

Acknowledgments

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Translator: Althea Muirhead (althea.muirhead@gmail.com)

Petition brought to the Regional Administrative Courts of Lazio by “Giù le Mani dai Bambini” against the resolution of the Italian Drug Agency (AIFA) taken in 2007 authorising the marketing in Italy of Methylphenidate and Atomoxetine to treat ADHD.

Scientific opinion by Professor Emilia Costa and Dr. Claudio Ajmone.

Legal Advisors: Stefania Tonini and Dario Forasassi of Studio Legale Associato, Viale E. Panzacchi, 19, 40136 Bologna, Italy. Tel. +39 051-580077, e-mail info@gliavvocati.it

Prof. Emilia Costa

Psychiatrist

1st Chair of Psychiatry at “La Sapienza” University, Rome

Chief Physician at the Department of Clinical Psychology and Psychopharmacology at

“Umberto I” Polyclinic Hospital, Rome

Expert of the Rome Law Courts

Piazza Passo dei Pordoi, 7 – 00135 Rome

emilia.costa@uniroma1.it

Dott. Claudio Ajmone

Psychologist, Psychotherapist

Founder of the *Osservatorio Italiano per la Salute Mentale*

Member of the European Association of Psychoanalysis

Via Domenico Cimarosa, 95 – 10154 Turin

claudio.ajmone@fastwebnet.it

Object: technical report and comparative statistical opinions on Attention Deficit Hyperactivity Disorder (known as “ADHD”) and the treatment of minors with psychoactive drugs based on methylphenidate (Ritalin®) and atomoxetine (Strattera®). Document drafted on a voluntary basis, by request of the National Committee of “Giù le Mani dai Bambini”®

In this report, it is important to highlight, first of all, that, in strictly scientific terms, the following issues are still under debate:

- A. whether the dysfunctional behaviour known as “ADHD” (Attention Deficit and Hyperactivity Disorder) may or may not be defined as a syndrome;
- B. whether molecules such as methylphenidate (commercial name Ritalin®) and atomoxetine (commercial name Strattera®) may or may not be used safely and effectively for the treatment of the supposed syndrome “ADHD”;

- C. whether, in relation to the issues examined in points (A) and (B), the need to safeguard the psychophysical wellbeing of minors is currently fully implemented in Italy, as emphasised by current international legislation on human rights protecting against the commercial speculation and improper use of drugs, with particular regard to psychoactive drugs.

QUESTION A: Whether ADHD can be defined as a syndrome.

The dysfunctional behaviour known as “ADHD” consists of a series of behavioural attitudes involving three categories: inattention, hyperactivity-impulsivity, as listed below.

A.1) six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

- (a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- b) often has difficulty sustaining attention in tasks or play activities
- (c) often does not seem to listen when spoken to directly
- (d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
- (e) often has difficulty organizing tasks and activities
- (f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
- (g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
- (h) is often easily distracted by extraneous stimuli
- (i) is often forgetful in daily activities

A.2) six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

- (a) often fidgets with hands or feet or squirms in seat
- (b) often leaves seat in classroom or in other situations in which remaining seated is expected
- (c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

(d) often has difficulty playing or engaging in leisure activities quietly

(e) is often "on the go" or often acts as if "driven by a motor"

(f) often talks excessively

Impulsivity

(g) often blurts out answers before questions have been completed

(h) often has difficulty awaiting turn

(i) often interrupts or intrudes on others (e.g., butts into conversations or games)

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

C. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

D. Some impairment from the symptoms is present in two or more settings (e.g., at school [or work] and at home).

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder, and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Many experts believe these symptoms to be too vague, badly defined for operative purposes, and they also believe the diagnostic criteria and procedures to be out of line with medical and scientific practice. When science gives no definite responses, experts express their convictions and opinions with a "consensus document" (or "Consensus"), providing useful guidelines for how best to proceed. Like the decisions of the Italian Supreme Court, in science a Consensus "*non fa legge ma fa giurisprudenza*" (it does not constitute legislation, but jurisprudence). In regard to this, 2005 was a somewhat particular year, in that two consensuses on ADHD were promoted, both very significant in terms of the number and nature of their signatories.

The first was promoted in Italy by the "Giù Le Mani Dai Bambini"® Committee (see www.giulemanidaibambini.org), made up of a consortium one hundred and twenty public and private bodies (including local health authorities, universities, hospitals, trade associations, professional bodies etc), as part of a wider campaign for awareness and pharmacovigilance for the paediatric age group, which includes over 230,000 "experts" including physicians and other specialists. The document was presented at San Giovanni Battista "Molinette" Hospital in Turin, Italy's third hospital trust, and also member of the Committee and co-promoter of this pharmacovigilance campaign. The document is entitled "*International consensus: adhd and abuse in the prescription of psychopharmaceutical drugs to minors*" (1).

The second was promoted in Argentina within the academic-university field, and is entitled "*Consensus of experts in the health sector concerning the so-called "Attention-deficit disorder with or without hyperactivity"*", and is addressed to the Ministry of Health of Argentina (2). Both consensuses dispute the nosography of ADHD on account of scientific inconsistencies, diagnostic criteria and the mostly pharmacological therapy orientation that it is currently given.

Indeed, the World Health Organization (WHO) denies that there are scientific bases supporting the existence of an attention disorder, thereby invalidating the nosography of Attention Deficit Hyperactivity Disorder (ADHD) defined in the DSM, Diagnostic and Statistical Manual of Mental Disorders, edited by the American Psychiatric Association, a private-based American association, which is currently used widely as the diagnostic “bible” (3).

Although, in this article, the Italian (3) Istituto Superiore di Sanità (ISS) makes an effort to minimise differences and maximise affinities, the fact remains that the WHO does not recognise the nosography of Attention Deficit (AD) and limits the diagnosis of “Hyperkinesis” to the simultaneous presence of hyperactivity, impulsivity and inattention. Furthermore, in the event of other concomitant pathologies, the exclusion mechanism is immediately activated.

On 29 September 2000, the American psychiatrist Peter Breggin, an internationally renowned expert in ADHD and director of the International Center for the Study of Psychiatry and Psychology (ICSPP), testified to the US congressional “Committee on Education and the Workforce” that (4):

“It is important for the Education Committee to understand that the ADD/ADHD diagnosis was developed specifically for the purpose of justifying the use of drugs to subdue the behaviors of children in the classroom. The content of the diagnosis in the 1994 Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association shows that it is specifically aimed at suppressing unwanted behaviors in the classroom...”

Once again, the diagnosis itself, formulated over several decades, leaves no question concerning its purpose: to redefine disruptive classroom behavior into a disease. The ultimate aim is to justify the use of medication to suppress or control the behaviors. Advocates of ADHD and stimulant drugs have claimed that ADHD is associated with changes in the brain. In fact, both the NIH Consensus Development Conference (1998) and the American Academy of Pediatrics (2000) report on ADHD have confirmed that there is no known biological basis for ADHD”.

The American neurologist Fred Baughman, renowned scientist, discoverer of new diseases, Upton Sinclair Award Winner in 2006, and member of the Scientific Committee of the Italian drug watchdog campaign “Giù Le Mani Dai Bambini”®, is considered one of the most authoritative experts internationally on ADHD. In a statement to the US Food and Drug Administration's (FDA - the US body responsible for monitoring and authorising the marketing of drugs) Psychopharmacologic Drugs Advisory Committee, made on 23 March 2006, he declared (5):

“The fact of the matter is that there is no such disease (objective abnormality = disease) as ADHD. It is a contrived, faux disease - an illusion. This being the case, children said to have it are normal/disease-free, and giving them ADHD drugs, or any psychiatric drugs, is not treatment, but poisoning. Once Ritalin or any psychotropic drug courses through their brain and body, they are, for the first time, physically, neurologically and biologically, abnormal”.

In a 2004 article, the first and most detailed and scientifically-based response to the unquestionably biopsychiatric and pro-pharmacological International Consensus Statement on ADHD (Barkley R. et al. 2002, Clinical Child and Family Psychology Review, 5, 89– 11), its authors, an authoritative group of 34 scholars and professionals, declare (6):

“The evidence does not support the conclusion that ADHD identifies a group of children who suffer from a common and specific neurobiological disorder. There are no cognitive, metabolic, or neurological markers for ADHD and so there is no such thing as a medical test for this diagnosis”.

Lastly, on 16 November 2006, the Italian national watchdog campaign “Giù le Mani dai Bambini”® sent a document to the Minister of Health, Senator Livia Turco, entitled *“Letter of recommendations to the Institutions on the therapeutic-diagnostic protocol for ADHD”*, which is the most detailed analysis available in Italian. The issue of the unsustainability of the thesis of ADHD as a disease is dealt with in several stages and from various viewpoints. The document was validated by this watchdog campaign's authoritative scientific committee (7).

The ADHD thesis as a disease characterised by attention deficit in executive faculties, impulsivity and hyperactivity, is also challenged by research done by Claudio Ajmone, psychotherapist and founder of the Osservatorio Italiano sulla Salute Mentale, which lists as many as 218 diseases and conditions which “mimic” ADHD, a list which is by no means final. The database of scientific research legitimising this list is presented as follows by the author (8):

“Comorbidity is sometimes a contradiction resulting from the overclassification of pathologies and does not always represent a real set of clinical entities. In psychiatry it is characterized by a high percentage of comorbidity and uniform symptomatology; this often makes differential diagnosis difficult, if not impossible. In the area of physical pathologies, there is a high percentage of comorbidity and varied symptoms.

The common statement that ADHD is characterised by a deficit of sustained and focused attention and executive skills, combined with impulsivity and hyperactivity, is disproved by the studies collected here, which highlight how these factors are common to a great variety of pathologies; hence, they are variables which, rather than characterising them, appear as natural and non-specific by-products seriously undermining a person's development and social adaptation. It thus follows that ADHD is a psychiatric nosology having no factors which characterise or justify it scientifically.”

The thesis upheld by Claudio Ajmone and the “Giù le Mani dai Bambini”® Committee is that, if an accurate differential diagnosis were made against the physical diseases and conditions listed which mimic ADHD, there would simply no longer be an ADHD diagnosis. If we remove the symptoms for which psychiatrists often give a diagnosis of comorbidity, there remain 181 cases of unfavourable medical pathologies and diseases which mimic ADHD.

The *“Diagnostic and therapeutic protocol for hyperactivity and attention-deficit syndrome for the national ADHD register”* (35), issued by the Istituto Superiore di Sanità (ISS), Department of Drugs, and the Italian Drug Agency (AIFA), and revised on 22 March 2007, is the official document to which child neuropsychiatrists operating in local ADHD centres, the only professionals authorised make this diagnosis, must adhere for diagnosis purposes. Yet, no room is given to differential diagnosis in this document (!).

The *“Guidelines for the diagnosis and pharmacological treatment of Attention-Deficit Hyperactivity Disorder during developmental age”* (9), drawn up by the Italian Society for Child and Adolescent Neuropsychiatry (SINPIA) in 2002, which are to be considered purely indicative, in that they are not issued by a public body, includes the differential diagnosis (in table 2,) for only eight physical pathologies and neurological disorders:

- sensory deficits (blindness and deafness)

- undesirable effects of drugs (antihistamines, beta-agonists, benzodiazepines, phenobarbital)
- epilepsy
- thyroid disorders
- abscesses, frontal lobe neoplasms
- cranial trauma
- substance abuse
- lead poisoning

This means a high probability of diagnostic error and a lack of minimum safety requirements for the health of minors.

Psychiatric literature establishes that children diagnosed with ADHD have a comorbidity of around 75-80% with other psychiatric disorders, and this has led many experts to affirm that this nosography is not able to sufficiently discriminate the mental problems of minors.

The aforementioned database provides confirmation of comorbidity rates so high that they call into question the possibility of making this kind of diagnosis. learning disabilities 94% (10), pervasive developmental disorders 85% (11), anxiety-depression 70% (12), psychosis 99.3% (13), Tourette's Disorder 100% (14), obsessive-compulsive disorders, 78.5% (15), oppositional-defiant disorder-developmental coordination disorder 87% (16), disruptive behaviour 100% (17).

In 2002, Dr. Mary Ann Block, an osteopathic physician, testified to the Texas Committee on House Government Reform:

“I have seen and treated thousands of children from all over the United States, who had previously been labeled ADHD and treated with amphetamine drugs. By taking a thorough history and giving these children a complete physical exam as well as doing lab tests and allergy testing, I have consistently found that these children do not have ADHD, but instead have allergies, dietary problems, nutritional deficiencies, thyroid problems and learning difficulties that are causing their symptoms. All of these medical and educational problems can be treated, allowing the child to be successful in school and life, without being drugged.” (46)

The 1998 National Institutes of Health (NIH) Consensus Development Conference, the most authoritative Consensus on ADHD promoted in the US, involved the most accredited institutions and most authoritative experts, and was sponsored by the following institutions:

- National Institute of Mental Health;
- National Institute on Drug Abuse;
- Office of Medical Applications of Research;

and co-sponsored by:

- National Institute of Environmental Health Sciences
- National Institute of Child Health and Human Development
- Food and Drug Administration
- Office of Special Education Programs, U.S. Department of Education

William B. Carey M.D., Clinical Professor of Pediatrics at the University of Pennsylvania School of Medicine and Director of Behavioral Pediatrics in the Division of General Pediatrics at the Children’s Hospital of Philadelphia, one of the leading international experts in the behavioral development of minors, told the Consensus committee (18):

“ADHD symptoms are not clearly distinguishable from normal temperament variations...The ADHD behaviors are assumed to be largely or entirely due to abnormal brain function. The DSM-IV does not say so, but textbooks and journals do.

Some preliminary brain imaging studies have shown inconsistent differences in children with the ADHD diagnosis, but there is no proof that they are deviations. We do know that various brain insults like lead poisoning, fetal alcohol syndrome, and low birth weight may lead to increased activity and decreased attention span.

