U.S. Department of Justice
Drug Enforcement Administration

METHYLPHENIDATE
(A Background Paper)

October 1995

Drug and Chemical Evaluation Section
Office of Diversion Control

Summary

Methylphenidate is a Schedule II stimulant which is structurally and pharmacologically similar to the amphetamines. It is indicated for the treatment of Attention Deficit/Hyperactivity Disorders (ADHD) and narcolepsy. Approximately 85 to 90 percent of all prescriptions for methylphenidate are written for young children and adolescents for the treatment of ADHD. Methylphenidate is available as the brand name product", default", Ritalin, manufactured by Ciba-Geigy, and as generic products manufactured by MD Pharmaceuticals.

The use of methylphenidate in the United States has increased dramatically in recent years. Since 1990, there has been a six-fold increase in the U.S. production and utilization of methylphenidate. This increase contrasts sharply with trends in medical practice seen in the rest of the world. According to the United Nations 1993 statistics on psychotropic substances (the latest data available from that body), the U.S. produces and consumes five times more methylphenidate than the rest of the world combined.

Internationally, methylphenidate is listed in Schedule II of the Convention on Psychotropic Substances, 1971, along with amphetamine and methamphetamine. Under treaty obligations, the United States must provide the United Nations International Narcotics Control Board (INCB) with data on the production, distribution and consumption of methylphenidate. The INCB has, on two recent occasions, written letters to U.S. officials expressing their concern about the sharp increase in the use of methylphenidate in the United States and has requested data on the legal requirements for the use of methylphenidate as well as data concerning trends in abuse and possible diversion from licit sources.

While stimulant pharmacotherapy for the treatment of ADHD in children is recognized by medical experts worldwide, no other nation prescribes stimulants in such volume to its children. Epidemiological data indicate that from 3-5 percent or more of all U.S. children are treated with methylphenidate for ADHD, frequently without the benefit of other services as recommended in treatment guidelines.

Support and advisory groups play an important role in the distribution of information regarding ADHD and its treatment. In recent years there have been large increases in membership in these organizations and participation in their activities. Children and Adults with Attention Deficit Disorder (CHADD) is the nation's largest ADHD support organization. CHADD has a membership of over 28,000 and has 600 chapters nationwide. CHADD sponsors parent support groups, convenes meetings featuring speakers, works with local school systems and provides information regarding ADHD related issues.

It has recently come to the attention of the DEA, that Ciba-Geigy (the manufacturer of the methylphenidate product marketed under the brand name Ritalin) contributed $748,000 to CHADD from 1991 to 1994. The DEA has concerns that the depth of the financial relationship with the manufacturer was not well-known by the public, including CHADD members that have relied upon CHADD for guidance as it pertains to the diagnosis and treatment of their children.

A recent communication from the United Nations International Narcotics Control Board (INCB), expressed concern about non-governmental organizations and parental associations in the United States that are actively lobbying for the medical use of methylphenidate for children with ADHD. The INCB further stated that "financial transfer from a pharmaceutical company with the purpose to promote sales of an internationally controlled substance would be identified as hidden advertisement and in contradiction with

Learning Centers
Nutritionists
Osteopathic Physicians
Speech and Language
Vision Specialists
Relevant Sites
Dr. Fred Baughman Jr. MD, he has been a adult & child neurologist, in private practice, for 35 years
Block Center
Wildest Colts
Gifted Children
Methylphenidate
Annie Armen Live
Peter Breggin, M.D.
Report Site Bugs. Email
web-admin@ritalindeath.com

the provisions of the 1971 Convention (Article 10, para 2)." In fact, a spokesman for Ciba-Geigy stated that "CHADD is essentially a conduit for providing information to the patient population". The relationship between Ciba-Geigy and CHADD raises serious concerns about CHADD's motive in proselytizing the use of Ritalin.

In conjunction with the American Academy of Neurology, CHADD has submitted a petition to reschedule methylphenidate from Schedule II to Schedule III under the Controlled Substances Act (CSA). CHADD denies that the financial contributions received from Ciba-Geigy have any relationship to their action. The basis for this petition is that methylphenidate has a lower abuse potential than amphetamines and that Schedule II controls are unduly burdensome on manufacturers of methylphenidate, physicians who prescribe it and patients who receive methylphenidate. In accordance with procedures set forth in the CSA, the DEA has gathered available data regarding methylphenidate, conducted an initial review of this information, and submitted our findings to the Department of Health and Human Services for their scientific and medical evaluation. The DEA is awaiting their input for consideration in making a final determination on the scheduling of methylphenidate.

Of particular concern is that most of the ADHD literature prepared for public consumption by CHADD and other groups and available to parents, does not address the abuse potential or actual abuse of methylphenidate. Instead, methylphenidate (usually referred to as Ritalin by these groups) is routinely portrayed as a benign, mild substance that is not associated with abuse or serious side effects. In reality, however, there is an abundance of scientific literature which indicates that methylphenidate shares the same abuse potential as other Schedule II stimulants. Case reports document that methylphenidate abuse (like other Schedule II stimulants) can lead to tolerance and severe psychological dependence1. A review of the literature and examination of current abuse/trafficking indicators reveals a significant number of cases where children are abusing methylphenidate.

Whereas the majority of children experience only minor side effects under medically supervised controlled conditions, there are a significant number of case reports documenting more severe abuse. These reports and scientific studies of abuse potential are routinely down-played, if referenced at all. As a consequence, parents of children and adult patients are not being provided with the opportunity for informed consent or a true risk/benefit consideration in deciding whether methylphenidate therapy is appropriate.

Another area of concern is that children under the age of six are being treated with methylphenidate contrary to labeling guidelines2, in the absence of controlled studies suggesting that this is appropriate.3 In addition, children are remaining on medication for longer periods of time, frequently into adolescence and adulthood. Given recent drug abuse trends which indicate that adolescents are abusing methylphenidate with serious consequences, the above issues require close consideration by health authorities.

This paper provides an overview of the growing availability and utilization of methylphenidate in the U.S. and outlines concerns regarding methylphenidate in light of its high potential for abuse. In preparing this paper, many data sources were reviewed including the scientific and medical literature, United Nations statistics on psychotropic substances, Drug Abuse Warning Network (DAWN) statistics and a number of data sources compiled by the DEA on drug thefts, manufacture and distribution, and investigative case files. Information was also supplied by law enforcement personnel, various state agencies and other interested parties.

