter, a mechanism which is presumed to enhance the flow of noradrenegic signals in the brain and spinal cord. Peripheral actions include the stimulation of the sympathetic nervous system, leading to increased blood pressure and heart rate, dry mouth, mydriasis (pupillary dilation), and urinary retention or hesitancy.

Like other stimulants, atomoxetine is believed to enhance alertness by altering norepinephrine activity in the frontal cortex and brainstem. Other *behavioral effects* include insomnia, anorexia, nervousness, suicidality, hostility, akathisia, and mania.

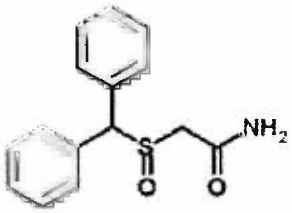
The fact that atomoxetine does not appear to enhance dopamine transmission in the striatum or the mesoaccumbens has encouraged some clinicians to suggest that atomoxetine is non-addictive. However, it should be noted that rats, pigeons, and monkeys have failed to distinguish between atomoxetine and low doses of cocaine or methamphetamine on drug discrimination tasks. Furthermore, the potential for atomoxetine to induce psychological rather than physiological dependence has not been systematically investigated or disproved.

What About Modafinil (Provigil, Sparlon) ?

Modafinil (Provigil, Sparlon) is classified by the World Health Organization as a centrally active stimulant with sympathomimetic effects. (This means that modafinil stimulates the sympathetic nervous system, increasing blood pressure and heart rate).



chemical structure of adrafinil



chemical structure of modafinil

Modafinil is a sulfinyl compound derived from adrafinil. The latter chemical is a central nervous system stimulant which was created in France in the late 1970s and subsequently tested as a treatment for narcolepsy.

The *pharmacological effects* of modafinil remain under investigation. Proposed mechanisms of action include the inhibition of dopamine reuptake (a feature shared by cocaine and methylphenidate), the activation of glutamate and orexin, the inhibition of GABA (a major inhibitory neurotransmitter), and the blockade of norepinephrine reuptake in the sleep promoting center of the brain.

The *behavioral effects* of modafinil qualify the drug as a super-stimulant. Originally approved by the FDA in 1998 as a treatment for narcolepsy, modafinil has been used by college students, shift workers, military pilots, and athletes to boost alertness, stamina, and wakefulness. Physicians have administered the drug to surgical patients to speed recovery from general anesthesia. The Drug Enforcement Agency classifies modafinil as a *controlled substance* (Schedule IV), based upon its potential for abuse. Rehabilitation centers have tested modafinil as a replacement for cocaine, and the International Olympic Committee has banned modafinil as an unauthorized, performance enhancing compound.

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ICSPP Press Conference

Grace E. Jackson, MD
March 22, 2006

Problem: Neuronal Imprinting

Re-wiring the Brain in Harmful Ways

Example: addiction

Study #1

Northern California Study

Northern California
[Lambert: 1998, 2005, & 2006]

- **492** children (282 hyperactive, 210 controls)
- 28 year prospective study
- began in 1973-1974, children in K-5
- data from multiple sources (parents, teachers, medical records, subjects)

Pre-exposure to Stimulants
DSMIIIR dependence

	ADHD		Stimulants	
	no	yes	no	yes
Tob dep	22%	45%	25%	**45%**
Coc dep	11%	23%	12%	**24%**

Duration of Treatment

Of ADHD children:

	no stim	<1 yr	1 yr or more
Tob dep	32%	39%	**49%**
Cocaine dep	15%	18%	**27%**

Among 202 cocaine users…

33% (n = 66) received stimulants for ADHD

ALL of the stimulant treated children began **cocaine** AFTER medication was started & withdrawn

(i.e., none were self-medicating with cocaine)

Predictors of Cocaine Dependence at age 26-30 & 36-40

	Adjusted Odds Ratios
Stimulant treatment	**1.756**
ADHD (DSMIV)	1.456
Conduct problems	**0.296**
Regular smoking	3.120
Drug liking	1.090
Drug wanting	3.362

All values significant at p <0.05, < 0.01, <0.001

Study #2

Barkley (Wisconsin) Study

Barkley et al. (2003)

- Wisconsin clinic-based study
- 239 children (158 ADHD, 81 controls)
- 15-year prospective study
- 3 check points in time:
  childhood, adolescence, early adulthood

Lifetime Use of Cocaine

Stimulants in childhood	**26%**	p = 0.037
No stimulants	5%	
Stimulants in high school	**40%**	p = 0.016
No stimulants	20%	

Intensity of Use

Childhood & High School Stimulant RX

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higher frequency of cocaine use
as young adult (mean age: 21)

Study #3

University of Michigan

University of Michigan
[McCabe et al., 2006]

Features of Study:

- undergrad survey
- March/April 2003
- 47% response rate
- final n = 9161

➢ 8% reported illicit use of prescription stimulant over lifetime

➢ 5.4% reported illicit use in past year

ADHD who began treatment with stimulants in middle school, high school, or college were **3 to 7X** more likely than non-stimulant prescribed ADHD to report illicit use of **prescription stimulants**.