Several lines of evidence oppose this supposed link for ADHD: (1) No consistent pattern of high activity or inattention is seen in children with established brain injury, (2) no consistent structural, functional, or chemical neurological marker is found with the current ADHD diagnosis (Cantwell, 1996), (3) on the other hand, differences in brain function have been demonstrated in healthy children with normal temperamental variations (e.g., frontal electroencephalogram differences).

Therefore, proof is needed that any test differences demonstrated with the ADHD diagnosis are signs of a disorder and not just a temperamental predisposition...The DSM-IV criteria for ADHD describe only the behaviors in the child and require the child to be having problems at home, at school, and so forth. The varying contributions of the setting to the problem are typically ignored.

Yet, there are indications that the environment can produce or at least worsen (Biederman, Milberger, Faraone, et al 1995) the ADHD symptoms... What is now most often described as ADHD in the United States appears to be a set of normal behavioral variations that sometimes lead to dysfunction through dissonant environmental interactions. This discrepancy leaves the validity of the construct in doubt.”

And regarding the reliability of ADHD diagnostic tests, Carey states:

“Diagnostic questionnaires now in use are highly subjective and impressionistic. Variations in experience, tolerance, emotional status of the asker and of the child interviewed are not allowed for in any way. Yet, despite this vagueness, and although scales cannot be regarded as having adequately met necessary psychometric criteria, proponents claim that the scales make an accurate all-or-nothing diagnosis, but that’s not so, and it will take more than a Register to solve the issue”.

Yet doubts about the “validity” of this disorder have even been expressed, and with no room for equivocation, by leading Italian psychiatrists, who certainly cannot be accused of having an “aversion” to psychoactive molecule-based therapies.

Emilia Costa, 1st Chair in Psychiatry at Rome's “La Sapienza” University, recently stated:

“... when speaking of behavioural disorders, and particularly those such as attention deficit hyperactivity disorder (ADHD), more than anything we are faced with a “fad” and inconsistent and vague diagnostic practices. Considering the simplistic manner in which they are made today, these diagnoses cannot and must not be made, and the Register for monitoring children in therapy will be of little use, if all protocols are not completely revised: what difference will it make if we register children who should not have been subjected to Ritalin therapy in the first place?”

A 10% reduction in the volume of the brains of children diagnosed with ADHD has been found using brain imaging methods, and it has been claimed that this represents a phenotype biological

marker supporting the existence of a genetic anomaly, even though it is also widely known in literature that psychostimulants themselves cause a reduction in brain volume.

A critical collection of this research was drawn up in 2004 (19) by Professors David Cohen of Florida International University and member of the scientific committee of “Giù Le Mani Dai Bambini”, and Jonathan Leo of Lake Erie College of Osteopathic Medicine Bradenton.

The collection also includes a critique of the most famous study in this field: Castellanos, F.X. Lee, P.P. Sharp, W., Jeffries, N.O., Greenstein, D.K., and Clasen, L.S. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit hyperactivity disorder. *Journal of the American Medical Association*, 288, 1740–1748.

The authors identify sufficient shortcomings in all these studies to cast doubt on their validity. These shortcomings concern the failure to control crucial variables for the evaluation of brain shrinkage, such as age, height and weight of subjects, the fact that they had taken stimulant medication until recently beforehand and the omission of data regarding the prior medication of subjects.

The thesis that ADHD may be caused by neurotransmitter chemical imbalances was contested by the Rapoport JL et al. as far back as 1978, as follows (20):

“The behavioral, cognitive, and electrophysiological effect of a single dose of dextroamphetamine (0.5 milligram per kilogram of body weight) or placebo was examined in 14 normal prepubertal boys (mean age, 10 years 11 months) in a double-blind study. When amphetamine was given, the group showed a marked decrease in motor activity and reaction time and improved performance on cognitive tests. The similarity of the response observed in normal children to that reported in children with “hyperactivity” or minimal brain dysfunction casts doubt on pathophysiological models of minimal brain dysfunction which assume that children with this syndrome have a clinically specific or “paradoxical” response to stimulants.”

The already cited Peter Breggin defines the chemical imbalance theory as follows (21):

“... the notion of a biochemical imbalance in the brains of children diagnosed with ADHD is wild speculation. Meanwhile, we know with certainty that every child treated with a stimulant will suffer from multiple drug-induced biochemical imbalances.”

Twelve specialist physicians in psychology and psychiatry, authoritative members of the International Center for the Study of Psychiatry and Psychology (ICSPP) and the American Psychological Association (APA), some of whom have signed the Consensus of the “Giù Le Mani Dai Bambini” campaign, wrote, using highly scientific arguments, to Alice Rubenstein, member of the American Psychiatric Association and consultant to Celltech Pharmaceuticals, to contest the contents of a brochure expounding the belief that ADHD is a neurochemical and "hereditary" disorder. They state that (22):

“... Although ADD/ADHD may be generally considered by popular opinion to be a ‘neuro-chemical disorder,’ there is no scientific evidence to back this claim...Because this evidence is entirely correlational and the brain is a living, functioning organ constantly responding to its environment with complex neurochemical and other neurofunctional changes, it is just as likely (and perhaps more likely) that the biological dynamics are a

result of an interplay of emotions, thoughts, intentions and behavior experienced by the diagnosed individuals...

Calling ADHD a “neurochemical disorder” with a “biological cause” implies that it has nothing to do with how a child thinks, feels, reacts, intends, perceives, adjusts and responds. It implies that the behaviors are not under the control of the child or those within the child’s world and have nothing to do with how the child finds and makes meaning in that world...

There is a body of research that purports to demonstrate that this disorder is essentially a result of genetic factors. Most of that research has used studies that compare interclass correlations between the rates of the disorder in monozygotic twins and dizygotic twins...All of this research is based on the assumption that monozygotic twins and dizygotic twins are raised in equivalent environments. That assumption is erroneous. As Jay Joseph (2003) has explained...

Findings of genetic influence over behavior are confounded by the fact that genes direct the synthesis of protein and protein synthesis can be affected by environmental factors such as stress, trauma and lack of parental responsiveness (Hubbard & Wald, 1993)...

Even without considering these powerful contaminating factors and obstacles, the research on genetic factors in ADHD accounts for no more than 50 % of the variance...Research on attachment dynamics and trauma demonstrate the profound influence that parent-child relationships in the first months of life have on the mental health of individuals (Holmes, 1995; Bretherton, 1995; Crittenden, 1995; Lewis, Amini & Lannon, 2000; Herman, 2000; van der Kolk, McFarlane & Weisath, 1996). None of the research on the incidence of ADHD in families controls for these crucial factors.”

In 2002, The Brain Foundation Netherlands was condemned for misleading advertising by the "Advertising Commission of Holland" for claiming that ADHD was an inborn brain dysfunction backed by the results of scientific research and articles on the causes of ADHD. Nevertheless, the information presented by the defendant did not provide sufficient evidence to prove that ADHD is an “inborn brain dysfunction”, nor did the documentation produced present unequivocal scientific opinions regarding this disorder (23).

There are no clinical tests capable of directly measuring the concentration levels of neurotransmitters in the human brain: this analysis can only be done post mortem (analysis of metabolites, intermediate or final products of chemical reactions of the metabolism present in organic fluids, is in fact an indirect measurement but is not completely accurate).

According to the already cited psychiatrist Peter Breggin, the distinction that is made between side effects and benefits produced by a drug is unrealistic, in that the assumed “benefits” often correspond to the side effects, which cause damaging changes to people and often involve all aspects of their being, making them more socially acceptable. He describes the exchange of the side effects of drugs with therapeutic benefits as a “pseudo-benefit”.

A child taking stimulants will become very tidy, and will work hard at all tasks given to him, repeating them several times to achieve the best result: this is interpreted as an improvement, while in fact it is a pseudo-benefit in that it is the result of the appearance of obsessive-compulsive behaviour caused by a neurological compromise induced by the drug. This is a frequent side effect (51%). A single dose of stimulant causes obsessive hyper-focusing in 42% of children, who are often incapable of completing a task assigned to them (c.f. Solano and Wender in Breggin, 21).

The following table shows the most common pseudo-benefits (21).

Table II: Stimulant adverse drug reactions (ADRs) potentially misidentified as “therapeutic” or “beneficial” for children diagnosed ADHD

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

Modified by Breggin (1999 b&c), reprinted with the permission of Springer Publishing Co. Reference to 20 clinical trials reported in Breggin (1999 b&c).

CONCLUSIONS relating to point A

The use of drugs is justified by the existence of a disease for which they have been tested as a treatment. Any other use is inappropriate. On the basis of what we have exposed so far, it emerges

that there is no definite scientific evidence to demonstrate that ADHD is a disease. No phenotype or genotype has been identified with certainty. Evidence-based proof points to the fact that psychiatric drugs have the same effects on healthy children as on children diagnosed with ADHD (60).

As further confirmation of this we call attention to the following facts:

- The Diagnostic and Statistical Manual, Revised Text, of the American Psychiatric Association (FDA), DSM-IV-TR, published in 2000 states on pages 88-89:

"There are no laboratory tests, neurological assessments, or attentional assessments that have been established as diagnostic clinical assessment of Attention-Deficit/Hyperactivity Disorder. Tests that require effortful mental processing have been noted to be abnormal in groups of individuals with Attention-Deficit/Hyperactivity Disorder compared with peers, but these tests are not of demonstrated utility when one is trying to determine whether a particular individual has the disorder. It is not yet known what fundamental cognitive deficits are responsible for such group differences."

And further:

The introduction to the DSM-IV, page xxi (APA, 1999), under the definition for Mental Disorder, states:

"Although this volume is titled the Diagnostic and Statistical Manual of Mental Disorders, the term mental disorder unfortunately implies a distinction between "mental" disorders and "physical" disorders that is a reductionistic anachronism of mind/body dualism. A compelling literature documents that there is much "physical" in "mental" disorders and much "mental" in "physical" disorders."

- The same statement is made in the final conclusion of the NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder, November 16–18, 1998 (18);
- the America's leading psychiatric newspaper, *Clinical Psychiatric News*, in an article by *Carl Sherman*, states (47):

"DSM has never contained a detailed definition that is useful as a criterion for deciding what is, or is not, a mental disorder."

Furthermore, the phrase "the etiology of this syndrome [ADHD] is unknown" is used by:

- the very manufacturer of the drug (Novartis ©) in the "Summary of product characteristics" for methylphenidate (Ritalin ®) drawn up by experts;
- Eli Lilly ©, in the "Summary of product characteristics" for atomoxetine (Strattera®) drawn up by experts;
- Food and Drug Administration (FDA)
- Drug Enforcement Administration (DEA)
- National Institute of Mental Health (NIMH), which declared the above in a testimony made by its representative, Dr. Richard Nakamura, before the "Committee on Government Reform, United States House of Representatives" (USA);
- Turin Consensus, May 2005.

The statement that "there are no established laboratory tests for clinical diagnosis of Attention-Deficit/Hyperactivity Disorder" should, according to the Aristotelian principle of non-contradiction, lead to the logical consequence that this diagnosis is not possible. And this is what we are affirming in this paper.

The inconsistency of the ADHD thesis as a disease also emerges from the excessive statistical variability of epidemiological surveys, as can be seen in these data taken from the diagnostic protocol of the ISS (35):

“A study conducted in two regions of central Italy on a sample of 232 children showed a prevalence of 3.6%, based on the presence of at least 8 major criteria from DSM III R. A further 6.9% were potential cases. The study, conducted in schools in Florence and Perugia in 1993, identified 9 cases out of 250 children examined. The 1998 study, with paediatricians in Turin, gave a prevalence of 2.52%. In this case, the population was 47,781 subjects and 1,203 cases were identified. In a 2002 study conducted in Friuli-Venezia Giulia, out of 64,800 children, there was suggestion of ADHD in 280 cases with a prevalence of 0.43%. In Rome, two studies were conducted in 1999 and 2003. In the first, the prevalence was 1.51% (12 cases out of 794 children examined), in the second, the prevalence was 0.91% (23 cases out of 2,511 children). Both studies were conducted with voluntary paediatricians. A 2003 study conducted in Cesena by the local services on a population of 11,980 subjects aged between 7 and 14, gave a prevalence of ADHD of 1.1% (131 cases).”

But who really makes the ADHD diagnosis?

For every medical speciality, the diagnosis is made by a physician, whereas in the diagnostic process for ADHD, parents and teachers play a role and their influence is such that it conditions the judgement of doctors and psychologists, as they alone complete the evaluation scales where symptoms (behaviours) are highlighted, which must last for at least six months, and this step is fundamental and indispensable in the subsequent diagnosis.

Psychiatrists may make a differential diagnosis and discover, for example, that it is not ADHD, but lead poisoning which "mimics" ADHD; however, in this case the diagnosis is for poisoning and not for ADHD. The psychiatrist may make a diagnosis of comorbidity and discover that the child also has, for example, oppositional-defiant disorder, but, again, in this case the diagnosis is "different" from ADHD. He or she may invalidate the ADHD diagnosis, in that the observations may coincide with the onset and prolongation of another mental disorder, such as anxiety, but even in this case, the diagnosis made is different from ADHD. He or she may also invalidate it if there is no correspondence between the parent's and teacher's observations, but in this case no diagnosis is made. It is well established in scientific literature that there is little use in taking children to a psychiatrist, since on these occasions they almost always behave well. It is also established that tests targeted to highlight deficits in executive, memory, impulsivity and hyperactivity factors have no diagnostic value, since they do not identify a trait, but rather a condition.