Background

Overview of Attention Deficit Disorder

The Merck Manual defines Attention Deficit Disorder as developmentally inappropriate inattention and impulsivity, with or without hyperactivity. ADHD is implicated in learning disorders and is diagnosed four times more frequently in boys than girls. Despite the frequent reference to ADHD as a neurobiological disorder, the cause of ADHD remains unknown.4

The primary signs of ADHD (with or without hyperactivity) are the display of inattention and impulsivity. ADHD with hyperactivity is diagnosed when signs of overactivity are obvious. Inattention is described as a failure to finish tasks started, easy distractibility, seeming lack of attention, and difficulty concentrating on tasks requiring sustained attention. Impulsivity is described as acting before thinking, difficulty taking turns, problems organizing work, and constant shifting from one activity to another. Hyperactivity is described as difficulty staying seated and sitting still, and running or climbing excessively.5

The American Psychiatric Association Diagnostic Criteria from DSM-IV lists symptoms of inattention, hyperactivity and impulsivity to be utilized in the diagnosis of the disorder. In order for a diagnosis of ADHD to be made, the symptoms must have persisted for at least 6 months to a degree that is maladaptive and inconsistent with the developmental level.6

Overview of Methylphenidate

Methylphenidate is a Schedule II central nervous system (CNS) stimulant and shares many of the

pharmacological effects of amphetamine, methamphetamine and cocaine. An abundance of literature indicates that methylphenidate is effective in the symptomatic management of narcolepsy and ADHD.

The beneficial effects of amphetamine administration to children with hyperactivity and behavioral problems was first reported in 1937.7 Since that time, central nervous system (CNS) stimulants have been used in the United States for the management of a triad of symptoms including hyperactivity, distractibility and impulsivity that has come to be known as Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate hydrochloride is the most commonly used psychopharmacological agent in children for the treatment of ADHD with about 85 to 90% of all prescriptions of methylphenidate written for this indication. The first published pharmacological study on methylphenidate hydrochloride was by Meier in 1954. Methylphenidate was introduced into therapeutics that same year and has since become the focus of hundreds of scientific studies.

Approved for use in the treatment of Attention Deficit Disorders (previously referred to as minimal brain dysfunction) and narcolepsy, methylphenidate has also been used experimentally for the treatment of mild depression, apathetic or withdrawn senile behavior, and drug-induced lethargy.

Methylphenidate is a CNS stimulant like amphetamine and methamphetamine, and thus produces a number of effects including dose related increases in blood pressure, heart rate, respiration and body temperature, appetite suppression and increased alertness8. Weight loss and growth retardation are common side effects of chronic methylphenidate pharmacotherapy in youngsters although drug holidays on weekends and/or summers can usually compensate for these deficits9. Serious side effects include facial ticks and muscle twitching10. Other adverse effects of methylphenidate, particularly at higher than therapeutic doses, include excessive CNS stimulation, euphoria, nervousness, irritability, and agitation.

Psychotic episodes, violent behavior, tolerance and severe psychological dependence are also reported when methylphenidate is abused. While it is uncertain as to how methylphenidate or other stimulants exert their effects on the CNS to bring about therapeutic efficacy in ADHD, a number of neurotransmitter systems are altered by both acute and chronic methylphenidate administration.

In the U.S., there are now three registered bulk manufacturers of methylphenidate: Ciba-Geigy which produces under the brand name of Ritalin, MD Pharmaceuticals which produces generic methylphenidate and the recent addition of Johnson Matthey who will be synthesizing methylphenidate for generic manufacture. Methylphenidate is available (as Ritalin and in the generic form) in 5, 10 and 20 mg tablets for oral consumption. Ritalin SR and a generic version are available as sustained release tablets of 20 mg for oral use.

FDA approved labeling states that methylphenidate is contraindicated in patients with marked anxiety, tension and agitation since the drug may aggravate these symptoms. Methylphenidate is contraindicated in patients known to be hypersensitive to the drug, patients with glaucoma and in patients with motor tics or with a family history or diagnosis of Tourette's Syndrome. In addition, methylphenidate should not be used in children under six years of age since safety and efficacy in this age group have not been established.11

Trends in ADHD Treatment in the U.S.

The use of methylphenidate has increased dramatically in the U.S. in recent years. The production and use of methylphenidate has increased almost 6-fold since 1990. For example, the aggregate production quota for methylphenidate has increased from 1,361 kg in 1985 to 10,410 kg in 1995 with the primary increases occurring in the last five years.

The United States now consumes more than 80 percent of the total world supply of methylphenidate or five times more than the rest of the world combined. While stimulant pharmacotherapy for the treatment of ADHD in children is recognized by medical experts worldwide, no other nation prescribes stimulants for its children in such volume. Epidemiological data indicate that from 3-5 % or more of all U.S. children are treated with methylphenidate for ADHD, frequently without the benefit of other services (e.g. behavioral modification training and psychotherapy) as recommended in treatment guidelines. Boys are 4 times more likely to be diagnosed with the disorder. Increased utilization is also supported by information from state studies, prescription audit systems and studies of patient visits.