Cocaine Use According to Stimulant Treatment History

Stimulant Rx for ADHD	Use of cocaine in past year %	Odds Ratio	
none	3.2%	1.00	
elementary	9.2%	**2.42**	
secondary	19.2%	**4.40**	$p < 0.001$
college	22.1%	**4.46**	$p < 0.001$

Study #4

University of Wisconsin

University of Wisconsin
[Hall et al., 2005]

Features of Study:

- questionnaire to residence hall occupants & intro psych students
- n = 381
- average age: 19.4

➢ illicit use of Rx stim:
17% of men
11% of women

➢ **4 of 10 currently receiving stimulants for ADHD reported using drugs for non-medical purposes**

Study #5

University of Charleston

College of Charleston
[Upadhyaya et al., 2005]

Features of Study:

- fall 2001
- 334 subjects (mostly 4 yr stated funded college)
- convenience sample in conjunction with annual Core EtoH and Drug Survey
- 30 minute survey given during class periods

Other important features:

61% of subjects were female	
85% were Caucasian	
clinically diagnosable ADHD:	25%
hx of stimulants for ADHD:	23%
currently on Rx stimulants:	20%
ever give meds away:	29%
ever got high on own meds:	**25%**

Just Say No !

FACT SHEET: ADDICTION & STIMULANTS

Grace E. Jackson, MD
March 18, 2006

According to several recent publications prepared by corporately sponsored clinicians, ADHD medications (predominantly, stimulants) "do not increase, but appear to decrease the risk for substance abuse." It would be difficult to imagine a more misleading or distorted presentation of the pertinent facts.

In reality, treatment with stimulant medications – whether it is initiated in early childhood, adolescence, or adulthood – appears to re-wire the brain in a way which increases the likelihood of future dependence upon chemical substances. Four studies will be briefly described here, challenging the veracity of the pharmaceutical industry's continuing media barrage, and presenting an argument for a more responsibly informed standard of care.

The Northern California Study

The largest and longest analysis of ADHD outcomes, to date, is the Northern California study performed by Dr. Nadine Lambert's research team at the University of California (Berkeley). Begun in 1973-1974, the study involved a 28-year investigation of 492 children recruited from classrooms throughout the Bay Area. Particular strengths of this study were the collection of data from multiple sources (parents, physicians, teachers, patients) at multiple points in time (eight separate interviews with the subjects and controls). A major finding of the study was a positive association between exposure to stimulants in childhood and the eventual *dependence* upon nicotine and cocaine:

(Lambert, 2006)

Effect of ADHD & Pre-Exposure to Stimulant

	ADHD		Stimulants	
	no	yes	no	yes
Tobacco dependent	22%	45%	25%	**45%**
Cocaine dependent	11%	23%	12%	**24%**

The duration of stimulant exposure in childhood was positively correlated with future addiction to nicotine and cocaine:

(Lambert, 1998)

Of ADHD Children receiving:

	No stimulant	stimulant < 1 year	stimulant for 1 yr or more
Tobacco dependent	32%	39%	**49%**
Cocaine dependent	15%	18%	**27%**

Of the original 492 children (282 with hyperactivity, 210 controls) in the Northern California study, 202 reported some cocaine use by the age of 40. Treatment with stimulants in early childhood was associated with a ***two-fold higher risk of cocaine dependence***, an association which was six times stronger than the link between conduct problems and later dependence upon cocaine.

The significance of Lambert's findings rests partly upon the fact that the use of cocaine and nicotine were carefully monitored *prospectively* over time. In all cases, substance abuse commenced *after* the initiation of treatment with stimulant medications. This suggests that prescription stimulants re-wired the subjects' brains in ways which *sensitized* neural pathways to future drug experimentation or compulsive use [see Robinson and Berridge, as referenced below].

The Barkley Study

Although the authors of a second large investigation (Barkley et. al.) have done their best to deny it, the raw data from their 15-year study support the theory of neural sensitization. In this Wisconsin, clinic-based exploration of 158 ADHD children, early exposure to stimulants was associated with a ***five-fold higher likelihood of lifetime cocaine use*** [p=0.037], and with the ***higher frequency of cocaine use as a young adult*** [p = 0.059]. The continuation of treatment with stimulants during adolescence was associated with similar outcomes: ***two-fold higher likelihood of cocaine use*** [p=0.016], and a ***higher frequency of cocaine use as a young adult*** [p = 0.043]. Tragically, the Barkley study has been misinterpreted in the medical literature as providing proof that stimulants do not increase the risk of later addiction, while conduct disorder and ADHD symptoms do. This confusion presumably arises from a failure of clinicians to carefully read the published study *in toto* and to contemplate the numerous flaws and statistical manipulations which have permitted the study's authors to declare "that stimulants do not lead to an increased risk of adult substance abuse."