So, a psychiatrist may "conclude" the diagnosis, but the diagnosis itself is made essentially by the observations of parents and teachers, who complete questionnaires. This diagnostic process is highly conditioned by the role of parents and teachers and casts doubt on medical deontology and diagnostic reliability, because parents and teachers are not trained to observe and are not neutral observers, since they are involved in an emotional relationship with the child. Furthermore, the assessment scales used are considered far from reliable by many observers (61) (62).

Robert Spitzer is a Professor of Psychiatry at Columbia University, New York. In the 1970s and 1980s he introduced the nosography of ADHD to the DSM and is considered the "father of ADHD". In a BBC2 documentary, part of the "The Trap" series, he recently declared that as many as 30% of youngsters are diagnosed erroneously. They simply manifest comprehensible signs of happiness and sadness, and many of these behavioural conditions are normal reactions to stimuli and the environment, and are not real mental disorders. This type of classification leads many people to be diagnosed as medically ill, when their mood changes and their behaviour simply expresses - perhaps in an uncustomary manner - a feeling of happiness or sadness.

It is also well known in psychiatric literature that when administration of the drugs used for ADHD is stopped, the behaviour of children and teenagers returns to what it was before the start of the "treatment". This, in practice, demonstrates that these drugs do not treat any disease, but are mere "symptom sedatives" which have a so-called paradox effect on minors (they tranquillize them, or rather, they help them focus their attention). Let's not forget that, in fact, no study has been done on child metabolism and that these drugs, originally studied for adults, are administered to minors merely by reducing the dosage, which is total folly in methodological terms, since the metabolism of a child is completely different from an adult's and a appropriate prescription certainly cannot be guaranteed through the nefarious practice of administering psychiatric drugs to children in half-doses on the basis that he or she weighs half as much as an adult (!).

From this brief examination, it emerges quite clearly that the drugs commonly used to treat ADHD are administered inappropriately as sedatives, more than anything to *control* the undesired behaviours of children and adolescents. The benefits are not medical in nature, no clinical treatment is implemented; it is a matter of making minors more socially acceptable for parents, teachers and their schoolmates. The cost-benefit balance is negative for the minor, owing to the numerous and serious side effects of the drug.

The cost-benefit paradigm, an important factor in the treatment of physical disease, is often inappropriately used in the area of mental disorders. For physical disease, the "risk" is placed against the "benefit" of a cure. Psychoactive molecules, by definition and by evidence, only intervene on symptoms and do not treat any disease, and hence, the risk is not relatable to the benefit of a cure.

A careful differential diagnosis and a targeted pedagogical approach tailored to the child and the family are more useful instruments for resolving these situations of malaise.

Lastly, we could produce more authoritative documents that prove the existence of conflicts of interest between the pharmaceutical multinationals and physicians, including national and international public institutions dealing with health. Today, it is a widely known fact and the constant focus of media attention that pharmaceutical companies put pressure, often unduly, on specialists to prescribe psychiatric drugs in massive amounts, and well beyond strict necessity to contain the suffering of patients with ADHD.

Here, it is necessary to stress that it is the definition of ADHD as a disease that justifies the existence and use of the drug, and this explains why some people defend this hypothesis beyond the reasonable limits of common sense and scientific evidence.

QUESTION B: Whether the molecules methylphenidate and atomoxetine can be used safely and effectively for the treatment of the supposed syndrome ADHD

PRELIMINARY STATEMENT

The safety and efficacy of drugs are tested at various stages during the research and development process (R&D) of a drug, and later, during the postmarketing phase, further controls are carried out: Briefly, the research and development stages are as follows:

1. basic research: during this stage, the disease is studied along with possible treatments based on the mechanisms of action of the disease itself. In the US, this stage is supported by public funds at the National Institute of Health (NIH) and/or Universities subsidized by the NIH (90% of its funds). This is the longest, most difficult and expensive stage;
2. development: this consists of identifying a drug molecule that treats the disease. This takes place in 2 phases:
 - a. **preclinical**: identification of candidate molecules for the treatment, with experimentation on animals and cell cultures;
 - b. **clinical**: experimentation on human beings;

During the preclinical and clinical phases, in particular (pre-marketing), pharmaceutical companies have a high level of control in the procedures, be it in partnership with universities or with private centres. During the clinical stage, experiments are done on human beings to test their safety and efficacy at certain doses and for defined pathologies.

All aspects of these trials are literally controlled by the pharmaceutical companies. During this stage, the multinational drug companies should promote proper experimentation, however it has emerged in many cases that they mainly aim to obtain marketing authorisation for the molecule from the competent bodies, often violating experimentation and ethics rules, and thus marketing drugs whose safety and efficacy are, to say the least, questionable. Over the last decades, the most commonly used expedient in clinical trials are the following:

1. omitting to report deaths in the documentation produced to the authorising body;
2. omitting to report in the documentation presented to the authorising body the people who have abandoned the trial because they could not withstand the side effects;
3. refusing subjects who are at risk of specific adverse effects through preliminary testing, thus "spoiling" the population sample;
4. attributing the cause of the side effects to the disease;
5. giving participants drugs which neutralise the side effects;
6. comparing the efficacy of a drug with placebo groups (who are given sugar, yet believe they are receiving the drug) instead of using a group taking a drug that is already on the market to demonstrate whether or not it is more effective;
7. not using the "spontaneous remission" group for comparison, i.e. a group of people who are cured spontaneously without any treatment;
8. when the trial is compared with drugs already on the market, the doses are not equivalent; the new "mee-too" drug is administered at double the dose compared to the drug that is already on the market in order to produce more significant results. Or instead, or in addition, giving the control drug orally instead of by injection to reduce the efficacy;
9. omitting to report unfavourable trials done on the drug;
10. not using the "double-blind" trial design, which is more reliable;

11. involving investigators in conflicts of interest (by far the majority of the editors of the DSM have been proven to have contracts and financial interests in the main pharmaceutical multinationals);
12. having the trial done by researchers from different universities and private centres. Each researcher does only one part of the trial and they do not communicate amongst themselves; only the drug company knows what the overall experimental design is and the overall data;
13. using young recruits to test drugs destined for the elderly, since young people bear the side effects more easily.

In the post-marketing phase, the safety of the drug is monitored via special surveillance systems set up by public administration. The capacity of these pharmacovigilance systems to detect the side effects of drugs is, to this date, at alarmingly low levels. The pharmacovigilance instrument used in the US by the Food And Drug Administration (FDA) is called “MedWatch”, and is a system of voluntary reporting that is capable of detecting less than 1% of severe adverse effects in the post-marketing phase (the British pharmacovigilance system reaches 10%, according to an official report of the FDA itself) (36). Yet, this report contains the following statement:

“... There are intrinsic limitations to premarketing human clinical trials with respect to their ability to detect adverse events. Short duration, narrow population, narrow set of indications and small size are major factors in this regard, irrespective of the type of medical product being studied. The capability of premarketing clinical trials to discover rare adverse events is particularly affected by their size. In order to have a 95% chance of detecting an adverse event with an incidence of 1 per 1,000, 3,000 patients at risk are required; with no more than 3,000 to 4,000 individuals usually exposed to a medical product prior to marketing, only those adverse events with approximately 1/1,000 or greater incidence can be expected to be found. While medical products are usually studied for several years before they are marketed, an individual patient in a clinical trial is generally exposed to the product for less than a year. Even long-duration premarketing clinical trials, which can last several years, do not provide the degree of patient exposure that will occur postmarketing with a chronically used medical product.”

And further:

“... Another major concern with any spontaneous reporting system is underreporting of adverse events. It has been estimated that rarely more than 10% of serious ADRs, and 2-4% of non-serious reactions, are reported to the British spontaneous reporting program. A similar estimate is that the FDA receives by direct report less than 1% of suspected serious ADRs. This means that cases spontaneously reported to any surveillance program, which comprise the numerator, generally represent only a small portion of the number that have actually occurred.”

Considering that 80% of the medicinal products used in the world are manufactured in the US and the UK, these data can also be adapted to the Italian population. What we have examined so far provides some useful general guidelines for interpreting the more specific data regarding a single medicinal product.

The first general deduction that emerges is that a drug is marketed without sufficient guarantees concerning its safety, and this is, moreover, somewhat difficult to quantify during the pre-marketing phase.

The second general deduction is that, during the post-marketing phase, monitoring of the drug's side effects in the general population is still unsatisfactory, and ranges from less than 1% in the US to 10% in the UK. This leads us to the inevitable conclusion that the official data available are only the tip of the iceberg (some experts retain that these data should be multiplied by an index of between 10 and 100).

A third reading is that there are no uniform criteria to guarantee the withdrawal of a drug from the marketplace. This sometimes occurs when a drug is responsible for an excessive death rate for a given pathology compared to the general population. On other occasions it is because use of the drug creates mental conditions that could induce or which induce suicide. Some decisions on this matter are contrasting from nation to nation.

In fact, we find that, sometimes, drugs causing a greater number of deaths remain on the market, while others causing much fewer are withdrawn.

Regarding this issue, we cite the case of Cylert (Pemoline), a central nervous system stimulant produced by Abbott, issued for sale in 1975, and widely used to treat ADHD. In 2002, an FDA warning cautioned against its use as a first line treatment for ADHD, owing to its liver toxicity, and warned against continued use of the drug, if improvement was not seen within three weeks of treatment.

At that time, 15 cases of liver failure were known, of which 12 resulted in death or liver transplantation. The incidence rate was 4 to 17 times higher than in the general population. In October 2005, the FDA issued a new warning (25) announcing the market withdrawal of this drug. 13 cases of liver failure were reported and it was stressed that this was 15 to 25 times the rate in the general population.

A drug used on a psychiatric population, associated with mortality below the comparable general population, might still be responsible for these deaths, since these drugs have specific effects on certain organs in the body. For instance, Ritalin® has specific pathogenic effects on the cardiovascular system (18), and Strattera® on the liver.

The comparison of the statistical incidence of mortality in the population taking a certain class of drugs and the incidence of spontaneous mortality in the comparable general population is compromised by the following methodological shortcomings:

- the WHO defines sudden death in minors as occurring within 24 hours of failure; in practice, many people are kept alive for more than 24 hours in intensive care and hence are excluded from this count;
- the instrument used to obtain the data is different. Consulting a database on sudden deaths means identifying all deaths, while the voluntary pharmacovigilance detection systems, as mentioned before, only identify an insignificant portion of deaths;
- studies on sudden death in the general population present statistics which sometimes include a population above the age of 18;
- there is a lack of specificity regarding the causes of death; for example, congenital heart defects in children are mostly corrected in the early stages of life, such that, congenital heart defects rarely cause sudden and unexpected death (39);
- comparisons sometimes refer to different periods of time.

In a 1996 review article in *The New England Journal of Medicine* (40), Liberthson, describes the rate of sudden cardiac death in the general paediatric population, examining two studies which

include samples aged 1-22 and 1-29. The lower limit was 1.3/100,000 in 1985 in Minnesota; the upper limit was 2.4-8.5/100,000 between 1981-1982 in St. Louis County.

If we only consider those studies with the 1-20 age range, the value becomes 4.6 per 100,000 people-years (annex 44, page16). This value would drop even further if the age range considered were 1-18; the higher the age, the higher the mortality rate, on average 100 per 100,000 people-years.

The Food and Drug Administration (FDA) recently reported (with MedWatch, whose limitations we mentioned earlier) the data for 1992-2004 on sudden cardiac deaths in the population below the age of 18, divided as follows (41):

- methylphenidate: 11 deaths out of 7,127,432 people-years, equivalent to an incidence of 0.2 per 100,000 person-years;
- amphetamine/dextroamphetamine: 13 deaths out of 3817.929 people-years, equivalent to an incidence of 0.3 per 100,000 person-years;
- atomoxetine: 3 deaths out of 601,246 people-years, equivalent to an incidence of 0.5 per 100,000 people-years.

The rate of 1.3-8.5/100,000 people-years is the figure considered as the reference in the US for sudden death in the population up to the age of 21.

However a simple correction rate of 10%, which is what Novartis® applies for Ritalin®, brings the value of 0.2/100,000 people-years to 1.9/100,000 people-years, but it is questionable whether a correction of 10% is sufficient for a voluntary detection system such as MedWatch which identifies less than 1% of the serious side effects.

Novartis® itself writes (42): “... *the voluntary nature of the FDA AERS reporting system has significant limitations, therefore, reporting rates may underestimate the true incidence rate by a factor of 10 or more.*” This allowance for “or more” can make a great difference to the calculations.

The same correction factor of 10% applied to atomoxetine leads to a value above the sudden cardiac death rate in the general paediatric population. Moreover, it is known that atomoxetine is 3 to 9 times more mortal than the other drugs considered here. Furthermore, it is worth noting that in none of the deaths associated with atomoxetine were congenital cardiovascular anomalies highlighted (44). It seems evident that, by slightly increasing the correction factor above 10%, mortality rate exceeds that of the general population.

A study by Morentin Benito on sudden and unexpected deaths between 1990 and 1997 in the population aged 1-19 in the north of Spain (Bizkaia), showed that the mortality rate was 1.7/100,000, of which 10 cases with cardiac aetiology, 13 with non-cardiac aetiology, 11 unexpected and in 17 cases there was no prior disease, while in 9 cases the disease was known (43).

Of course, the number of deaths is much higher if we consider other causes of mortality and deaths beyond the 24-hour mark. Such data easily lead to the conclusion that psychiatric drugs can be prescribed with apparent safety, but only if we do not take account of the methodological shortcomings outlined earlier.

The data exposed in the pre-marketing phase show that these psychiatric drugs are tested at the clinical stage with experimental limitations that make their safety profile truly inestimable. Many psychiatric drugs are designed with trials that last a few weeks on very small population samples. This reduces even more drastically the level of safety of these psychiatric drugs.