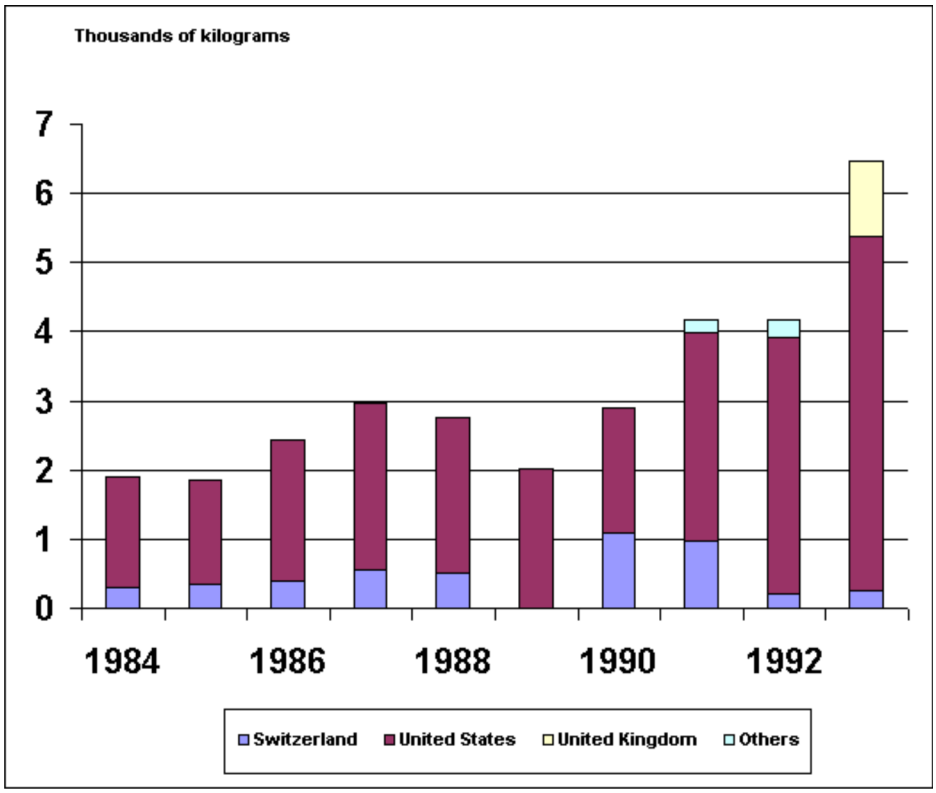
World Perspective

Internationally, methylphenidate is viewed as having a very high potential for abuse and is listed in Schedule II of the Psychotropic Convention. Under treaty obligations, the United States must provide the United Nations with data on the production, distribution and consumption of methylphenidate. Methylphenidate is the only psychoactive substance listed in Schedule II under international treaty whose worldwide medical use has increased. According to the 1993 United Nations Report on Psychoactive Substances, the worldwide medical use of methylphenidate has increased from less than 3 tons in 1990, to more than 6 tons in 1993. This global trend largely reflects increased consumption of methylphenidate in the United States.

The United Nations International Narcotics Control Board (INCB) has, on two recent occasions, written letters to U.S. officials expressing their concern about the sharp increase in the use of methylphenidate in the United States and have requested data on the legal requirements for the use of methylphenidate (i.e.

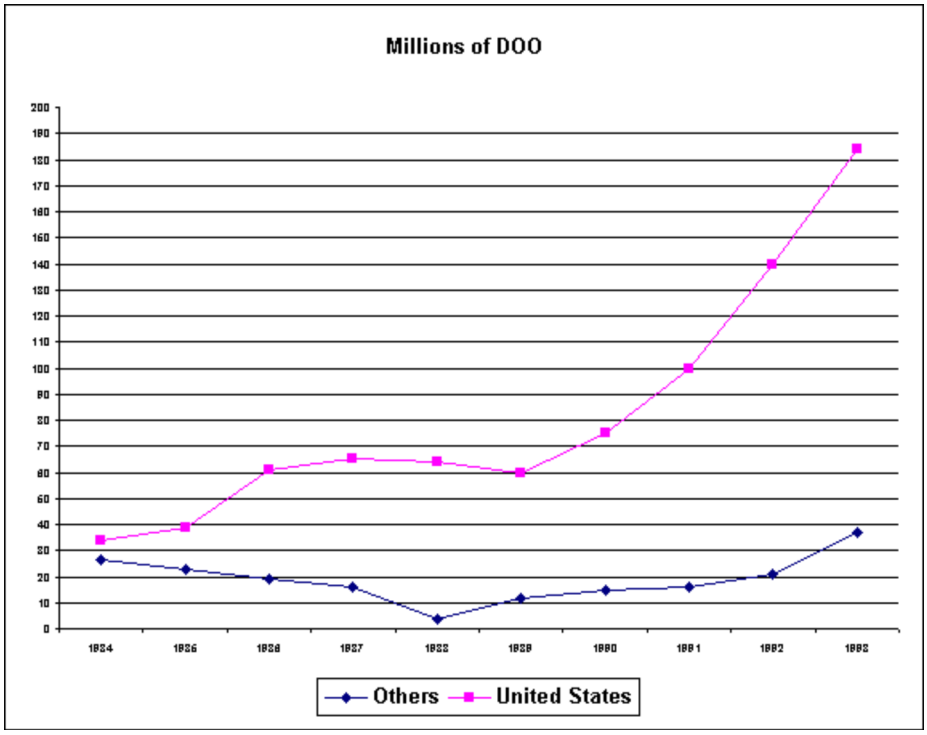
prescription in accordance with sound medical practice – Article 9 of the 1971 Convention) as well as data concerning trends in abuse and possible diversion from licit sources.

The following chart depicts world production of methylphenidate. As can be seen, there have been vast increases in U.S. production of methylphenidate in recent years12:



While U.N. data is not yet available, data for 1994 and 1995 will show substantial increases in U.S. production of methylphenidate.

The reported worldwide consumption of methylphenidate is depicted below.13 The vast proportion of methylphenidate is consumed by the United States. In addition, U.S. consumption has increased dramatically in recent years.



Prescribing Patterns/Treatment Guidelines

A multimodal approach to the treatment of ADHD would incorporate the utilization of a stimulant such as

methylphenidate as part of a total treatment program that includes other remedial measures (psychological, educational and social) for a stabilizing effect on individuals with ADHD. The utilization of behavioral therapy in conjunction with drug therapy is supported, in principle, by most practitioners. While most practitioners ascribe to such a multimodal approach to the treatment of ADHD, most children are prescribed methylphenidate chronically as their sole treatment.14 15

Diagnostic criteria established by the American Psychiatric Association are not applied uniformly16 resulting in some children not being identified as having ADHD and others being falsely diagnosed with ADHD when other psychiatric problems may be overlooked. The manner in which a diagnosis of ADHD is made and the singular treatment approach of psychostimulant therapy contributes to claims that methylphenidate is overprescribed and used indiscriminantly in place of disciplinary measures at home and at school.