(Barkley et. al., 2003)

Lifetime Use of Cocaine

Medicated with stimulants in early childhood	**26%**	p = 0.037
Not medicated with stimulants in early childhood	5%	
Medicated with stimulants in high school	**40%**	p = 0.016
Not medicated with stimulants in high school	20%	

Recent College Surveys – Childhood Treatment Does Not Prevent Substance Abuse

Given the fact that the ADHD epidemic in America exploded in the early 1990s, it stands to reason that many children from this age group have only recently graduated from high school and matriculated in college programs. Several cross-sectional surveys of undergraduate students lend further support to the theory that pre-exposure to stimulants changes the brain in ways which make addictions more, rather than less, likely.

For example, a 2003 survey administered to undergraduates at the University of Michigan (n = 9161) revealed that 8% of the respondents had used prescription stimulants illicitly in the course of their lifetime (five per cent within the past year). Among students who had been diagnosed with ADHD, the initiation of treatment with stimulants (versus no stimulants) during middle school, high school, or college was associated with a higher likelihood of illicit stimulant use, ***and*** with a ***two- to four-fold higher likelihood of cocaine use over the course of the past year***. A 2001 survey administered to undergraduate students at the University of Charleston (n = 334) revealed that 25% of the students who had received stimulants for ADHD had used their medications at some time to "get high," further disproving the hypothesis that treatment with medication decreases the risk of future stimulant abuse or dependence.

In conclusion, the comments of certain opinion leaders in the field of psychiatry have been egregious and misleading. If these opinions continue to be accepted uncritically and continue to be widely disseminated, they could have dire consequences from a public health perspective. ***The published findings from several large studies of ADHD children who have been followed into early or middle adulthood suggest that treatment with prescription stimulants increases, rather than prevents, the likelihood of certain chemical dependencies***. The sensitization theory of addiction predicts that some substances have the potential to re-wire the brain in ways which enhance the propensity for drug liking or drug wanting. Based upon the available research evidence, the sensitization theory for stimulants has been impressively affirmed in non-human and human subjects. It is time for physicians to incorporate this knowledge into their daily practices; to modify the information which they may now be sharing with their patients and with patients' families; and to elevate the quality of medical care, accordingly.

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FDA Hearing on Stimulants – March 22, 2006
Grace E. Jackson, MD

Stimulants Damage the Heart

In 1977, Drs. Vernon Fischer and Hendrick Barner wrote a Letter to the Editor at *JAMA*, in which they described the cellular changes associated with cardiomyopathy (enlarged heart) in a patient who had taken Ritalin for 4 ½ years. A tissue sample was obtained from the patient during open heart surgery. That biopsy demonstrated abnormal membrane accumulations in the left ventricle.

Curious to know if the Ritalin had played any role in these changes, Fischer later teamed with Theodore Henderson to conduct animal studies. A causal effect was confirmed. Ritalin in mice and rats produced the same kinds of membrane proliferation in the heart cells seen previously. These changes were consistent with the cardiomyopathy observed earlier in the human subject.

Strattera – America's Most Famous "Non-Stimulant"

Strattera is classified as a ***psychostimulant*** by the World Health Organization. Because of its ***stimulant*** effects, Strattera has been adopted by neurologists as a treatment for narcolepsy. Because of its ***stimulant*** effects, Strattera has been investigated by clinical trialists as a potential treatment for obesity.

In January 2006, the Office of the Chief Medical Examiner in North Carolina reported the discovery of ventricular abnormalities in the hearts of two young people who died while taking therapeutic doses of Strattera. It is important for the FDA to appropriately characterize Strattera as a stimulant, and to issue warnings about its potential cardiovascular risks.

Stimulants Reduce Cortical Blood Flow

In 1984, researchers discovered that Ritalin reduced cortical blood flow in children with ADD. In 1994, a team at Brookhaven Laboratory in Long Island replicated this finding, when they administered Ritalin intravenously to a group of healthy volunteers. The participants experienced a 20-30% **global** reduction in cerebral blood flow. The investigators concluded that these changes were most likely due to direct, vasoactive properties of Ritalin. They warned that oral doses of the same drug might produce similar, but even longer lasting, decrements.

Although the neurovascular effects of Ritalin are seldom considered by physicians or the FDA, the neuroscientific evidence has been undeniably clear. Numerous studies have confirmed that Ritalin, like cocaine and other street drugs, impedes neurodevelopment and shrinks the brain. The drug-induced impairment of blood flow is a likely causal mechanism about which medical professionals and consumers must be warned.