Strattera (Atomoxetine)

It was authorised for the treatment of ADHD in the US on 26 November 2002 and in the UK on 27 May 2004. In Europe it is authorised for administration to children aged 6 upwards. It is estimated that, at November 2005, it had been administered to 3.7 million patients in the world.

Atomoxetine (commercial name Strattera®) is a selective norepinephrine reuptake inhibitor (SNRI), according to the information provided by its manufacturer, Eli Lilly®, and the FDA. The mechanism by which it produces its effects in ADHD is not known, according to statements made by the manufacturer and the FDA itself. Its efficacy was assessed on children and adolescents aged 6-18 in four randomised, double-blind, placebo-control trials, for market release as follows (27) (28).

1. Trial 1: duration 8 weeks; number of subjects 297; age 8-18
2. Trial 2: duration 6 weeks; number of subjects 171; age 6-16
3. Trial 3: duration 9 weeks; number of subjects 147; age 7-13
4. Trial 4: duration 9 weeks; number of subjects 144; age 7-13

2 trials have been conducted on adults with a duration of 10 weeks (N=280; N=256).

Thus, trials with a very small number of subjects and very short duration. The probability that these trials effectively tested the efficacy and safety of this psychiatric drug is close to zero. In the postmarketing phase, other trials were conducted to bridge this gap.

It is a molecule which, in the 1980s was denied FDA marketing authorisation as an antidepressant, owing to its side effects, and was later recycled to treat ADHD. Debates have been raised regarding the nature of this molecule, in that it is a “mee-too” variant of phenylpropanolamine (PPA), a stimulant banned by the FDA on 6 November 2000, owing to its causing haemorrhagic stroke.

Atomoxetine's stimulant status is demonstrated in the e-mail exchange (26) shown here, between the well-known American psychiatrist Grace Jackson and Hege Salvesen Blix, in reference to the classification of atomoxetine in the Anatomical Therapeutic Chemical Classification System (ATC) of the Centre for Drug Statistics Methodology, widely used in Europe and recognised by the World Health Organization (personal e-mail communication with Claudio Ajmone).

Fra: gracejackson [mailto:gracejackson1@cox.net]

Sendt: 26. august 2004 18:18

Til: Whocc

Emne: question about atomoxetine

Question:

I am a psychiatrist in practice in the USA. I have a question about the new drug: atomoxetine, which is a norepinephrine reuptake inhibitor touted as a non-stimulant on the basis of addition potential. However, the New Drug Application shows pharmacodynamic actions that include an

increase in dopamine release in the frontal lobe. More recently (2001), sleep experts have found that the drug works like stimulants in treating narcolepsy. I understand that the drug lacks cocaine/amphetamine-like effects on the nucleus accumbens, but the mechanism of action in the frontal lobes and also in the reticular activating system (with re: narcolepsy) suggest that it may be functioning more as a STIMULANT than a tranquilizer. How has the World Health Organization classified this drug? How are new drugs classified as stimulants: Is it based upon chemical similarity to cocaine; dopamine effects; or behavioral effects (self administration – and if so, how much self-administration is required before a substance meets the criterion for being a stimulant ?) thank you for your help !

Grace E. Jackson, MD

-----Original Message-----

From: Blix, Hege Salvesen [mailto:Hege.Salvesen.Blix@fhi.no]

Sent: Wednesday, October 13, 2004 8:26 AM

To: gracejackson

Subject: SV: question about atomoxetine

Dear Grace E Jackson

I refer to your question regarding ATC classification of atomoxetine. Atomoxetine has been classified in ATC group N06B Psychostimulants, agents used for ADHD and nootropics, further in the ATC 4th level N06BA centrally acting sympathomimetics i.e. in the same 4th level as e.g. amphetamine and modafinil. The 5th level code of Atomoxetine is N06BA09. Drugs are classified into the ATC system according to the main therapeutic use, and according to the organ or system on which they act and their chemical, pharmacological and therapeutical properties. A main purpose of the ATC system is drug utilisation. At the time of assigning an ATC code for atomoxetine it was concluded that all drugs used for ADHD should preferably be classified in the same ATC group. Further, since no solid documentation against classifying atomoxetine as a centrally acting sympathomimetic was available, this was decided.

I hope this was clarifying.

Best regards

Hege Salvesen Blix

WHO Collaborating Centre for Drug Statistics Methodology

Norwegian Institute of Public Health

P.O.Box 4404 Nydalen

NO-0403 Oslo, Norway

As further confirmation, we present several studies that attest to the psychostimulant properties of atomoxetine (reboxetine used in Europe is chemically similar to atomoxetine).

Sleep. 2005 Jun 1;28(6):754-63.

Emerging therapies in narcolepsy-cataplexy.

Mignot E, Nishino S.

Howard Hughes Medical Research Institute, Stanford University School of Medicine, Stanford, CA, USA. mignot@leland.stanford.edu

In the past, narcolepsy was primarily treated using amphetamine-like stimulants and tricyclic antidepressants. Newer and novel agents, such as the wake-promoting compound modafinil and more selective reuptake inhibitors targeting the adrenergic, dopaminergic, and/or serotonergic reuptake sites (i.e. venlafaxine, atomoxetine) are better-tolerated available alternatives.

The development of these agents, together with sodium oxybate (a slow-wave sleep-enhancing agent that consolidates nocturnal sleep, reduces cataplexy, and improves sleepiness), has led to improved functioning and quality of life for many patients with the disorder.

However, these treatments are all symptomatically based and do not target hypocretin, a major neurotransmitter involved in the pathophysiology of narcolepsy. In this review, we discuss emerging therapies in the area of narcolepsy. These include novel antidepressant or anticataplectic, wake-promoting, and hypnotic compounds. We also report on novel strategies designed to compensate for hypocretin deficiency and on the use of immunosuppression at the time of narcolepsy onset.

PMID: 16477963 [PubMed -indexed for MEDLINE]

Sleep. 2001 May 1;24(3):282-5. Links

Stimulant and anticataplectic effects of reboxetine in patients with narcolepsy: a pilot study.

Larrosa O, de la Llave Y, Barrio S, Granizo JJ, Garcia-Borreguero D.

Dept. of Neurology, Fundacion Jimenez Diaz, Universidad Autonoma de Madrid, Spain.

STUDY OBJECTIVES: To investigate potential stimulant and anticataplectic effects of 10 mg reboxetine in patients diagnosed with narcolepsy. **DESIGN:** 12 patients were treated for a 2-week period with 10 mg reboxetine under open conditions. The dosage of reboxetine was gradually increased between Day 1 and Day 9. Outcome parameters consisted of nighttime polysomnography (PSG), Multiple Sleep Latency Test (MSLT), Epworth Sleepiness Scale (ESS), Visual Analog Scale for Sleepiness (VAS), Ullanlinna Narcolepsy Scale (UNS), and the Beck Depression Inventory (BDI). **SETTING:** Sleep Disorders Clinic at a University Hospital. **PATIENTS:** 12 patients meeting ICD-criteria for narcolepsy. **INTERVENTIONS:** Pharmacological treatment with reboxetine. **RESULTS:** Following treatment for two-weeks, a significant improvement in daytime sleepiness could be observed, as reflected by a mean decrease of 48.6% on the Epworth Sleepiness Scale and a mean increase of 54.7% in sleep latency on the MSLT. Furthermore, a significant reduction in the cataplexy subscore of the Ullanlinna Narcolepsy Scale and in REM-sleep was found. **CONCLUSIONS:** Our results suggest that reboxetine exerts stimulant and anticataplectic effects in narcolepsy. Contrary to previous thinking, by which stimulant action would require dopaminergic facilitation, noradrenergic mechanisms might be relevant to the control of wakefulness.

PMID: 11322710 [PubMed -indexed for MEDLINE]

We feel it is necessary to emphasise that, if a physician is not accurately informed as to the nature and effects of a molecule, he or she cannot accurately implement pharmacological therapy.

Adverse Effects of Atomoxetine
As Come indicated by the manufacturer and the FDA (27) (28)

Adverse reaction	Minors	Adults	?
Compromised motor skills			X
Aggressiveness	X		
Agitation	X		
Akathisia	X		
Anxiety	X		
Dry mouth	X	X	
Rigors		X	
Mood swings	X		
Dizziness	X	X	
Constipation	X		
Stunted growth	X		
Severe liver injury	X		
Depression	X		
Decreased libido	?	X	
Dermatitis	X		
Diarrhea	X		
Erectile disturbance	?	X	
Dysmenorrhoea	?	X	
Sleep disorder		X	
Ejaculation disorder	?	X	
Dyspepsia	X		
Abdominal pain upper	X		
Angioneurotic edema	X		
Fever	X	X	
Raynaud's phenomenon			X
Flatulence		X	
Suicidal ideation	X		
Impulsivity	X		
Ejaculation failure	?	X	
Indigestion	X	X	
Ear infection	X		
Influenza	X		
Impotence	?	X	
Decreased appetite	X		
Skin inflammation	X		
Orthostatic hypotension	X		
Hypomania	X		
Irritability	X		
Insomnia		X	
Peripheral vascular instability			X
Lethargy		X	
Headache	X	X	
Sinus headache		X	

Mania	X			
Irregular menstruation	?	X		
Menstrual disorder	?	X		
Delayed menses	?	X		
Myalgia		X		
Mydriasis	X			
Sudden death	X	X		
Nausea	X			
Urticaria	X			
Hostility	X			
Abnormal orgasm	?	X		
Panic attacks	X			
Parasuicide or suicide attempts	X			
Paraesthesia		X		
Weight loss	X	X		
Crying	X			
Prostatitis		X		
Psychosis	X			
Colds			X	
Urinary retention	X			
Sinusitis		X		
Abnormal dreams		X		
Somnolence	X			
Fatigue			X	
Increased sweating		X		
Tachycardia	X	X		
Tingling		X		
Cough	X			
Hot flushes		X		
Vomiting	X			
Total	72	42	32	4

Note: The "?" symbol in the "Minors" column indicates that probably no controls were done for the adverse effect; the "?" column indicates adverse effects which could not be classified.

On 17 December 2004, the Food and Drug Administration (FDA) issued a warning (48) stating that Atomoxetine potentially causes severe liver injury progressing to liver failure resulting in death or the need for a liver transplant.

At 3 October 2005, a total of 173 reports of 471 atomoxetine-associated reactions had been received in the United Kingdom, with the following typology (38):

- **Psychiatric disorders:** Aggression 23, anxiety 8, tic 8, suicidal ideation 8, agitation 7, depressed mood 7, insomnia 7, tearfulness 6, mood swings 6, depression 5, irritability 5, abnormal behaviour 5;
- **Suicide attempts/suicidal ideation:** suicidal ideation 8, suicidal attempts 2, suicidal depression 1, overdose attempt 1;

- **Gastrointestinal disorders:** nausea 29, vomiting 29, abdominal pain 9, upper abdominal pain 3;
- **Nervous system disorders:** Headache 24, dizziness 12, epilepsy/convulsions/simple partial seizures 6, somnolence 5, syncope 4;
- **General disorders:** feeling abnormal 8, fatigue 4, chest pain 4, malaise 3, influenza-like illness and condition aggravated 3;
- **Investigations:** Weight decreased 10, heart rate increased 3, blood alkaline phosphatase increased 3, blood bilirubin increased 3, liver function test abnormal 3, blood pressure increased 2, weight increased 2, aspartate aminotransferase increase 1, urine analysis abnormal 1;
- **Drug dependence/abuse:** none;
- **Hepatic disorders:** jaundice 4, liver disorder 1;
- **Cardiac disorders:** Tachycardia 6, palpitations 5, arrhythmia 1, cyanosis 1;
- **Blood and lymphatic disorders:** neutropenia 5, leukopenia 1, lymphopenia 1, thrombocytopenia 1.

Between 27 November 2004 and 26 May 2005, there were 1020 reports of adverse events in the world, out of a population of 1,272,000 patients. There were 7 deaths.

On 29 September 2005, the FDA issued a warning for atomoxetine asking the manufacturer of Strattera to report the risk of suicidal thinking in minors (0.4%) on its product packaging (29).

On 21 September 2007, the FDA issued a warning for ADHD drugs, including atomoxetine, advising that these drugs involve cardiovascular and psychiatric risks, and asking for a review of their product labelling (30).

The Swedish journalist, Janne Larsson, published the following press releases:

“The British medical agency MHRA will soon issue new warnings for Strattera but didn't care to investigate the reported 12000 "psychiatric reactions" from the drug and 600 cases of suicidality. And even if number of reports of suicidality has doubled since last year the MHRA has accepted the PR-analysis of Eli Lilly as its own”. (20 November 2006) (31)

“A not released discussion paper from the British medical agency (MHRA) reveals 130 reports of suicidality in one month from treatment with Strattera. In addition the paper tells about 766 spontaneous reports of cardiac disorders and 172 of liver injury, and about 20 completed suicides. (16 February 2006) (32)”

“In less than three years 10,988 adverse "psychiatric reactions" have been reported to Eli Lilly for the ADHD drug Strattera. This is revealed in a document treated as a "state secret" by the British and Swedish medical agencies”. (1 August 2006) (33)

“The Swedish Medical Products Agency (MPA) knows that Gillberg's and Lilly's clinical trial of Strattera is a catastrophe. It has nevertheless been allowed to continue. [...] Only 20 persons got enrolled in the trial. And what happened to them? Ten (10) persons "disappeared" - 3 with the given reason that the drug did not have any effect, 2 never came to their next visits, 1 patient ended without any stated reason - and 4 never got started! Of the 10 remaining, 5 (!) patients had to be taken out of the trial due to harmful effects: 1 patient had to be taken out due to liver problems, 2 due to aggressiveness/hostility and 2 due to depression”. (4 January 2006) (34)

Ritalin (Methylphenidate)

It is the most widely used drug of all time against ADHD, and is analogous to amphetamines. It was patented in 1954 by Ciba Pharmaceutical Company® (later Novartis®), and initially employed to treat depression, chronic fatigue syndrome and narcolepsy. Since the 1960s it has been used to treat ADHD, at the time called "minimal brain dysfunction". More than 75% of methylphenidate is prescribed to children and 80% to males.