Long-term studies indicate that a multimodal treatment approach is necessary to achieve significantly improved outcomes for ADHD children. These studies indicate that treatment with psychostimulants alone does not improve the outcomes of most ADHD children17. These data suggest that there may be a serious underutilization of other treatment modalities and that the medical community may not be meeting the needs of many ADHD children. More promising outcomes have been reported when multimodal approaches are used in the treatment of ADHD18. However, data on physician prescribing practices imply that few general practitioners or pediatricians provide treatment other than pharmacotherapy with psychostimulants.19

Epidemiological data indicate that U.S. medical practitioners vary greatly in the diagnosis and treatment of ADHD. One study indicates that a small percentage of primary care physicians are writing nearly half of all methylphenidate prescriptions for children20. Another area of concern, is that children under the age of six are being treated with methylphenidate contrary to labeling guidelines21 in the absence of controlled studies suggesting that this is appropriate.22

There is a considerable body of literature on the short-term efficacy of stimulant pharmacotherapy on the symptoms of ADHD23. From 60 to 90% of children have been judged as positive drug responders to methylphenidate medication. However, contrary to popular belief, stimulants like methylphenidate will affect normal children and adults in the same manner that they affect ADHD children24. Behavioral or attentional improvements with methylphenidate treatment therefore is not diagnostic of ADHD.

Scheduling History of Methylphenidate

In the United States, methylphenidate was placed in Schedule II of the Controlled Substance Act in 1971. This action was based, in part, on a review by the Department of Health and Human Services (DHHS). The recommendation by the Secretary reflected advice from the National Academy of Science/National Research Council Committee on Problems of Drug Dependence and the Commissioner of the Food and Drug Administration. Both recommended that methylphenidate be placed in Schedule II of the CSA. It was found that methylphenidate's pharmacological effects are essentially the same as those of amphetamine and methamphetamine and that it shares the same abuse potential as these Schedule II stimulants.

While Schedule II regulation prohibits prescription refills, Federal Law does not limit the number of dosage units per prescription nor prevent physicians from issuing several prescriptions at one time as long as they are dated when the physician issues them.

Quota Setting Process and 1994 Methylphenidate Shortage

Because methylphenidate is a Schedule II controlled substance, it is subject to quotas as outlined in Section 306(a) of the Controlled Substances Act (CSA). The CSA requires that the Attorney General establish limits or quotas on the amount of Schedules I and II controlled substances which may be produced in a calendar year. Quotas take into consideration the estimated change in medical requirements as provided by the Department of Health and Human services. Quotas are established to limit the diversion of drugs from legitimate channels while ensuring that legitimate medical need is satisfied. Each year an aggregate production quota (APQ) for each Schedule I and II substance is set based on sales and inventory needs. Each company is given a manufacturing quota (MQ) to provide for these needs. Adjustments may be made at any time throughout the year provided that adequate material remains within the APQ. Also, revisions to the APQ are made midyear based on the previous years' year-end data. These revisions take into consideration any changes in the company's needs up to that point in the year. Additionally, if these revisions prove insufficient, an interim notice may be published to satisfy additional legitimate needs.

The APQ for Schedule I and II controlled substances is published in the Federal Register as a proposal for public comment. Subsequently, these quotas are finalized through a second Federal Register Notice. Since 1983, these Federal Register Notices have required a review by the Office of Management and Budget (OMB) prior to publication. In 1988 additional reviews before publication of each Federal Register Notice were required by the Department of Justice, Office of Policy Development (OPD). Both reviews added to the amount of time required publish the aggregate production quotas. This was particularly troublesome in 1992 and 1993 when it took approximately two months for external reviews before certain quota Federal Register Notices could be published. Beginning in 1994, these external reviews by OMB and OPD were eliminated, thereby greatly reducing the time required for quota

revisions.

The Quota Process and Alleged Shortage

In response to the delay created by the external review process in revising the 1993 aggregate production quota (APQ), Ciba-Geigy (the manufacturer of Ritalin) issued a press release and over 400,000 letters to health care professionals accusing the DEA of creating an impending shortage of their product, Ritalin. This was done at a time when it was known by Ciba-Geigy that a proposal was pending to increase the methylphenidate quota. The issuance of such statements caused great concern within the medical community, and created an environment of panic for parents of children being treated with methylphenidate. Groups such as CHADD were also notified of Ciba-Geigy's allegations. CHADD, in turn, urged parents to write their Congressional Representatives and to the DEA to voice complaints regarding DEA creating a shortage. In addition, many parents rushed to their physicians to get multiple prescriptions for methylphenidate in order to ensure they had several months supply on-hand. In short, Ciba-Geigy was contributing to a situation which promoted the increased sale of product through panic buying.

It should be noted that in 1993, DEA set APQs for more than 60 substances and established revised manufacturing quotas for more than 150 companies. The extended external review process affected each company yet only one company making one product chose to accuse DEA of failing to respond to their needs. All other companies worked with the DEA to ensure that adequate amounts of their products were available until the revisions could be completed. As a result of Ciba-Geigy's actions, the DEA sampled several distributors and pharmacy chains which indicated concern over their ability to obtain Ritalin and the generic form of methylphenidate. DEA could not conclude that a shortage of Ritalin or the generic form existed. MD Pharmaceuticals, the other manufacturer of methylphenidate products, maintained throughout that they had sufficient quota to manufacture methylphenidate as long as the revision was published and an increase granted before the end of the year.

Although both manufacturers of methylphenidate (Ciba-Geigy and MD Pharmaceuticals) were granted revised quotas late in the year (October), neither company stopped manufacturing and sales continued. In addition, each company ended 1993 with inventory on hand.

In 1994 the manufacturing quotas were initially established and then subsequently revised twice during the year due to increased demand for methylphenidate. This is not surprising since there was increased publicity regarding Attention Deficit Disorder and treatment using Ritalin by CHADD and other advocacy groups. Both Ciba-Geigy and MD Pharmaceuticals were granted quotas near the end of 1994 which were the full amount each company requested. Ciba-Geigy ended 1994 with a substantial inventory on hand.