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FDA Hearing on Stimulants
March 22, 2006

Grace E. Jackson, MD
Diplomate, American Board of Psychiatry and Neurology

Disclosures:

- expert witness on behalf of Law Project for Psychiatric Rights;
- invited lecturer in the United Kingdom, receiving speaker's and/or travel fees from the University of Central England, the Shrewsbury Public Health Trust, the Overload Network, and the British Psychological Society

Section I

Stimulants damage the heart

methylphenidate (Ritalin)
[Fischer & Barner, 1977]

Letter to the Editor:

cardiomyopathic changes in patient treated with MPH for 4 ½ years

myocardial biopsy was obtained during coronary bypass surgery

Methylphenidate (Ritalin)
causal effects in mice and rats
[Henderson & Fischer, 1994]

30 male mice
IP injections
0.5, 2.5, 5.0 mg/kg
3x per week x 4 or 14 wks

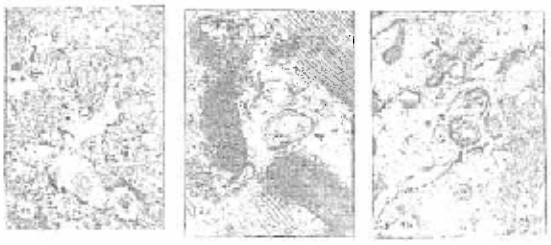
6 controls

6 mice
oral exposure
5 mg/kg x 4 or 14 weeks

14 male SD rats
IP injections
2, 20, 100 mg/kg
X 3, 6, or 9 weeks

2 rats
IP injections
2 mg/kg or 20 mg/kg
X 12 weeks
Recovery for 12 weeks

Human vs. Mouse vs. Rat
membrane proliferation, sarc. sequestration



Significance

- Cellular abnormalities appeared quickly (within three weeks)
- Cellular abnormalities persisted (even 12 weeks after MPH withdrawn)
- Lower doses of MPH approached same mean as higher doses after 9 weeks
- Doses c/w therapeutic doses in humans (including oral protocol in mice)

Clinical Implications

"Findings may have clinical consequences for long term side effects of MPH . . .

"Future studies of the cellular and electrophysiological effects of this drug are indicated."

[*American Journal of Cardiovascular Pathology*, 1994]


Strattera.com - About Strattera

strattera

This page may be found at: http://www.strattera.com/L_L_about_strattera/L_L_about.jsp

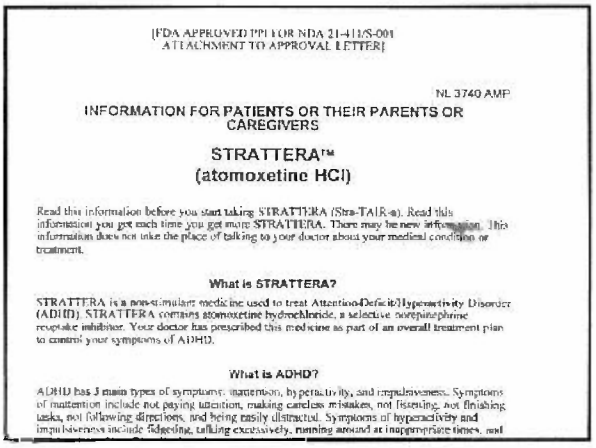
About Strattera

What is Strattera?
(Pronounced Stra-tair-a)

Strattera is the first and only non-stimulant medication approved by the US Food and Drug Administration (FDA) for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. Strattera is a [illegible] reuptake inhibitor, a class of ADHD treatment that works differently from the other ADHD medications available. Strattera is available by prescription only.

What are the Benefits of Strattera?

- **Proven Safe and Effective**
  Six clinical trials have proven Strattera to be safe an effective in treating all symptoms of ADHD. Over 2 million prescriptions for Strattera have been filled since the FDA approved it in 2002.


[FDA APPROVED PPI FOR NDA 21-411/S-001
ATTACHMENT TO APPROVAL LETTER]

NL 3740 AMP

INFORMATION FOR PATIENTS OR THEIR PARENTS OR CAREGIVERS

STRATTERA™
(atomoxetine HCl)

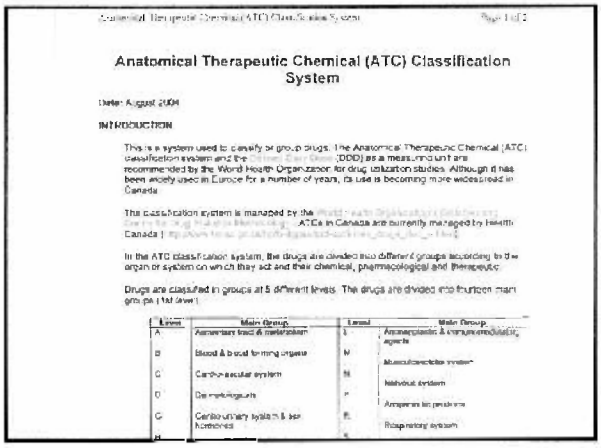
Read this information before you start taking STRATTERA (Stra-TAIR-a). Read this information you get each time you get more STRATTERA. There may be new information. This information does not take the place of talking to your doctor about your medical condition or treatment.

What is STRATTERA?

STRATTERA is a non-stimulant medicine used to treat Attention-Deficit/Hyperactivity Disorder (ADHD). STRATTERA contains atomoxetine hydrochloride, a selective norepinephrine reuptake inhibitor. Your doctor has prescribed this medicine as part of an overall treatment plan to control your symptoms of ADHD.