It is manufactured in the United States, Mexico and Argentina. In 2000 the FDA approved extended-release Ritalin®, which allows single daily administration. In April 2006, a patch was approved for transdermal use called Daytrana®. Ritalin® is a central nervous system stimulant (CNS). It has a paradoxical calming effect on children. Little is known about its mechanism of action. It is subject to the risk of abuse and addiction, and its long-term effects are not known.

The effect on humans is similar to that of cocaine, but is much more potent. In an article entitled "Ritalin is More Potent Than Cocaine" appearing in "The Observer" on 9 September 2001, the journalist, Jean West, reported an interview with Dr. Nora Volkow, psychiatrist and brain imaging expert at Brookhaven National Laboratory, in Upton, New York, who said:

"They say [Ritalin's] like cocaine. Even in pill form, Ritalin blocked far more of the brain transporters that affect mood change and had a greater potency in the brain than cocaine ... A normal dose administered to children blocked 70 per cent of the dopamine transporters. The data clearly show the notion that Ritalin is a weak stimulant is completely incorrect. Cocaine is known to block around 50 per cent of these transporters, leaving a surfeit of dopamine in the system, which is responsible for the hit addicts crave... As a psychiatrist I sometimes feel embarrassed [...] because this is by far the drug we prescribe most frequently to children."

The World Health Organization lists Ritalin® among the world's 300 most dangerous drugs.

In a letter of recommendations to the ISS, the "Giù Le Mani Dai Bambini" campaign (7) lists the 100 side effects of Ritalin, 41 indicated in the product insert and 59 identified in a special study conducted by "Giù Le Mani Dai Bambini®".

The US Food & Drug Administration's (FDA), MedWatch programme for post-marketing monitoring, identified the following adverse reactions for Ritalin between 1990 and 1997 (45):

1. 160 deaths (MedWatch, 1990-1997) + 26 (FOIA, 1997-2000) = 186 deaths
2. 569 hospitalizations -36 life threatening
3. 949 central or peripheral nervous system occurrences
4. 126 cardiovascular occurrences:
 - 6 cardiomyopathy
 - 12 arrhythmia
 - 7 bradycardia
 - 5 bundle branch block
 - 4 EKG abnormality
 - 5 extrasystole
 - 3 heart arrests
 - 2 heart failure, right

- 10 hypotension
- 1 myocardial infarction
- 15 tachycardia

In 2006, the FDA's Office of Drug Safety (ODS) published the summary data on the safety of central nervous system stimulants used for the treatment of ADHD for the period from 1 January 1999 to 31 December 2004 (51). It reports that 50% of the total (494 since 1969 for methylphenidate, rough calculation) of reports of serious adverse events occurred during this period. Among the 50 most frequent side effects were cardiovascular and cerebrovascular events and, for methylphenidate (in order of frequency): tachycardia, cardiac arrest, death, chest pain, syncope, hypertension, coronary artery disease, myocardial infarction.

Still referring to methylphenidate (Ritalin), 163 cases of death and sudden death were reported. For the 1-18 paediatric age group, 7 cases of sudden death were considered, 3 with Ritalin and 4 with Concerta. Of these 7 cases, only case no. 3240721 presented pre-existing cardiac anomaly documented by autopsy. 8 cases of serious nonfatal cardiovascular events are also listed. In total, 46 deaths were recorded by the FDA (death and sudden death at all ages) as relatable to methylphenidate, 19 of which were due to sudden death (see table on page 47 of annex 51 for case study).

Below are listed the side effects of Ritalin® and amphetamines, summarising the data presented by the already cited psychiatrist Peter Breggin a the US Consensus in 1998 (18)

Adverse drug reaction (ADR)	%
CNS Adverse Effects in Double-Blind Placebo-Controlled Studies	
Mayes and colleagues (1994)	
Lethargy	18,8
Irritability	26,1
Severe ADR including: manic-like reaction with “incessant talking,” 1 “wild” and “out of control”, 1 aggressive behavior	7
Schachar and colleagues (1997)	
Drop-outs due to: sadness and behavioral deterioration , irritability, withdrawal, violent behavior, withdrawal and mild mania, withdrawal and dysphoria	10
Barkley and colleagues (1990)	
Proneness to crying during the low-dose condition	10
were unable to complete the protocol because of serious adverse reactions including one with manic-like symptoms	3,6
Gillberg and colleagues (1997)	
Hallucinations	4,8
Psychosis	2
higher rates for other CNS effects	x
Borcherding and colleagues (1990)	
- Perseverative/compulsive behaviors - 1 drop-out due to severe tic	51
Solanto and Wender (1989)	

"Overaroused" with cognitive perseveration (obsessive/compulsive reaction)	42
Castellanos and colleagues (1997)	
Largely transient obsessive/compulsive behavior (comorbid for Tourette's)	25
Psychostimulant-induced motor or vocal tics	
Borcherding and colleagues (1990)	
Abnormal movements	59
Barkley and colleagues (1990)	
Tics	10
Handen and colleagues (1991)	
Motor tics (comorbid with mental retardation)	11
Lipkin and colleagues (1994)	
Tics or dyskinesias, one severe, irreversible case	9
Psychostimulant Addiction, Withdrawal, and Rebound	
Rapoport and colleagues (1978) - Controlled, single amphetamine dose of 0.5 mg/kg	
Rebound including excitability, talkativeness, and, for three children, apparent euphoria	71
Dulcan, 1994, Porrino, Rapoport, Behar et al. 1983	
Case reports of "crashing" with depression	
Psychostimulant Growth Suppression and Retardation	
Disruption of growth hormone cycles	
Aarskog, Fevang, Klove, et al., 1977; Barter, Kammer, 1978; Brown, Williams, 1976; Joyce, Donald, Nicholls, et al., 1986; Shaywitz, Hunt, Jatlow, et al., 1982; reviewed in Dulcan, 1994, and Jacobvitz, Sroufe, Stewart, et al., 1990	
Inhibition of growth (weight and height)	
Klein, Mannuzza, 1988; Safer, Allen, Barr, 1975	
Methylphenidate (Ritalin) Cardiovascular Adverse Effects	
2,821 spontaneous reports to the FDA 1985-1997 include arrhythmias and conduction problems (120), heart arrests and failure (13) (Breggin, 1998b). Psychostimulants have direct cardiotoxic effects: (Henderson, Fischer, 1994; Ishiguro, Morgan, 1997)	8
Further Review of the FDA Spontaneous Reporting System Indicating symptom clusters often overlooked in reviews Number of reports	
Dependency, addiction, withdrawal	110
Hair loss	250
Various skin disorders	
Various blood disorders including leukopenia	
Abnormal liver function tests	
Convulsions	69
Depression	48
Psychotic depression	11

Overdose, intentional overdose and suicide attempt	50	
Personality disorders	89	
Agitation	55	
Hostility	50	
Abnormal thinking	44	
Hallucinations	43	
Psychosis	38	
Emotional lability	33	

Methylphenidate-Induced (Ritalin) Abnormalities of Brain Function

Porrino and Lucignani, 1987: alterations in glucose metabolism in the brain of conscious rats
Bell and colleagues, 1982: glucose metabolic rates reduced in the motor cortex and increased in the substantia nigra and other deep structures
Volkow and colleagues, 1997, PET in normals: reduced relative metabolism of basal ganglia and varied other effects
Wang and colleagues, 1994, PET in normals: decreased overall flow of blood into brain by 23-30%
Nasrallah and colleagues, 1986, PET: brain atrophy in more than 50% of 24 young adults

Psychostimulant-Induced Abnormalities of Brain Chemistry in Animals

Wagner, Ricaurte, Johanson, et al., 1980, Methamphetamine: chronic exposure can produce irreversible CNS damage to dopamine receptors and norepinephrine function	
Battaglia, Yeh, O'Hearn, et al., 1987: large chronic doses cause the death of serotonergic nerves in animals	
Melega and colleagues, 1997b: dopamine depletions in vervet monkeys, 2 doses of 2mg/kg	55-85
Sonsalla and colleagues, 1996: dopaminergic cell death in the substantia nigra of mice	40-45
Wagner, Ricaurte, Johanson, et al., 1980, amphetamine: long-lasting loss of dopamine and dopamine uptake sites in rhesus monkeys	
Barnett, Kuczenski, 1986: down-regulation in the dopamine neurotransmitter system	
Melega and colleagues, 1997b, PET, vervet monkeys: decreases in dopamine synthesis	25
Melega and colleagues, 1997a: gradual recovery from neurotoxicity in the striatum over 2 years	
Barnett, Kuczenksi, 1986, methylphenidate: down-regulation of dopamine receptors	
Mathieu, Ferron, Dewar, et al., 1989: reduction of the density of the norepinephrine receptors	
Lacroix, Ferron, 1988: locus coeruleus loses responsiveness	
McCann, Seiden, Rubin, et al., 1997, fenfluramine: death of serotonergic neurons	

Psychostimulant Indirect Adverse Effects

Children lose their sense of responsibility for their own behavior (Breggin, 1997, 1998a; Jensen, Bain, Josephson, 1989) and experience many negative emotional reactions that they may not report (Sroufe, Stewart, 1973).

Psychostimulant Mechanism of Action

Spontaneous or self-generated activities - play, mastery, exploration, novelty seeking, curiosity, and zestful socialization - are central to the growth and development of animals and humans and necessary for the full elaboration of CNS synaptic connections (Greenough, Black, 1992; Weiler, Hawrylak, Greenough, 1995).
Arakawa, 1994; Hughes, 1972; Randrup, Munkvad, 1967; Schiørring, 1979, 1981; Wallach, 1974: stimulants suppress normal spontaneous or self-generated activity and socialization
Bhattacharyya, Ghosh, Aulakh, et al., 1980; Costall, Naylor, 1974; Koek, Colpaert, 1993; Kuczenski, Segal, 1997; Mueller, 1993; Randrup, Munkvad, 1967; Rebec, Bashore, 1984; Rebec, Segal, 1980; Segal, 1975; Segal, Weinberger, Cahill, 1980; early studies reviewed in Wallach, 1974, and Schiørring, 1979: stimulants promote abnormal stereotyped, obsessive/compulsive, asocial behaviors that are repetitive and meaningless
Risk/Benefit Ratio
Swanson, 1993; Breggin, 1998a; Jacobvitz, Sroufe, Stewart, et al., 1990; Popper, Steingard, 1994; Richters, Arnold, Jensen, et al., 1995; Whalen, Henker, 1997: there are no positive long-term psychostimulant effects beyond 7 to 18 weeks
the “therapeutic effects” are in reality toxic effects

On 21 September 2007, the FDA issued a warning for ADHD drugs, advising that these drugs involve cardiovascular and psychiatric risks, and asking for a review of their product labelling. All methylphenidate preparations are involved (30).

- Concerta (methylphenidate hydrochloride) Extended-Release Tablets
- Daytrana (methylphenidate) Transdermal System
- Desoxyn (methamphetamine HCl) Tablets
- Focalin (dexmethylphenidate hydrochloride) Tablets
- Focalin XR (dexmethylphenidate hydrochloride) Extended-Release Capsules
- Metadate CD (methylphenidate hydrochloride) Extended-Release Capsules
- Methylin (methylphenidate hydrochloride) Oral Solution
- Methylin (methylphenidate hydrochloride) Chewable Tablets
- Ritalin (methylphenidate hydrochloride) Tablets
- Ritalin SR (methylphenidate hydrochloride) Sustained-Release Tablets
- Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules

The following table summarises the adverse effects (21).

Table I: Harmful effects caused by Ritalin, Dexedrine, Adderall and other Stimulants

Cardiovascular Function	Palpitations, tachycardia, hypertension, arrhythmias, chest pain, cardiac arrest
Mind and Brain Function	Mania, psychosis, hallucinations, agitation, anxiety, nervousness, insomnia, irritability, hostility, aggression, depression, emotional, sensitivity, easy crying, social withdrawal, drowsiness 'dopey,' reduced alertness, confusion, mental, impairments (decreased cognition and learning), zombie-like

	(robotic) behavior with loss of emotional spontaneity, obsessive-compulsive behavior, convulsions, abnormal movements, tics, Tourette's, nervous habits (e.g. picking at skin, pulling hair)
Gastrointestinal Function	Anorexia, nausea, vomiting, bad taste, stomach ache, cramps, dry mouth, constipation, diarrhea, liver dysfunction
Endocrine and Metabolic Function	Pituitary dysfunction, including growth hormone and prolactin disruption, weight loss, Growth suppression, disturbed sexual function
Other Functions	Blurred vision, headache, dizziness, hypersensitivity reaction with rash, conjunctivitis
Withdrawal and Rebound Reactions	Insomnia, evening crash, depression, rebound worsening of ADHD-like symptoms, overactivity and irritability

Modified from Breggin (1999a & c) by permission of Springer Publishing Company. Sources include Arnold and Jensen (1995, Table 38-5, p. 2306; Table 38-7; and p. 2307), Drug Enforcement Administration (1995b, p. 23), Dulcan (1994, Table 35-6, p. 1217), Maxmen and Ward (1995, pp. 365-366), and Food and Drug Administration (1997c, March). Quotations in Breggin (1999a&c).

The following table presents the adverse obsessive-compulsive effects of Ritalin and Dexedrine (Amphetamine) (21).