Results of GAO Review

In 1993, an external review process caused a 2-month delay in publishing the proposed revised 1993 APQs for several controlled substances. This created concerns about an impending shortage of some forms of methylphenidate. In response, CIBA-Geigy sent 400,000 letters to health care professionals and CHADD warned its members and Congress about this impending shortage. This created a near panic situation for patients who thought that they couldn't get their medicine because they were told that DEA failed to allow adequate amounts of methylphenidate to be produced. Fortunately no widespread shortage materialized in spite of the panic buying which was prompted. As a result of this incident, however, the oversight and review procedures for the establishment of quotas have been revised. Additionally a General Accounting Office (GAO) investigation was conducted in January 1995. The GAO report indicated that in 1993, all DEA's quota regulations had to be reviewed and approved by OPD (a unit within the Justice Department) and OMB before publication. Because OPD misplaced the Federal Register for the revision of 1993 APQ's, including that for methylphenidate, a 2-month delay in publishing the revised quota ensued. In February, 1994, OMB declared DEA quota regulations to be exempt from OMB centralized review. Under this new procedure, once the DEA Deputy Administrator approves either the proposed or final quota notices, they are forwarded directly to the Federal Register for publication. This new procedure eliminates the cause of the delays in publishing Federal Register Notifications that occurred in 1993 and there is no reason to believe that any such delays will occur in the future. Prompt publication of quota Federal Registers have occurred since the revised procedures were initiated and no shortages of any controlled substance have been a result of DEA not providing quotas to meet medical needs.

Current Industry Practices\Concerns

CHADD/Ciba-Geigy Relationship

Children and Adults with Attention Deficit Disorders (CHADD) is the nation's largest ADHD support organization. CHADD was begun in 1987 by a small group of parents and professionals. Today, CHADD has grown to over 28,000 members and 600 chapters nationwide. CHADD works at the local, state and national levels. On the local level, CHADD sponsors parent support groups, convenes meetings featuring speakers, works with local school systems to ensure appropriate educational services for children with ADHD and publishes local newsletters. The national office of CHADD provides information on the latest

developments in ADHD related issues.

A DEA review reveals that most of the ADHD literature prepared for public consumption and available to parents, does not address the abuse liability or actual abuse of methylphenidate. Instead, methylphenidate is routinely portrayed as a benign, mild stimulant that is not associated with abuse or serious side effects. In reality, however, there is an abundance of scientific literature which indicates that methylphenidate shares the same abuse potential as other Schedule II stimulants. Case reports document that methylphenidate abuse (like other Schedule II stimulants) can lead to tolerance and severe psychological dependence25. In addition, a review of the literature reveals cases where children are abusing methylphenidate.

Whereas the majority of children experience only minor side effects under medically supervised controlled conditions, the case reports documenting more severe abuse and scientific studies of abuse potential are routinely down-played, if referenced at all. As a consequence, parents of children and adult patients are not being provided with the opportunity for informed consent or a true risk/ benefit consideration in deciding whether to initiate methylphenidate therapy.

It has recently come to the attention of the DEA, the Ciba-Geigy (the manufacturer of the methylphenidate product marketed under the brand name Ritalin) contributed $748,000 to CHADD from 1991 to 1994.26 The DEA has concerns that the depth of the financial relationship with the manufacturer was not well-known by the public, including CHADD members that have relied upon CHADD for guidance as it pertains to the diagnosis and treatment or their children. A recent communication from the United Nations International Narcotics Control Board (INCB), expressed concern about non-governmental organizations and parental associations in the United States that are actively lobbying for the medical use of methylphenidate for children with ADHD. The INCB further stated that “financial transfer from a pharmaceutical company with the purpose to promote sales of an internationally controlled substance would be identified as hidden advertisement and in contradiction with the provisions of the 1971 Convention (Article 10, para 2).”

In 1993 and 1994 when Ciba-Geigy warned of an impending shortage of Ritalin, CHADD was active in having its members write their Congressional Representatives to complain about the situation. In letters to members and interviews with the media, CHADD officials also were active in perpetuating concerns that a shortage of Ritalin was imminent. The DEA received more than 135 inquiries from Congressional Representatives. In these communications, CHADD routinely referred to a “Ritalin shortage” as opposed to a “methylphenidate shortage”. The relationship between Ciba-Geigy and CHADD raises serious concerns about CHADD’s motive in proselytizing the use of Ritalin through the use of the brand name as opposed to the generic name methylphenidate in its literature.

In conjunction with the American Academy of Neurology, CHADD has submitted a petition to reschedule methylphenidate from Schedule II to Schedule III under the Controlled Substances Act. Ciba-Geigy stands to benefit from a change in scheduling of methylphenidate. However, CHADD denies that the financial contributions received from Ciba-Geigy have any relationship to the scheduling petition.

Advocacy Groups and Promotion of Methylphenidate Dissemination of Information which is Inconsistent with Scientific Literature

The documentation in this report directly refutes the assertions that methylphenidate is a benign, mild stimulant that is not associated with abuse or serious side effects. The majority of the literature prepared for public consumption and available to parents does not address methylphenidate’s abuse liability or actual abuse. The abuse reports demonstrate that even adolescents who are abusing methylphenidate do not view this activity as dangerous. Whereas the majority of children experience only minor side effects under medically supervised controlled conditions, as reported broadly in short-term efficacy studies, the smaller number of case reports documenting more severe abuse and scientific studies of abuse potential is down-played , if referenced at all. As a consequence, parents of children and adult patients are not being provided with the opportunity for informed consent or a true risk/benefit consideration in determining if they want their children or themselves taking methylphenidate.

Current Public Health Concerns:

Abuse Liability of Methylphenidate

Summary

Methylphenidate is a psychomotor stimulant structurally and pharmacologically related to the amphetamines. Studies and case reports indicate that methylphenidate has the same dependence profile as other Schedule II stimulants. Like other Schedule II stimulants, abuse of methylphenidate can lead to tolerance and severe psychological dependence.27 Psychotic episodes, violent behavior and bizarre mannerisms have been reported.28 Intravenous29 and intranasal abuse can result in serious medical complications.

Studies

Methylphenidate produces d-amphetamine and cocaine-like reinforcing effects in both humans and non-human animals. Preclinical self-administration studies show that methylphenidate is self-administered by animals30 under a variety of conditions, including when substituted for cocaine or d-amphetamine in drug-experienced animals or when initiated in drug-naïve animals. Methylphenidate has reinforcing efficacy similar to cocaine and d-amphetamine. In non-human primates, methylphenidate can maintain high rates of self-injection in progressive ratio studies and is chosen over cocaine in preference studies. In clinical studies methylphenidate is self-administered by humans and produces patterns of reinforcing and subjective effects similar to d-amphetamine. Methylphenidate and d-amphetamine produces similar patterns of subjective effects, including increases in rating of euphoria, drug liking and activity and decreases in sedation.