What is ADHD?

ADHD has 3 main types of symptoms: inattention, hyperactivity, and impulsiveness. Symptoms of inattention include not paying attention, making careless mistakes, not listening, not finishing tasks, not following directions, and being easily distracted. Symptoms of hyperactivity and impulsiveness include fidgeting, talking excessively, running around at inappropriate times, and


Anatomical Therapeutic Chemical (ATC) Classification System

Anatomical Therapeutic Chemical (ATC) Classification System

Date: August 2004

INTRODUCTION

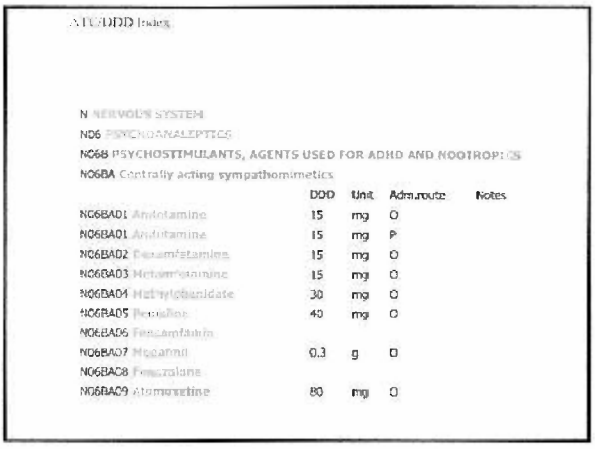
This is a system used to classify or group drugs. The Anatomical Therapeutic Chemical (ATC) classification system and the [illegible] (DDD) as a measurement unit are recommended by the World Health Organization for drug utilization studies. Although it has been widely used in Europe for a number of years, its use is becoming more widespread in Canada.

The classification system is managed by the [illegible] ATCs in Canada are currently managed by Health Canada [illegible]

In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacological and therapeutic

Drugs are classified in groups at 5 different levels. The drugs are divided into fourteen main groups (1st level).

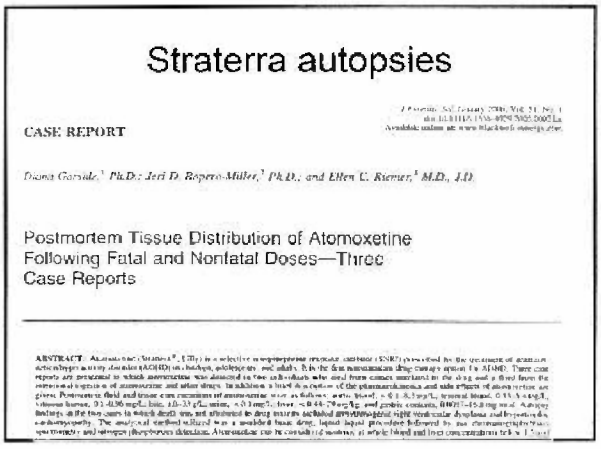
Level	Main Group	Level	Main Group
A	Alimentary tract & metabolism	L	Antineoplastic & immunomodulating agents
B	Blood & blood forming organs	M	Musculoskeletal system
C	Cardiovascular system	N	Nervous system
D	Dermatologicals	P	Antiparasitic products
G	Genito urinary system & sex hormones	R	Respiratory system
H	[illegible]	S	[illegible]


ATC/DDD Index

N NERVOUS SYSTEM
N06 PSYCHOANALEPTICS
N06B PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
N06BA Centrally acting sympathomimetics

	DDD	Unit	Adm.route	Notes
N06BAD1 Amfetamine	15	mg	O	
N06BA01 Amfetamine	15	mg	P	
N06BAD2 Dexamfetamine	15	mg	O	
N06BA03 Metamfetamine	15	mg	O	
N06BA04 Methylphenidate	30	mg	O	
N06BA05 Pemoline	40	mg	O	
N06BAD6 Fencamfamin				
N06BA07 Modafinil	0.3	g	O	
N06BAC8 Fenozolone				
N06BA09 Atomoxetine	80	mg	O	

Straterra autopsies


CASE REPORT

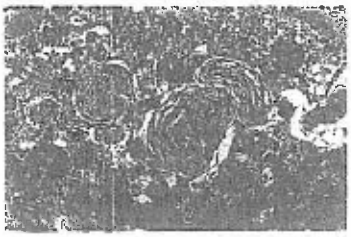
Diana Garside,[1] Ph.D.; Jeri D. Rupert-Miller,[1] Ph.D., and Ellen C. Riemer,[1] M.D., J.D.