Table 3: Obsessive-Compulsive Harmful Drug Reactions		
to Ritalin and Dexedrine (Amphetamine)		
23 of 45 children (51%) in a Controlled Clinical Trial		
Age	Drug	Adverse Drug Reaction
1. 6	Dexedrine	Perseverative [obsessive-compulsive] drawing and writing at home; counting puzzle pieces
2. 6	Dexedrine	Perseverative play with Legos and puzzles (36-hours with Legos with no break to eat or sleep)
3. 6	Ritalin	Perseverative playing of piano
4. 6	Dexedrine	Perseverative playing of piano
5. 7	Dexedrine	Rewriting work; over-erasing; repetitive checking of work; overly neat and organized at home
6. 7	Ritalin	Rewriting work;
	Dexedrine	Compulsively lining up crayons
7. 8	Ritalin	Overly detail oriented
8. 8	Ritalin	Coloring over and over the same area;
	Dexedrine	Repetitive checking of work; frantically goal-oriented; solitary activities

9. 8	Ritalin	Perseverative playing of video games;
	Dexedrine	Cleaning room compulsively, buttoning and then folding dirty laundry
10. 8	Dexedrine	Repetitive checking of work; perseverative with work in school
11. 8	Ritalin	Over-erasing; redrawing; excessive pressure on pencil
	Dexedrine	Over-erasing
12. 8	Ritalin	Markedly detail oriented in drawings
13. 9	Dexedrine	Over-erasing; making lists (TV shows, model cars)
14. 9	Dexedrine	Cleaning room compulsively; overly orderly at home
15. 9	Dexedrine	Perseverative at school
16. 9	Ritalin	Over-erasing; rewriting; excessive pressure on pencils and crayons; perseverative speech;
	Dexedrine	Overly meticulous; inability to terminate school & play activities; perseverative speech
17. 9	Ritalin	Inability to stop school and play activities; repetitive erasing and redoing projects; overly detail oriented
18. 10	Dexedrine	Cleaning room compulsively; folding dirty laundry
19. 10	Dexedrine	Repetitive checking behavior; lining things up; excessive pressure on pencil; repetitive erasing and rewriting
20. 11	Dexedrine	Overly meticulous work; overly neat and organized; cleaning room compulsively; raking leaves for 7 hours and then as they fell individually
21. 11	Dexedrine	Lining up crayons; repetitive erasing and redrawing
22. 11	Ritalin	Repetitive erasing; "perfectionistic;" excessive pressure on pencil and crayons
23. 12	Dexedrine	Overly detail oriented; excessive pressure on pencil & crayons
Data taken from Borcharding et al. (1990). Both drugs increased the likelihood of "repetitious, perfectionistic, overfocused behaviors" (p<.01). Ritalin caused a combination of abnormal movements and obsessive-compulsive reactions (p=.009).		

From "Talking back to Ritalin" by Peter Breggin (21).

Causing Obsessions and Compulsions. Stimulant drugs impair the function of a portion of the brain called the basal ganglia. Dysfunction in the basal ganglia results in a variety of mental and physical symptoms, including impaired higher mental functions, obsessions and compulsions (OCD), and abnormal movements. A study by Borcharding and his colleagues at NIMH specifically looked for the production of OCD symptoms and abnormal movements caused by both Ritalin and amphetamine, (It was a crossover study so that each of the children was exposed to each drug at different times.)

The researchers found that 23 of 45 (51%) of children developed symptoms of OCD. Some of the OCD symptoms were extremely severe. One child became so obsessed with doing a good job raking the leaves, he would wait for each one to fall from the tree. Another played Legos for a 36-hour period without breaking to eat or sleep. Table 3 contains a summary of these drug-induced obsessive-compulsive reactions.

The NIH study was double-blind and placebo controlled, and specifically looked for obsessive-compulsive reactions. Most clinical studies don't focus on these drug-induced symptoms and instead completely overlook them. Borcharding also found a high rate of drug-induced abnormal movements. Thirty-four of the 45 (76%) children suffered from either tics or obsessive-compulsive reactions caused by the drugs and many had a combination of both (see below).

Borcharding's results are confirmed by Castellanos, who found that 25% of children developed OCD while taking Ritalin. Solanto and Wender (Table 2[omitted]) discovered that a single dose of stimulant drugs produced an obsessive over-focusing in 42% of children. The children were sometimes unable to stop performing the tasks that were assigned to them.

The production of OCD in children taking stimulants is typically mistaken for an "improvement." If the child sits stoically in his or her classroom seat while bearing down hard on the pencil obsessively copying every detail from the book, the teacher considers it an improvement. If a child endlessly plays the same game on his computer, his parents may feel relieved by the child's absence. In fact, as Borcharding notes, parents and especially teachers almost never report drug-induced OCD as an adverse effect.

Instead, they think it's an improvement. But drug-induced OCD is a form of severe brain dysfunction. It is an involuntary obsession that the child often cannot stop on his or her own. It enforces social isolation and will not lead to genuine learning. Chapter 4 [omitted] looks in more detail at how adverse drug reactions are confused with improvement in children treated with stimulant drugs.

Causing Tics. *The production of tics can also become a serious problem. These stimulant-induced abnormal movements commonly disfigure the face. These abnormalities can make a child look strange and harm his self-esteem and social acceptance. On occasion, the tics can become permanent. Borcharding found a rate of 58% for tics and abnormal movements in his study of 45 children on stimulants. As already mentioned, many also had obsessive-compulsive symptoms. Castellanos reported a worsening of pre-existing tics.*

A group led by Paul Lipkin (1994) from the Long Island Jewish Medical Center and Albert Einstein College of Medicine did a retrospective evaluation of 122 children with ADHD currently or recently treated with stimulants. They found that 9% of the children developed tics or dyskinesias. Other tics and dyskinesias found in the study included mouth movements (5 children), eye blinking, rolling, or deviation (4), throat clearing or vocalizations (2), eye "bugging" (1), neck turning (1), and face rubbing (1).

Five of the children had more than one type of dyskinesia or tic. One child did not recover. He developed an irreversible syndrome with "facial twitching, head turning, lip smacking, forehead wiping, and vocalizations." The development of at least one permanent severe neurological disorder among 122 children treated with stimulants at ordinary doses should give pause to many parents before starting their own child on the drug.

Stimulants should not be started if a person already has a history of tics and should be stopped if tics develop during treatment. The official label for Ritalin states that Ritalin is contraindicated "in patients with motor tics or with a family history or diagnosis of Tourette's syndrome." Remember, a contraindication is an absolute prohibition against using the drug under the specified conditions.

A study by Mark Schmidt (1994) from NIMH, and a string of other researchers, found changes in calcium, and magnesium concentrations in the blood during treatment with Ritalin and Dexedrine. They suggested that this might be the cause of abnormal movements produced by the stimulants. These findings once again emphasize that the harmful impact of these drugs is widespread in the body and little understood."

On 13 September 2003, the Drug Effectiveness Review Project (49) of the Oregon Health and Science University published the most extensive investigation into the effectiveness of drugs used for ADHD, a 731-page report examining 2287 studies and 27 drugs. The report concludes that there is little evidence on the effectiveness and safety of these drugs in the long term, or regarding whether or not they can increase school results.

Experimental data exist demonstrating the direct harmful effects of methylphenidate (Ritalin®) on the cardiovascular system.

- Mammalian Myocardial Ultrastructures: Henderson 1994 (52)
- Ferret papillary muscles: Ishiguro Y 1997 (53)
- heart rate, blood pressure, and oxygen consumption: Ballard JE 1976 (54) , Kelly KL 1988 (55), Brown RT 1989 (56), Stowe CD 2002 (57)
- Structural abnormalities in the myocardium: Fischer VW 1977 (58)
- atrioventricular nodal re-entrant tachycardia: Gracious BL 1999 (59)

This study confirms that therapeutic doses of Ritalin statistically increase cell mutations and the possible risk of cancer.

Cytogenetic effects in children treated with methylphenidate

Randa A. El-Zein, Sherif Z. Abdel-Rahman, Matthew J. Hay, Mirtha S. Lopez, Melissa L. Bondy, Debra L. Morris and Marvin S. Legator.

Department of Epidemiology, Box 189, The University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA; Department of Preventive Medicine and Community Health, The University of Texas Medical Branch, 2.102 Ewing Hall, Galveston, TX 77555-1110, USA.

In recent years there has been a surge in methylphenidate (Ritalin) use for treatment of attention deficit/hyperactivity disorder (ADHD) in children. However, there is a paucity of information on whether this drug poses any potential health risks, such as mutagenicity or carcinogenicity, for humans. To address this issue, we investigated whether this central nervous system stimulant produces cytogenetic abnormalities in pediatric patients at therapeutic levels. In a population composed of twelve children treated with therapeutic doses of methylphenidate, we analyzed three cytogenetic endpoints in peripheral blood lymphocytes obtained before and three months after initiation of treatment with this drug. In all participants, treatment induced a significant 3, 4.3 and 2.4-fold increase in chromosome aberrations, sister chromatid exchanges and micronuclei frequencies, respectively ($P=0.000$ in all cases). These findings warrant further investigations of the possible health effects of methylphenidate in humans, especially in view of the well-documented relationship between elevated frequencies of chromosome aberrations and increased cancer risk.

Source: <http://psychrights.org/Drugs/cytogenetic-ritalin.pdf>

CONCLUSIONS relating to point B

From the information so far, it seems clear that the safety and effectiveness of these drugs are not proven, and that there is much scientific evidence to advise against their use. They are not used for therapeutic purposes, but, inappropriately as “symptomatics”, to control the unwelcome behaviour of minors to the benefit of the parents and teachers.

Moreover, it is our opinion that the Ministry of Health is gravely negligent in this issue:

- the total absence of mandatory, preliminary and standardised diagnostic procedures, geared to identifying and intercepting medical problems that "mimic" ADHD and other forms behavioural malaise, their joint causes and related pathologies (differential diagnosis);
- the adverse effects of the methylphenidate molecule, as declared by the manufacturers themselves, have in part been “eradicated” from informed consent forms, and this is particularly so for the more severe ones;
- in the references lists to scientific research on this subject, only those studies that are in line with the Ministry's current strategies for the administration of drugs are cited, and no mention whatsoever is made of any of the numerous and authoritative university research studies which, in recent years, have raised doubts and critical questions about their administration;
- Documentation contains a serious underestimation of the risks;

It is also well known from international data that, wherever psychostimulants are used, they are overprescribed by physicians under direct or indirect pressure from pharmaceutical companies. Furthermore, a black market that is practically impossible to monitor has been created, with pharmacies robbed, along with the schools where the drugs are deposited for use by students, and partly espoused by patients themselves, who obtain excess medication in order to resell it.

We do not deny the existence of problematic children, however, we believe that, for their benefit, serious medical screening is of paramount importance, with an in-depth differential diagnosis, followed by an evaluation of the various psychiatric problems.

Concerning the psychological problems sometimes borne by children, we believe that the best approach can be found in the following statement made by Professor Emilia Costa, **1st** Chair in Psychiatry at Rome's "La Sapienza" University and co-signatory of this opinion:

“...the success of psychotherapy is well documented in scientific literature, but often ignored in therapy. Psychiatric drugs are used lightly and non-pharmacological treatments are thought to be not as successful. The truth is that they have long been “snubbed” in favour of solutions with more immediate effects. It is time for professional therapists to admit what is already widely known: psychotherapy modifies in measurable terms the structure of the brain, and has a concrete and positive effect on behaviour. I do not understand why, therefore, these facts continue to be ignored, integrated therapy is ignored, always in favour of the biological, organistic and pharmacological approach, and the superficial declassification of all the rest as “a nice chat” between the therapist and patient.” (50)

QUESTION C: The need to safeguard the psychophysical wellbeing of minors through the current international legislation on human rights, which protects against commercial speculation and improper use of drugs.

We believe it fundamental to point out the existence of legislation on this issue, which confirms our thesis for the need to safeguard the psychophysical wellbeing of minors and protect them against commercial speculation and the improper use of drugs, in favour of psychopaedagogical approaches.

- **European Convention on Human Rights and Biomedicine, Oviedo, 1997 - COE - Council of Europe**

URL to source <http://conventions.coe.int/Treaty/en/Treaties/Html/164.htm>

Chapter I – General provisions

Article 1 – Purpose and object

"Parties to this Convention shall protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms with regard to the application of biology and medicine. Each Party shall take in its internal law the necessary measures to give effect to the provisions of this Convention."

Article 2 – Primacy of the human being: "The interests and welfare of the human being shall
preval over the sole interest of society or science. »

Note 1: Also known as the Convention on Human Rights and Biomedicine, or Oviedo Convention. Opened for signing in Oviedo (Spain), 4 April 1997. It entered into force on 1 December 1999. Ratification and implementation order in Italy given with Law 145 on 28 March 2001 (*Gazzetta Ufficiale* no. 95, 24 April 2001). Instrument of ratification not yet deposited.

Note 2: It is thus clear that there is a need for a therapeutic approach which is first and foremost pedagogical in nature, in the broadest sense of the term, involving all professional figures suitable for intervening with word-based methods and active and involved re-education of the minor. This is particularly true when dealing with disciplinary problems, since the minor is provided with a model for a solution to the problems which they can replicate with friends and eventually with his or her own children.

- **Norms on the responsibilities of transnational corporations and other business enterprises with regard to human rights – UN**

URL to source

<http://www.unhchr.ch/huridocda/huridoca.nsf/%28Symbol%29/E.CN.4.Sub.2.2003.12.Rev.2.En>

F. Obligations with regard to consumer protection

13: "Transnational corporations and other business enterprises shall act in accordance with fair business, marketing and advertising practices and shall take all necessary steps to ensure the safety and quality of the goods and services they provide, including observance of the precautionary principle. Nor shall they produce, distribute, market, or advertise harmful or potentially harmful products for use by consumers."