Drug discrimination procedures provide an indirect measure of a drug's reinforcing effects and its abuse potential.31 Years of drug discrimination research show that methylphenidate is (1) discriminable, (2) can be used as a discriminative stimulus training drug, and (3) generalizes to a number of psychomotor stimulants including cocaine, and d-amphetamine.32 In preclinical studies, chronic administration of methylphenidate produces tolerance to its disruptive and stimulus effects and shows cross-tolerance with d-amphetamine and cocaine.33

In animals, chronic or acute administration of high doses of psychomotor stimulants, such as methylphenidate, cocaine, and d-amphetamine and some substituted phenethylamines, produce a syndrome of behavioral effects characterized by aggression, agitation, disruption in food intake, visual tracking, stereotypies and death.34

In humans, methylphenidate produces behavioral, physiological, subjective, and reinforcing effects similar to those of d-amphetamine35 including increases in rating of euphoria, drug liking and activity, and decreases in sedation. Methylphenidate produces stimulant-like discriminative stimulus effects in humans.36

Abstinence from stimulants, such as d-amphetamine and cocaine, after chronic use results in the appearance of withdrawal signs within one to three days, including depression, sleep disturbances, anxiety, fatigue, anger/hostility, dysphoria, psychomotor agitation, confusion and drug craving.37 Case studies document the same type of syndrome with methylphenidate abstinence after chronic use.38 Methylphenidate has been used experimentally to alleviate the abstinence syndrome associated with cocaine dependence.

It is clear that methylphenidate substitutes for cocaine and d-amphetamine in a number of behavioral paradigms and there is cross-stimulant sensitivity in animal studies. Taken together, studies suggest that a similar form of sensitization may be occurring in humans that are exposed to stimulants (e.g., methylphenidate) and that this drug history may predispose individuals to cocaine's reinforcing effects.39 In a study of the incidence of cocaine use and abuse in adult subjects exposed to methylphenidate as children, medicated ADHD subjects who tried cocaine reported higher levels of drug dependence than non-medicated ADHD subjects and controls.40

Actual Abuse and Diversion of Methylphenidate

Actual Abuse

A review of the available literature shows that methylphenidate is associated with patterns of abuse similar to other Schedule II stimulants. Like amphetamine and cocaine, abuse of methylphenidate can lead to marked tolerance and psychic dependence. The pattern of abuse is characterized by escalation of dose, frequent episodes of binge use followed by severe depression, and an overpowering desire to continue the use of this drug despite medical and social consequences. The abuser may alter the mode of administration from oral use to snorting or intravenous injection to intensify the effects of the drug. Typical of other CNS stimulants, high doses of methylphenidate often produce agitation, tremors, euphoria, tachycardia, palpitations and hypertension. Psychotic episodes, paranoid delusions, hallucinations and bizarre behavior characteristic of amphetamine-like psychomotor stimulant toxicity have all been associated with methylphenidate abuse. Severe medical consequences, including death, have been reported. Case reports document that methylphenidate abuse can lead to marked tolerance and psychic dependence in children41 and adults.42 Although the majority of cases cited in the literature pertain to adult substance abusers, there are indications of adolescent abuse. The literature indicates that the addiction produced by methylphenidate abuse is neither benign nor rare in occurrence, and methylphenidate is more accurately described as producing severe dependence.

In the petition to reschedule methylphenidate, petitioners argue that children do not become dependent on methylphenidate. While that assessment is essentially true for a vast majority of youngsters that are being administered therapeutic doses of methylphenidate or d-amphetamine under a doctor's order, DEA's review indicates that children are abusing methylphenidate and abuse can lead to dependence and addiction.

Severe medical consequences including death have been associated with high doses of methylphenidate and where methylphenidate has been abused by snorting or intravenous injection.43 Like other psychomotor stimulants, utilization of methylphenidate within normal therapeutic dose ranges for the treatment of narcolepsy and ADHD are associated with some risks.44 45 Recent data suggest that pre-exposure to stimulants, including methylphenidate, in childhood may predispose these same individuals to the reinforcing effects of cocaine.46 ADHD adults have a high incidence of substance abuse disorders.47 With three to five percent or more of today's youth being administered methylphenidate on a chronic basis, these issues are of concern.

A significant body of literature is available that describes the actual abuse of methylphenidate and

consequences associated with that abuse. Some of the earliest reported abuse cases came out of Sweden[48] where the widespread abuse of methylphenidate led to its withdrawal from the Swedish market in 1968.[49]

Early reports of methylphenidate abuse in the United States are documented in the scientific and medical literature. Most of the U.S. abuse literature cite case reports of individuals while limited studies were conducted on certain groups or populations. Methylphenidate has been abused orally, intranasally and intravenously. It has been used alone and in combination with narcotics producing the same kinds of effects as those seen with amphetamine alone or in combination with these same drugs. Throughout the 1970's and 1980's several articles in the medical literature documented the serious medical consequences associated with intravenous abuse of methylphenidate.[50] A number of papers documented the abuse of Talwin NX and Ritalin combination that was so prevalent in Kansas City, Missouri and other cities in the U.S. and Canada.[51] The prevalence of the use of methylphenidate among heroin addicts has been reported[52] as well as the use of methylphenidate among methadone clients.[53] Two citations in the literature documented the abuse of prescribed medication in adolescents treated for ADHD.[54]

High School surveys (1994 Texas School Survey and Monitoring for the Future) indicate an increased use of stimulants among high school students. Nationally, about 10% of 1994 high school seniors reported using amphetamines (designated as Benzedrine, Dexedrine, Methedrine, Ritalin, Preludin, Dexamyl and methamphetamine, specifically excluding non-prescription and over-the counter drugs) without a doctor's order. Of those reporting using amphetamines nonmedically, 16.6% reported using Ritalin, up from 7.8% in 1993 and 3.5% in 1992, representing the greatest increase in use among drugs mentioned. For perspective, the report of Ritalin abuse by high school seniors indicates that more seniors in 1994 were using this drug nonmedically than those prescribed methylphenidate for ADHD. Additionally, of those seniors that admitted to using amphetamines without a doctor's order, 55.9% reported getting a little high to moderately high while 16% reported staying high for more than seven hours, indicating a more serious pattern of abuse.