Postmortem Tissue Distribution of Atomoxetine Following Fatal and Nonfatal Doses—Three Case Reports

ABSTRACT: Atomoxetine (Strattera®, Lilly) is a selective norepinephrine reuptake inhibitor (SNRI) prescribed for the treatment of attention deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults. It is the first nonstimulant drug therapy option for ADHD. There are reports of suicidal ideation associated with atomoxetine use in children who used it for conditions other than ADHD and a third from the commercial ingestion of atomoxetine and other drugs. In addition, a brief discussion of the pharmacokinetics and side effects of atomoxetine are given. Postmortem fluid and tissue concentrations of atomoxetine were as follows: aortic blood, < 0.1–8.3 mg/L; femoral blood, 0.13–3.4 mg/L; vitreous humor, 0.2–0.96 mg/L; bile, 10–33 g/L; urine, < 0.1 mg/L; liver, < 0.04–79 mg/kg; and gastric contents, 0.007–15.0 mg total. Autopsy findings in the two cases in which death was not attributed to drug toxicity included arteriosclerotic right ventricular dysplasia and hypertrophic cardiomyopathy. The analytical method utilized was a modified basic drug, liquid liquid procedure followed by gas chromatography/mass spectrometry and nitrogen phosphorous detection. Atomoxetine can be successfully isolated in whole blood and liver concentrations below 1.0 mg/L

Strattera Deaths

11 yo female, 5'5" 118 lbs	24 yo male, 6'5" 180 lbs
cheerleader collapsed at school ball game	Strattera 20 mg b.i.d.
Strattera & dextroamphetamine	found dead at home by case manager
death from cardiomyopathy (RV dysplasia)	death from LV cardiomyopathy, cardiomegaly, pulm. edema



Left ventricular myocardium with lamellated bodies (arrows) measuring approximately 500 to 3,000 nm and sequestering portions of myocardial sarcoplasm. N indicates nucleus (× 12,000).

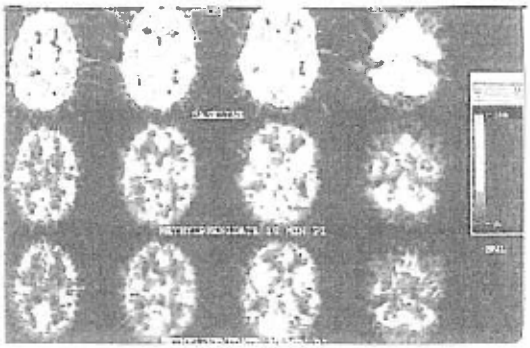
Section II

Other Vascular Effects

Methylphenidate & Blood Flow

[Wang et al., 1994]

- In a PET imaging study of 5 healthy volunteers, MPH (Ritalin) 0.5 mg/kg was given intravenously
- 20-30% global reduction in blood flow persisted for at least 30 minutes



"The lack of a regional effect in CBF suggests that these changes probably reflect direct vasoactive properties of MP and not its effects on neuronal tissues since changes in glucose metabolism after MP are regionally specific..."

"Though CBF changes after oral MP are probably smaller than with intravenous MP, its pharmacokinetics may be slower and the CBF decrements may last longer…"

Implications

If the **cortex** is deprived of oxygen, cortical neurons malfunction or die.

Result: cortical atrophy.

FDA on Stimulants

- 2000: requested manufacturers to remove phenylpropanolamine from cold remedies and OTC
- 2004: issued rule prohibiting sale of dietary supplements containing ma huang (ephedra)
- 2006: issued warning about Brazilian diet pills containing stimulant Fenproporex

FDA Hearing on Stimulants – March 23, 2006
Grace E. Jackson, MD

Stimulants Suppress Growth of Bones & Brain

Stimulant treatments for ADHD have been shown to suppress the growth rates of children in numerous studies. In the largest government investigation to date, 579 children were evaluated prospectively over the course of 2 years. Medicated children suffered a persistent suppression of growth equal to 1 cm (0.39 inches) per year. Unmedicated children grew normally.

Although stimulant package inserts continue to deny a causal effect between prescription drugs and growth suppression, a causal mechanism was clearly demonstrated by *in vitro* experiments reported in 1979. Researchers at the University of Arkansas described *how* stimulants suppress the formation of cartilage in bone tissue. That study has been overlooked by scientists for more than 20 years.

The potential effects of stimulants upon craniofacial development should be seriously considered. The human skull undergoes significant growth through age seven, along with important remodeling well into adolescence. Impairments in this process could have dire consequences for the normal development of the brain.

The neuroimaging studies of subjects addicted to street drugs, such as cocaine and amphetamine, share a common finding: reduced gray matter and smaller brains. Such findings are consistent with the studies of children who have been medicated with stimulants. The implication is that prescription drugs, just like street drugs, shrink the human brain.

Stimulants Cause Neuronal Imprinting - Example: Addiction

The phenomenon of neuronal imprinting refers to the process by which medications alter the development of entire pathways or systems within the brain. While this process is especially important in children, it is no less critical in adults. Stimulants, such as methylphenidate and amphetamine, re-wire the brain in harmful ways which increase the likelihood of future chemical dependencies (such as nicotine and cocaine).

Stimulant Are Futile Treatments for ADHD

The U.S. government's largest (MTA) study demonstrated diminishing effects for medication over time. By the 14 month endpoint, previously unmedicated children enjoyed a numerically superior outcome if they remained drug free. At a 24 month follow-up, previously medicated children who remained on drugs began to experience a reversal of fortune. The benefits of behavioral therapy were enduring. The benefits of stimulants did not persist.