Note 1: Document adopted on 13 August 2003 by the United Nations Sub-Commission on the Promotion and Protection of Human Rights, 55th session, UN Doc. E/CN.4/Sub.2/2003/12/Rev.2, 26 August 2003.

Note 2: From this it can be seen that the risk of mass medicalisation, with the consequent abuse of drug prescriptions, is a deplorable phenomenon by way of principle and intolerable when implemented on children, and these products should thus genuinely be considered as the very last therapeutic resort.

- **Convention against Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment - UN**

URL to source <http://www2.ohchr.org/english/law/cat.htm>

Article 16: "Each State Party shall undertake to prevent in any territory under its jurisdiction other acts of cruel, inhuman or degrading treatment or punishment which do not amount to torture as defined in article I, when such acts are committed by or at the instigation of or with the consent or acquiescence of a public official or other person acting in an official capacity. In particular, the obligations contained in articles 10, 11, 12 and 13 shall apply with the substitution for references to torture of references to other forms of cruel, inhuman or degrading treatment or punishment."

Note: Code 24841, which entered into force on 26/06/1987. Authorisation for ratification and implementation order in Italy given with Law 489 on 3 November 1988 (*Gazzetta Ufficiale* no. 271 S.O. of 18 November 1988).

- **The Charter of Fundamental Rights of the European Union**

URL to source http://www.europarl.europa.eu/charter/default_en.htm

CHAPTER I - DIGNITY

Article 1: "Human dignity is inviolable. It must be respected and protected."

Article 3: 1.: "Everyone has the right to respect for his or her physical and mental integrity."

Article 4: "Prohibition of torture and inhuman or degrading treatment or punishment."

c) the prohibition on making the human body and its parts as such a source of financial gain.

Note 1: Code 2000/C364/01, EN, published in the Official Journal of the European Union, C 364/1, on 18 December 2000. The Charter is the Second Part of the European Union Constitution Project debated by the Intergovernmental Conference in December 2003.

Note 2: These norms clearly state that invasive and degrading treatments such as electric shock, violent shocks of various kinds, such as insulin shock and others, psychosurgery such as lobotomy and other methods, genetic manipulations and the long-term prescription of psychiatric drugs should be prohibited, in that, among other things, the risk-benefit paradigm is completely inappropriate, including in terms of the cost of such obsolete therapeutic approaches. Furthermore, in the cases where there are no definite scientific proof of the strictly genetic or physical origin of mental disorders in minors, there is a clear need to promote a culture that is not geared towards the hypermedicalisation of children, with the additional purpose of not favouring "genetic prevention" techniques, initially theorised by the regimes in the 20th century and, unfortunately, aimed at supporting research whose goal is the prenatal "genetic rectification" of children.

- **The Universal Declaration of Human Rights – UN**

URL to source <http://www.un.org/en/documents/udhr/>

Article 5: "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment."

Note: Code A/RES/217 A (III), adopted and proclaimed by General Assembly resolution 217 A (III) of 10 December 1948, with 48 votes in favour and 8 abstentions: Saudi Arabia, Czechoslovakia, Yugoslavia, Poland, South African Republic, Ukraine, Soviet Union.

- **Convention on the Rights of the Child**

Article 37 - States Parties shall ensure that: "No child shall be subjected to torture or other cruel, inhuman or degrading treatment or punishment. Neither capital punishment nor life imprisonment without possibility of release shall be imposed for offences committed by persons below eighteen years of age."

- **UN Convention on the Rights of the Child**

URL to source <http://www2.ohchr.org/english/law/crc.htm>

Article 33: "States Parties shall take all appropriate measures, including legislative, administrative, social and educational measures, to protect children from the illicit use of narcotic drugs and psychotropic substances...»

Article 36: "States Parties shall protect the child against all other forms of exploitation prejudicial to any aspects of the child's welfare."

Article 12/1: "States Parties shall assure to the child who is capable of forming his or her own views the right to express those views freely in all matters affecting the child, the views of the child being given due weight in accordance with the age and maturity of the child."

Note 1: Adopted by the General Assembly of the United Nations with Provision 44/25 of 20 November 1989. It entered into force on 2 September 1990. Authorisation for ratification and implementation order in Italy given with Law 176 of 27 May 1991 (*Gazzetta Ufficiale* no. 35 S.O. of 11 June 1991)

Note 2: Prevention is a priority which must therefore be actualised with proper support given to families, schools and children, providing them with the professional figures necessary and, furthermore, as part of the responsibilities of public administration, suitable measures should be taken to improve the quality of life of minors.

- **Principles for the protection of persons with mental illness and the improvement of mental health care - UN**

URL to source

Principle 10 – Medication – 1: "Medication shall meet the best health needs of the patient, shall be given to a patient only for therapeutic or diagnostic purposes and shall never be administered as a punishment or for the convenience of others. Subject to the provisions of paragraph 15 of principle 11 below, mental health practitioners shall only administer medication of known or demonstrated efficacy."

Note 1: Prot. A/RES/46/119, 17 December 1991

Note 2: It is therefore quite clear that, in cases that are considered severe, where the administration of synthetic or natural psychiatric medication is considered necessary, even for short periods, there should be the banning of those drugs which provoke side effects involving serious physical and mental suffering, which cause permanent iatrogenic pathologies, which induce suicide or acts of violence and murder, which may cause the death of the patient at therapeutic doses, which create psychophysical dependency, both to better protect the patients and to avoid the ensuing impact of therapeutic costs on public administration. To safeguard the patient and their families, informed consent should always be requested in writing and with provision of thorough explanations, both on the therapeutic limits of the psychiatric drug and on any side effects.

- **European Social Charter (revised)**

URL to source <http://conventions.coe.int/treaty/en/treaties/html/163.htm>

Part I –

Article 7: "Children and young persons have the right to a special protection against the physical and moral hazards to which they are exposed."

Article 17 – The right of children and young persons to social, legal and economic protection -1. b.:" to protect children and young persons against negligence, violence or exploitation."

Note: The European Social Charter was adopted by the Council of Europe in Turin, on 18 October 1961, entering into force on 26 February 1965. The contents of the 1961 Social Charter were later reproduced and integrated with other rights (including those introduced with an Additional Protocol on 5 May 1988, entering into force on 4 September 1992) in a revised version of the Charter, adopted and opened for signature on 3 May 1996. The new Charter entered into force on 1 September 1999. The cited text is from the revised version of the European Social Charter. The system of control on the European Social Charter is the one set in place by the 1961 Charter, and later integrated, for those States which ratified the

Additional Protocol of 19 November 1995, with a provision for a system of collective complaints.

Notes on ratification in Italy: Authorisation for ratification and implementation order in Italy given with Law 929 on 3 July 1965 (*Gazzetta Ufficiale* no. 193 S.O. of 3 August 1965), entering into force in Italy on 21 November 1965. Revised European Social Charter: authorisation for ratification and Implementation order in Italy given with Law 30 on 9 February 1999 (*Gazzetta Ufficiale* no. 44 S.O. of 23 February 1999). At the time of deposit of the ratification, on 5 July 1999, the Permanent Representative for Italy to the Council of Europe presented the following Note Verbale to the Secretary General of the Council of Europe: “Italy does not consider itself bound by Article 25 of the Charter (the right of workers to the protection of their claims in the event of the insolvency of their employer).”

- **Convention for the Protection of Human Rights and Fundamental Freedoms**

URL to source <http://conventions.coe.int/Treaty/en/Treaties/Html/005.htm>

Article 3 – Prohibition of torture: “No one shall be subjected to torture or to inhuman or degrading treatment or punishment.”

Note: Adopted by the Council of Europe Committee of Ministers on 4 November 1950. Entered into force on 3 September 1953. Ratified and implemented in Italy with Law 848 on 4 August 1955 (*Gazzetta Ufficiale* no. 221 of 24 September 1955. Text coordinated with amendments with Protocol no. 3, entered into force on 21 September 1970; Protocol no. 5, entered into force on 20 December 1971 and Protocol no. 8, entered into force on 1 January 1990; also coordinated with the amendments of Protocol 2, as an integral part of the Convention from its entry into force on 21 September 1970. All the provisions of the above Protocols were further replaced by Protocol 11, signed in Strasburg on 11 May 1994 and entered into force on 1 November 1998, with validity from the date of its entry into force. By force of the provisions of Protocol 11, the provisions of Protocols 9 and 10 are no longer valid. Protocol 11 was implemented with law 296 of 28 August 1997 (*Gazzetta Ufficiale* no. 213 of 12 September 1997).

- **Declaration on the Responsibilities of the Present Generations Towards Future Generations – UN**

Article 3 - Maintenance and perpetuation of humankind

“The present generations should strive to ensure the maintenance and perpetuation of humankind with due respect for the dignity of the human person. Consequently, the nature and form of human life must not be undermined in any way whatsoever.”

Article 6 - Human genome and biodiversity

“The human genome, in full respect of the dignity of the human person and human rights, must be protected and biodiversity safeguarded. Scientific and technological progress should not in any way impair or compromise the preservation of the human and other species.”

Note: Adopted by the UNESCO General Conference on 12 November 1997.

- **Draft Elements of a Comprehensive and Integral International Convention on the Protection and Promotion of the Rights and Dignity of Persons with Disabilities – UN**

URL to source <http://www.un.org/esa/socdev/enable/rights/wgcontrib-chair1.htm>

Part II - Article 13 - Right to be free from torture or cruel, inhuman or degrading treatment or punishment

1. No person with disability shall be subjected to torture or cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his or her free consent to medical or scientific experimentation or intervention.
2. Everyone has the right not to be subjected to forced or coerced interventions of a medical nature or otherwise, aimed at correcting, improving, or alleviating any actual or perceived impairment.
3. States Parties shall take all appropriate legislative, administrative, social and educational measures to protect persons with disabilities, in particular, women and children with disabilities, from all forms of physical or mental violence, injury or abuse, neglect or negligent treatment, maltreatment or exploitation, including sexual abuse.

Note: Text drafted by the Chair of the Ad Hoc Committee on a Convention for the Rights of Persons with Disabilities, 2003. The Draft limits itself to a range of substantive matters, and does not include a draft Preamble, any provisions concerning implementation or monitoring mechanisms, or the formal elements of a convention. It is not intended to be an exhaustive listing of the issues that might need to be covered in a convention.

Again, we find the following position worthy of note.

Annual Report of the International Narcotics Control Board, UN body

URL to source: http://www.incb.org/incb/en/annual_report_2000.html

"Longer-term negative effects are often disregarded, underestimated, or subordinated to short-term cost savings. There is a wide range of complementary or alternative treatment approaches for many of the mental disorders and painful conditions treated today with pharmaceuticals (psychotherapy, counselling, traditional medicine), and such alternatives may often be culturally more relevant and more effective... Several recent studies, however, show that the use of multiple drugs (polypharmacy), often in irrational combinations, in inadequate dosages and for excessively long treatment periods, continues to be quite common. Such medical practice is contrary to the principles of cost-effectiveness and rational evidence-based therapy and is a waste of resources. Health authorities should promote the use of culturally relevant and proven complementary or alternative treatment modalities, keeping in mind that, by relying on such therapeutic options rather than on pharmacotherapy per se, cost savings can be substantial."

Note: NCB Report", year 2000.

References

1. Information publication of “Giù Le Mani Dai Bambini”®
 - URL to source: <http://www.giulemanidaibambini.org/consensus/?ln=en>
2. Reference documents:
 - Consensus_ADHD_Argentino_versione_spagnolo_originale.doc
 - Consensus_ADHD_Argentino_versione_italiana.rtf, translated into Italian by Giù Le Mani Dai Bambini and including references and subscriber profiles in Spanish
 - The coordinator of the Argentine Consensus is Beatriz Janin, psychologist and psychoanalyst, Professor of “Child Psychoanalysis” and Director of the specialisation in “Child and Adolescent Psychoanalysis” at UCES University of Social Sciences (<http://www.uces.edu.ar/>) in Buenos Aires, Argentina, Professor of “Child Psychoanalysis” at the UBA University of Buenos Aires (<http://www.uba.ar/homepage.php>) in Argentina.
 - Contact details for Beatriz Janin:
Argentina
Home: Avenida Córdoba 3431. 4° “A”. Cap. Fed.
Professional residence: Av. Córdoba 3431. 10° “A”. Cap. Fed.
Telephone: 4865-0047(C) 4963-2777 (P) Fax: 4963-2777
E-mail: beatrizjanin@yahoo.com
 - Curriculum Vitae of Beatriz Janin in Spanish: see annex “Beatriz_Janin_cv.pdf”
3. ANN IST SUPER SANITÀ 2006 | VOL. 42, NO. 2: 231-245, paragrafo “Sistemi nosografici”
4. Document to be produced:
 - Breggin_deposizione_giurata_2000_USA_en.doc (English version)
 - Breggin_deposizione_giurata_2000_USA_It.pdf (Italian version)
 - Official website of P. Breggin: <http://www.breggin.com/>
 - Link to P. Breggin's sworn testimony:
http://breggin.com/index.php?option=com_content&task=view&id=200
5. Document to be produced:
 - Baughman_deposizione_giurata_2006_fda_it.pdf (Italian version)
 - Baughman_Testimony_2006_FDA.doc (English version)
 - Official website of Fred Baughman: <http://www.adhdfraud.org/>
 - Web page of the 2006 Upton Sinclair Awards:
<http://www.ednews.org/articles/5387/1/Upton-Sinclair-Awards-2006/Page1.html>
6. Sami Timimi, *A Critique of the International Consensus Statement on ADHD*, Clinical Child and Family Psychology Review, Vol. 7, No. 1, March 2004
 - Sami_Timimi_una_critica_al_consensus_ADHD_it.pdf (Italian version)
 - Sami_Timimi_A_critique_of_consensus_ADHD_en.pdf (English version)
7. Document to be produced:
 - GLMDB_raccomandazioni_ISS.pdf
 - URL to document: <http://www.giulemanidaibambini.org/doc/LetteraISSdefinitiva.pdf>
8. “Giù Le Mani Dai Bambini”® leaflet

- URL to C. Ajmone database : <http://adhd.altervista.org/en/index.htm>
- URL to list of pathologies and conditions that mimic ADHD compiled by C. Ajmone: http://adhd.altervista.org/en/doc/list_pathologies.htm

9. SINPIA_Linee guida_ADHD.pdf

10. Brook U, Boaz M., *Attention deficit and hyperactivity disorder (ADHD) and learning disabilities (LD): adolescents perspective*, Patient Educ Couns., 2005, Aug;58(2):187-91. ;

- Brook_U_2005_it.htm (Italian version)
- Brook_U_2005_en.htm (English version)

➤ URL to source:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16009295&query_hl=1&itool=pubmed_docsum

11. Yoshida Y, Uchiyama T., *The clinical necessity for assessing Attention Deficit/Hyperactivity Disorder (AD/HD) symptoms in children with high-functioning Pervasive Developmental Disorder (PDD).*, Eur Child Adolesc Psychiatry. 2004 Oct;13(5):307-14.