The Drug Abuse Warning Network (DAWN) indicates that from 1990 through 1993, most DAWN emergency room mentions for methylphenidate involved whites (75% to 89%) who were taking the drug orally (90% to 96%) to commit suicide (47% to 67%). A significant number of these estimated episodes, 28 to 40%, were associated with abuse for dependence or psychological effects. The percentage of episodes involving youngsters between the ages of 10 and 19 increased from about 24% in 1990 to about 55% in 1993. Seattle, Washington, Washington D.C., and Detroit, Michigan reported the greatest percentage of mentions per 100,000 population. About 90% of the mentions in 1990 were for drug combinations compared to about 60% of the 1993 mentions suggesting increasing abuse of methylphenidate as a primary drug of abuse. Among those drugs listed in combination with methylphenidate, alcohol and at least one narcotic were consistently ranked among the top five most frequently mentioned. The high percentage of attempted suicides is consistent with the high frequency of depression associated with stimulant abuse. As a point of reference, only 6 DAWN emergency room mentions were associated with all Schedule III stimulants in 1992, and only one mention in 1993.

Diversion

Methylphenidate has been in Schedule II of the CSA since 1971. This schedule provides the highest level of control available in the U.S. and is intended to limit diversion and abuse. Despite the unprecedented availability of other highly abusable stimulants like cocaine and methamphetamine, methylphenidate is still highly sought after by the drug abusing population. The abuse data documented herein all suggest that methylphenidate is abused by diverse segments of our population (from street addicts to children) and that significant amounts of methylphenidate have been diverted to illicit use.

Law enforcement data including STRIDE, theft reports, DEA case reports and reports submitted from various states indicate that even under Schedule II control, diversion and abuse of methylphenidate remains a problem in some segments of our population. Methylphenidate has been targeted by organized drug traffickers in several states, is among the top 10 controlled drugs involved in drug thefts and is diverted and abused by health professionals as well as street addicts. At least two states, Nebraska and Ohio, have experienced significant diversion and abuse of methylphenidate. The most recent trend in methylphenidate diversion centers around the use of this drug for the treatment of ADHD. Cases document parents abusing their child's medication, children selling or giving their medication to classmates and friends, adolescents crushing the methylphenidate tablets and snorting the powder (two deaths were associated with this activity in March of this year) and thefts of school supplies of methylphenidate.

Unlike cocaine, amphetamine and methamphetamine where illicit manufacture and illegal importation into the U.S. account for practically all of the available drugs for abuse, pharmaceutical products diverted from legitimate channels are the only sources of methylphenidate available for abuse. The DEA is not aware of any clandestine production of methylphenidate, which probably reflects its rather arduous chemical synthesis. Diversion of methylphenidate has been identified by drug thefts, illegal sales by health care professionals and prescription forgery. Law enforcement encounters involving illegal activities with methylphenidate are also good indicators of the scope of its diversion and trafficking. The control of methylphenidate in Schedule II, which has the most stringent regulatory requirements and penalties associated with illegal activity, has certainly limited diversion and abuse of this drug. Nevertheless, the following information shows that methylphenidate is diverted and trafficked in a manner and amount similar to other legitimately produced Schedule II substances (e.g. morphine, meperidine, pentobarbital).

DEA maintains a data base of reports of stolen/missing controlled substances from pharmacies, practitioners, manufacturers, hospitals/clinics, distributors and any other licensed handler of controlled substances.

The following table shows the total number of reports and mentions (units of medication, i.e. a bottle of 100, 20mg tablets and a bottle of 500, 10mg tablets would be considered two mentions) for methylphenidate and other CII substances provided for comparison of activity (data for 1990 through May, 1995).

SUBSTANCE, CONTROL STATUS	NUMBER OF REPORTS	NUMBER OF MENTIONS
AMPHETAMINE, CII	710	1325
FENTANYL	640	858
PHENMETRAZINE, CII	34	39
METHYLPHENIDATE, CII	1937	4592
MORPHINE, CII	2118	4163
OXYCODONE, CII	3132	6886
HYDROMORPHONE,CII	1247	2151
HYDROCODONE, CII	2109	4575
MEPERIDINE, CII	2911	5380

In summary, a total of 1,937 instances of drug theft have been reported for methylphenidate since 1990, most reports were generated from pharmacies and most thefts were associated with night break ins. An analysis of the data entered into the system reveals that methylphenidate ranks in the top 10 most frequently reported pharmaceutical drugs diverted from licensed handlers.

Where methylphenidate diversion was documented, activities involved illegal sales of methylphenidate by health professionals, prescription forgery, and overprescribing of methylphenidate by physicians and pharmaceutical theft. Additionally it is important to note that despite Schedule II controls on methylphenidate and its predominant use in treating children and adolescents, methylphenidate is associated with the following types of criminal drug trafficking activities:

1. Street sales as determined by undercover buys
2. Multi-state distribution rings
3. Multi-drug distribution rings (with cocaine, LSD, marijuana, hydromorphone and diazepam)
4. Smuggling from Mexico
5. Distribution to and use by narcotic addicts

While DEA investigators and laboratory analyses generally involve wholesale level dealers, state/local investigations provide more information at the retail or user levels. DEA does not routinely receive summaries of submissions of drug evidence to laboratories or law enforcement case reports from state and local agencies. However, a number of states have provided data to DEA concerning illicit activities with methylphenidate. Although this information is not from a systematic survey, it provides further support that methylphenidate is sought after by segments of the drug abusing community.

In summary, methylphenidate has been diverted in a number of ways by individuals and organized groups. Large quantities of methylphenidate have been obtained illegally by “doctor shoppers”, organized theft rings, ADHD and narcolepsy scams, forged or altered prescriptions and through cooperating physicians or pharmacists. At least two states, Ohio and Nebraska, have identified themselves as having significant problems associated with methylphenidate diversion. Recent trends indicate that adolescents are giving and selling their prescription medication and youngsters are crushing the tablets and snorting the powder like cocaine. Two deaths in March, 1995 are known to have been associated with this practice.