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FDA Hearing on Modafinil
March 23, 2006

Grace E. Jackson, MD
Diplomate, American Board of Psychiatry and Neurology

Disclosures:

- expert witness on behalf of Law Project for Psychiatric Rights;
- invited lecturer in the United Kingdom, receiving speaker's and/or travel fees from the University of Central England, the Shropshire County Primary Care Trust, the Overload Network, and the British Psychological Society

Class Effects of **Stimulants**

- Growth suppression
- Neuronal imprinting
- Futility for ADHD

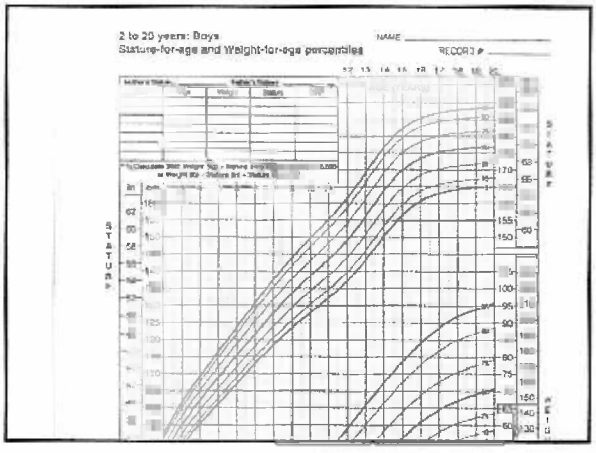
ATC/DDD Index

N NERVOUS SYSTEM
N06 PSYCHOANALEPTICS
N06B PSYCHOSTIMULANTS, AGENTS USED FOR ADHD AND NOOTROPICS
N06BA Centrally acting sympathomimetics

	DDD	Unit	Adm.route	Notes
N06BA01 Amfetamine	15	mg	O	
N06BA01 Amfetamine	15	mg	P	
N06BA02 Dexamfetamine	15	mg	O	
N06BA03 Metamfetamine	15	mg	O	
N06BA04 Methylphenidate	30	mg	O	
N06BA05 Pemoline	40	mg	O	
N06BA06 Fencamfamin				
N06BA07 Modafinil	0.3	g	O	
N06BA08 Fenetylline				
N06BA09 Atomoxetine	80	mg	O	

Point #1

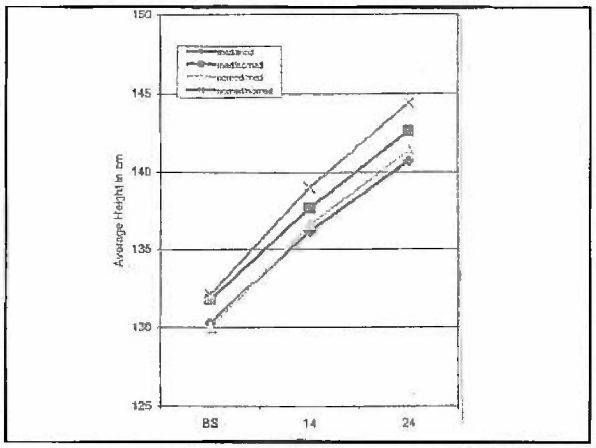
Stimulants suppress growth



MTA Study (1992-1994)
Multimodal Treatment Study of ADHD

- commissioned by NIMH and Dept. of Ed.
- 579 children, ages of 7– 9.9 (grades 1-4)
- results published for 14 and 24 mo. f/u
- analyses have been done for ITT* and naturalistic subgroups

* ITT = intention to treat



Persistent **Effects of Stimulants**

Growth Rate:

- 1 cm per year = - 0.39 inches per year
- 1.25 kg per year = - 2.75 lbs per year

ADHD does not stop growth. Stimulants do.

- The MTA study found no evidence that ADHD was the cause of suppressed growth
- This finding has been consistently replicated in longitudinal studies of children, measuring growth rates

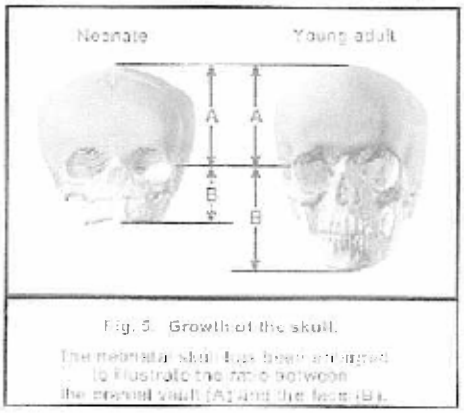
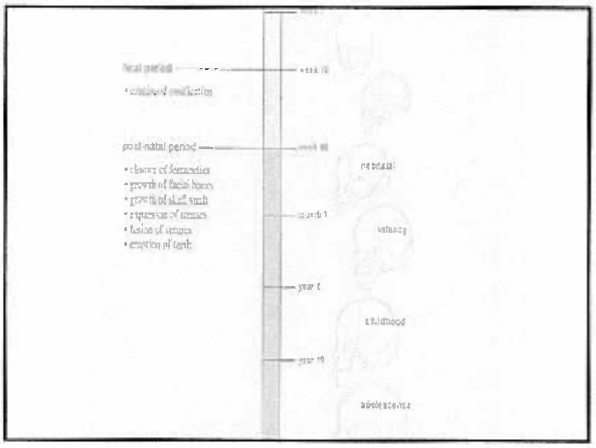


Fig. 5. Growth of the skull.