- Yoshida Y_2004_it.htm (Italian version)
- Yoshida Y_2004_en.htm (English version)

➤ URL to source:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15490278&query_hl=1&itool=pubmed_docsum

12. Hesslinger B, Tebartz van Elst L, Mochan F, Ebert D., *A psychopathological study into the relationship between attention deficit hyperactivity disorder in adult patients and recurrent brief depression*, Acta Psychiatr Scand. 2003 May;107(5):385-9.

- Hesslinger B_2003_it.htm (Italian version)
- Hesslinger B_2003_en.htm (English version)

➤ URL to source:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12752035&query_hl=1&itool=pubmed_DocSum

13. Balazs J, Gadoros J., *Comorbidity in child psychiatry: is the comorbidity of pediatric mania and ADHD really that high?*, Psychiatr Hung. 2005;20(4):293-8.

- Balazs J_2005_it.htm (Italian version)
- Balazs J_2005_en.htm (English version)

➤ URL to source:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16462006&query_hl=1&itool=pubmed_docsum

14. Budman CL, Bruun RD, Park KS, Olson ME., *Rage attacks in children and adolescents with Tourette's disorder: a pilot study*, J Clin Psychiatry. 1998 Nov;59(11):576-80.

- Budman CL_1998_it.htm (Italian version)
- Budman CL_1998_en.htm (English version)

➤ URL to source:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9862602&query_hl=4&itool=pubmed_DocSum

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9862602&query_hl=4&itool=pubmed_DocSum

15. Possa Mde A, Spanemberg L, Guardiola A., *Attention-deficit hyperactivity disorder comorbidity in a school sample of children*, Arq Neuropsiquiatr. 2005 Jun;63(2B):479-83. Epub 2005 Jul 25.
 - Possa Mde A_2005_it.htm (Italian version)
 - Possa Mde A_2005_en.htm (English version)
 - URL to source: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16059602&query_hl=11&itool=pubmed_docsum
16. Kadesjo B, Gillberg C., *The comorbidity of ADHD in the general population of Swedish school-age children*, J Child Psychol Psychiatry. 2001 May;42(4):487-92.
 - Kadesjo B_2001_it.htm (Italian version)
 - Kadesjo B_2001_en.htm (English version)
 - URL to source: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=Abstract&list_uids=11383964&query_hl=1&itool=pubmed_DocSum
17. Lalonde J, Turgay A, Hudson JI., *Attention-deficit hyperactivity disorder subtypes and comorbid disruptive behaviour disorders in a child and adolescent mental health clinic*, Can J Psychiatry. 1998 Aug;43(6):623-8.
 - Lalonde J_1998_it.htm (Italian version)
 - Lalonde J_1998_en.htm (English version)
 - URL to source: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=pubmed&cmd=Retrieve&dopt=AbstractPlus&list_uids=9729691&query_hl=1&itool=pubmed_docsum
18. NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder, November 16–18, 1998
 - NIH_Consensus_ADHD_1998.pdf (English version)
19. David Cohen, Jonathan Leo, *An Update on ADHD Neuroimaging Research*, The Journal of Mind and Behavior, Spring 2004, Volume 25, Number 2, Pages 161–166
 - Cohen_neruoimaging_update.pdf (English version)
20. Rapoport JL, Buchsbaum MS, Weingartner H, et al. *Dextroamphetamine. Cognitive and behavioral effects in normal prepubertal boys*. Science. 1978;199:560-563.
21. Peter Breggin MD, *Talking back to Ritalin*, Perseus Publishing, 2001
22. Document to be produced:
 - ICSPP_it.pdf (Italian version)
 - ICSPP_en.doc (English version)
 - URL to ICSPP website: <http://www.icspponline.org/>
 URL to ICSPP document: <http://www.academyanalyticarts.org/galvесеalker.htm>
23. Olanda_publicita_ingannevole_ADHD_GLMDB.pdf (Italian version)
24. cylert_FDA-warning_2002.pdf (English version)
25. Cylert_FDA_warning_2005.pdf (English version)
26. E-mail Claudio Ajmone-Grace Jackson- Hege Salvesen Blix

27. lilly_2005.pdf (English version)
28. lilly_2006.pdf (English version)
29. FDA_warning_suicidi_atomoxetina_2005.mht (English version)
 - URL to source: <http://www.fda.gov/cder/drug/advisory/atomoxetine.htm>
30. FDA_ADHD_warning_tutti_i_farmaci_2007.mht (English version)
 - URL to source:
31. Janne Larsson_Strattera_MHRA_2006.mht (English version)
 - URL to source: http://www.24-7pressrelease.com/view_press_release.php?rID=21052&tf7sid=3a031ad05e2f9e271dd8709c95cd50f4
32. Janne Larsson_Strattera_suicidi_2006.mht (English version)
 - URL to source: <http://www.24-7pressrelease.com/>
33. Janne Larsson_Strattera_10.988_ADR.mht Atomoxetina_EN_ADR.pdf
 - URL to source: http://www.24-7pressrelease.com/view_press_release.php?rID=16662&tf7sid=3a031ad05e2f9e271dd8709c95cd50f4
34. Janne Larsson_Christopher Gillberg_Strattera.mht (English version)
 - URL to source: <http://www.24-7pressrelease.com/>
35. ADHD diagnostic protocol, ISS-AIFA
 - Protocollo diagnostico ADHD 22 03 2007.pdf (Italian)
36. MedWatch, *The clinical impact of adverse event reporting*, October 1996
 - The clinical impact of adverse event reporting_medwach_2006.pdf
37. MHRA documento FOIA 2006
38. Atomoxetina_EN_ADR.pdf (English version)
39. Gillette, Paul C. MD; Garson, Arthur jr. MD, *Sudden Cardiac Death in the Pediatric Population - Sudden Cardiac Death in Specific Populations*, Circulation, 85(1) Supplement:I-64-I-69, January 1992
 - Gillette_1992_EN.pdf
 - URL to source: <http://pt.wkhealth.com/pt/re/circ/pdfhandler.00003017-199201001-00010.pdf;jsessionid=GTvZtTjmp2MFhNJHH8687V1NCpS47yMMzVCxDYbtRVXWDXQT6GLn!881462685!-949856144!8091!-1>
40. Liberthson RR. Sudden death from cardiac causes in children and young adults. N Engl J Med. 1996;334:1039-1044.

41. ADHD Individual Drug Risk Studies To Be Considered By Drug Safety Committee. Press release. February 8, 2006.
42. CONCERTA® (methylphenidate hydrochloride) Extended-release Tablets Briefing Document, Edition: February 2006
 - Concerta_2006.pdf (English version)
43. Morentin Benito, Aguilera Beatriz, Garamendi Pedro Manuel, Suarez-Mier M Paz, *Sudden unexpected non-violent death between 1 and 19 years in north Spain*, Archives of Disease in Childhood, 2000.
44. Lourdes Villalba, *Postmarketing safety review of sudden deaths during treatment with drugs used to treat ADHD*, , 2006
 - FDA_Sudden death with drugs used to treat ADHD_2006.pdf (English version)
45. Fred A. Baughman Jr., MD, *The case against diagnosis and treatment of adhd and related disorders and their treatment with stimulants*, presentation to the Parliamentary Assembly, Council of Europe, November 23, 2001
 - Pompidou Group 2000.doc (English version)
46. Mary Ann Block, Osteopath, sworn testimony before the Texas *Committee on House Government Reform*
 - Mary Anne Block_committee hearing.mht
 - Link to source:
http://www.ablechild.org/documents%20and%20reports_files/house%20government%20ref orm%20committee%20transcripts%209-26-02.htm
47. Carl Sherman, *Antisuicidal Effect Of Psychotropics Remains Uncertain: 'We have to ask if medication is the only way' to approach the prevention of suicide*, Clinical Psychiatric News, August, 2002, Volume 30, issue 8, page 1
 - URL to source:
<http://www.clinicalpsychiatrynews.com/article/PIIS0270664402706310/fulltext>
48. FDA Talk Paper, New Warning for Strattera, December 17, 2004
 - FDA_Warning_Strattera_2004.mht
49. Marian S. MacDonagh, PharmaD, and Kim Peterson, MS, “Drug Class Review on Pharmacologic Treatment for ADHD: Final Report,” Oregon Health and Science University, Sept. 05, pp. 13-20.
50. GiùLeManiDaiBambini Press Release of 28 March 2007 “*Prozac® ai bambini di 8 anni anche in Italia: è definitivo*”
 - GLMDB_comunicato Prozac Italia 27 03 07.pdf
51. Report of the Office Of Drug Safety (ODS), 2006
 - FDA_SuddenDeaths_1999-2003.pdf (English version)
52. Henderson TA, Fischer VW, *Effects of Methylphenidate (Ritalin) on Mammalian Myocardial Ultrastructure*, The American Journal of Cardiovascular Pathology. 1994;5:68-78.
 - cardio_an_1994_stimo_lamel-mioc_Henderson_it.rtf (Italian version)
 - cardio_an_1994_stimo_lamel-mioc_Henderson_en.rtf (English version)

53. Ishiguro Y, Morgan JP., *Biphasic inotropic effects of methamphetamine and methylphenidate on ferret papillary muscles*, J Cardiovasc Pharmacol. 1997 Dec;30(6):744-9.
 ➤ cardio_an_1997_stimo_IN_Ishiguro Y_en.rtf (English version)
 ➤ cardio_an_1997_stimo_IN_Ishiguro Y_it.rtf (Italian version)
54. Ballard JE, Boileau RA, Sleator EK, Massey BH, Sprague RL., *Cardiovascular responses of hyperactive children to methylphenidate*, JAMA. 1976 Dec 20;236(25):2870-4.
 ➤ cardio_um_1976_stimo_infa_pres-sang_Ballard JE_en.rtf (English version)
 ➤ cardio_um_1976_stimo_infa_pres-sang_Ballard JE_it.rtf (Italian version)
55. Kelly KL, Rapport MD, DuPaul GJ., *Attention deficit disorder and methylphenidate: a multi-step analysis of dose-response effects on children's cardiovascular functioning*, Int Clin Psychopharmacol. 1988 Apr;3(2):167-81.
 ➤ cardio_um_1978_stimo_infa_cardiovasc_Kelly KL_en.rtf (English version)
 ➤ cardio_um_1978_stimo_infa_cardiovasc_Kelly KL_it.rtf (Italian version)
56. Brown RT, Sexson SB., *Effects of methylphenidate on cardiovascular responses in attention deficit hyperactivity disorder adolescents*, J Adolesc Health Care. 1989 May;10(3):179-83.
 ➤ cardio_um_1989_stimo_adol_pres-sang_Brown RT_en.rtf (English version)
 ➤ cardio_um_1989_stimo_adol_pres-sang_Brown RT_it.rtf (Italian version)
57. Stowe CD, Gardner SF, Gist CC, Schulz EG, Wells TG., *24-hour ambulatory blood pressure monitoring in male children receiving stimulant therapy*, Ann Pharmacother. 2002 Jul-Aug;36(7-8):1142-9.
 ➤ cardio_um_2002_stimo_infa_pres-sang_Stowe CD_en.rtf (English version)
 ➤ cardio_um_2002_stimo_infa_pres-sang_Stowe CD_it.rtf (Italian version)
58. Fischer VW , *Cardiomyopathic findings associated with methylphenidate*, J. Am. Med. Assoc.; VOL 238 ISS Oct 3 1977, P1497, (REF 2)
 ➤ cardio_um_1997_stimo_lamel-mioc_Fischer VW_en.rtf (English version)
 ➤ cardio_um_1997_stimo_lamel-mioc_Fischer VW_it.rtf (Italian version)
59. Gracious BL, *Atrioventricular nodal re-entrant tachycardia associated with stimulant treatment*, J Child Adolesc Psychopharmacol. 1999;9(2):125-8.
 ➤ cardio_um_1999_stimo_adol_tachi_Gracious BL_en.rtf
 ➤ cardio_um_1999_stimo_adol_tachi_Gracious BL_it.rtf
60. Rapoport JL, Inoff-Germain G., *Aggiornamento del 2002 sulle risposte del Metilfenidato in bambini normali e con deficit attentivo/disordine di iperattività*, J Atten Disord. 2002;6 Suppl 1:S57-60
61. Lydia Furman, MD, *What Is Attention-Deficit Hyperactivity Disorder (ADHD)?*, J Child Neurol. 2005;20(12):994-1003.
62. William B. Carey, *NIH Consensus Development Conference on Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder*, November 16–18, 1998, William H. Natcher Conference Center, National Institutes of Health, Bethesda, Maryland