The neonatal skull has been enlarged to illustrate the ratio between the cranial vault (A) and the face (B).



Suggested Mechanisms

decreased growth hormone ?
changes in pulsatile secretion ?
GH receptor change ?
decreased IGF (somatomedins) ?
hyperprolactinemia ?
leptin ?
neuropeptide Y ?
serotonin ?

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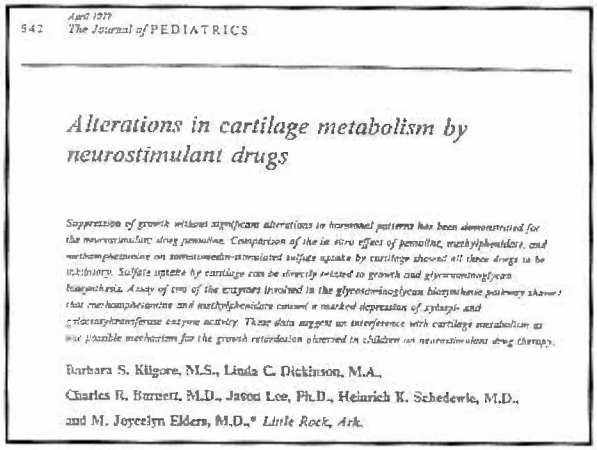


April 1977
542 The Journal of PEDIATRICS

Alterations in cartilage metabolism by neurostimulant drugs

Suppression of growth without significant alterations in hormonal patterns has been demonstrated for the neurostimulatory drug pemoline. Comparison of the in vitro effect of pemoline, methylphenidate, and methamphetamine on somatomedin-stimulated sulfate uptake by cartilage showed all these drugs to be inhibitory. Sulfate uptake by cartilage can be directly related to growth and glycosaminoglycan biosynthesis. Assay of two of the enzymes involved in the glycosaminoglycan biosynthesis pathway showed that methamphetamine and methylphenidate caused a marked depression of xylosyl- and galactosyltransferase enzyme activity. These data suggest an interference with cartilage metabolism as one possible mechanism for the growth retardation observed in children on neurostimulant drug therapy.

Barbara S. Kilgore, M.S., Linda C. Dickinson, M.A., Charles R. Burnett, M.D., Jason Lee, Ph.D., Heinrich K. Schedewie, M.D., and M. Joycelyn Elders, M.D.,* *Little Rock, Ark.*

Inhibitory Effect on Biosynthesis

- decreased uptake of sulfate into cartilage
- decrease in activity of enzymes associated with first steps of glycosaminoglycans (GAG) pathway:

	enzyme 1	enzyme 2
MPH	79%	63%
methamphetamine	65%	65%

Point #2

Stimulants cause neuronal imprinting

Neuronal Imprinting

"…chronic, early childhood exposure to stimulants and antidepressants may actually exacerbate symptoms later in life…rather than reduce them, or even result in a new constellation of psychiatric symptoms…"

[Andersen & Navalta, 2004]

Example: Addiction

Stimulants given to children and teens re-wire the brain in a harmful way which causes an increased likelihood of future chemical dependencies

Point #3

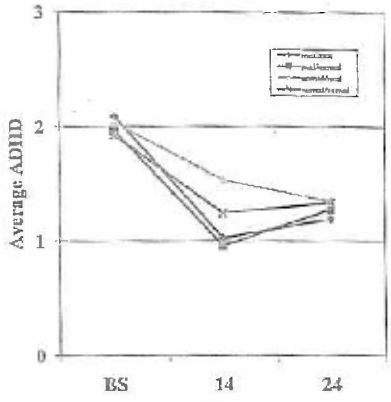
Stimulants are futile treatments for ADHD, as demonstrated by the government's (MTA) largest study to date.

FUTILITY

For previously unmedicated children, the MTA study showed no statistically significant difference between any of the four interventions (2 medication groups, behavioral therapy, combined treatment)

2 year outcomes: MTA

Trajectories of symptoms REVERSED



Long Term Futility of Stimulants

- Behavioral therapy effects endured
- Medication benefits declined

BLACK BOX NOT ENOUGH !

CONTRAINDICATIONS

For ADHD, stimulants should be contraindicated for children with ADHD

WHY ?

- Stimulants suppress growth
- Stimulants cause neuronal imprinting
- Stimulants are futile treatments for ADHD

Just Say No !