As noted above, severe medical consequences have been associated with the abuse of methylphenidate. The recent trend in the abuse of methylphenidate among adolescents is particularly alarming because this

is the group that has the greatest access to methylphenidate from legitimate prescriptions.

Adverse Effects (Short and Long Term)

The potential adverse effects of methylphenidate and d-amphetamine are almost identical and are summarized in the table below:[1]55

Organic system affected	Methylphenidate	Dextroamphetamine
Cardiovascular	Palpitation Tachycardia Increased blood pressure	Palpitations Tachycardia Increased blood pressure
Central nervous system	Excessive CNS stimulation Psychosis Dizziness Headache Insomnia Nervousness Irritability Attacks of Gilles de la Tourette or other tic syndromes	Excessive CNS stimulation Psychosis Dizziness Headache Insomnia Nervousness Irritability Attacks of Gilles de la Tourette or other tic syndromes
Gastrointestinal	Anorexia Nausea Vomiting Stomach pain Dry mouth	Anorexia Nausea Vomiting Stomach pain Dry mouth
Endocrine/metabolic	Weight loss Growth suppression	Weight loss Growth Suppression
Other	Leukopenia Hypersensitivity reaction Anemia Blurred vision	Skin rash or hives Blurred vision

Ahmann et al. (1993) evaluated Ritalin's side effects in a randomized double-blind placebo-controlled cross-over study with 234 children ages 5 to 15 who met the diagnostic criteria for ADHD. Five of the side effects studied, insomnia, decreased appetite, stomachache, headache and dizziness, increased during Ritalin therapy even at relatively low doses (0.3 mg/kg). This data is consistent with other studies.56 Adverse effects of irritability and sadness have not been well studied, but have been reported in up to 22% of children receiving stimulant medication.57

The effects of methylphenidate on growth and the induction of motor tics have been matters of concern and controversy. Safer et al. (1972) was the first to report growth suppression in children receiving methylphenidate or dextroamphetamine. Subsequent studies have reported growth rebound when stimulant medication is temporarily discontinued.58 However, the longer the drug treatment, the more severe growth suppression will be in adolescence and some drug-treated children are at risk for considerable growth decrements.59 Several reports have indicated that tics may be induced or exacerbated by psychostimulants.60 Stevenson and Wolraich (1989) estimated the risk of tic

development in stimulant treated children to be about 1.3% or higher in children with a family history of Gilles de la Tourette's disease or other tic syndromes. Lipkin et al. (1994) reported that approximately 9% of children with ADHD treated with stimulant medication develop tics and dyskinesias, with less than 1% developing chronic tics or Tourette's syndrome.

The cardiovascular safety of stimulant therapy in children has been a concern of many physicians and researchers. Varying alterations in blood pressure and heart rate after methylphenidate administration have been reported.61 A review by Safer (1992) indicated that in 15 controlled studies using test doses of methylphenidate, a significant elevation of resting heart rate was found in previously unmedicated children (mean + 11 beats/min), but with continued drug treatment, only a minor increase in heart rate was observed (mean + 4 beats/min). Both systolic and diastolic blood pressure increases have been noted but are usually minor after oral administration of therapeutic doses. Large increases in heart rate, diastolic and systolic blood pressure have been reported following i.v. administration and cardiovascular toxicity and death have been reported infrequently. Wang et al. (1994) reported that 0.5 mg/kg i.v. methylphenidate produced significant decreases in cerebral blood flow (CBF) in 5 healthy male subjects. Decrements in CBF were 25 $\pm$ 11% after 5-10 minutes and 20 $\pm$ 10% after 30 minutes. The authors concluded that the lack of regional effects suggest that the decrease in CBF is probably a direct vasoactive property of methylphenidate and proposed caution in administration of methylphenidate chronically or to subjects who may already be cardiovascularly compromised.

The possibility of drug abuse as a consequence of methylphenidate treatment remains unresolved. In a review of the literature, Hechtman (1985) concluded that there was no evidence to suggest that stimulant medication increases the likelihood of drug or alcohol use in adolescents. However, a number of recent studies, drug abuse cases, and trends among adolescents from various sources, indicate that methylphenidate use may be a risk factor for substance abuse. Reports of adults with ADHD have consistently demonstrated elevated rates of lifetime psychoactive substance use disorders (PSUD).62 In particular, 17 to 45% of ADHD adults had alcohol abuse problems or dependence and 9 to 30% had drug abuse problems or dependence. Recent prospective studies that have followed hyperactive children and normal controls into adulthood have found that hyperactive adults with a history of ADHD are more likely than controls to have substance-use disorders.63 Chronic preexposure to stimulants, including methylphenidate, increases the rate of acquisition to cocaine self-administration in rats.64 Further, treatment with methylphenidate in childhood, predisposes these same individuals as adults to cocaine's reinforcing effects.65 Clearly, this is an issue that needs further research.

Risks of Abuse with Aging Treatment Population

In light of methylphenidate's abuse liability, it is important to note the tremendous increase in availability of this substance and the expanded population (adolescents and adults) receiving prescriptions for the treatment of ADHD. Prescription data as well as aggregate production quota information indicate that the use of methylphenidate has increased substantially in the past few years. For example, the aggregate production quota for methylphenidate has increased from 1,361 kg in 1985 to 10, 410 kg n 1995 with the primary increases occurring in the last five years (almost a 6-fold increase since 1990). Epidemiological data indicate that approximately 85 to 90% of all prescriptions for methylphenidate are written for young children and adolescents.

Abuse data indicate a growing problem among school-age children. Children are remaining on medication for longer periods of time, frequently into adolescence and into adulthood. In addition, because so many families with young children and adolescents are in daily contact with this stimulant, a growing problem with abuse of methylphenidate in this setting has been documented.66 The aging treatment population is of major concern given evidence of abuse by adolescents.

In addition, ADHD adults have a high incidence of substance abuse disorders.67 With three to five percent or more of today's youth being administered methylphenidate on a chronic basis, these issues are of great concern.

References

Aarskog, D., Fevag, F., Klove, H., Stoa, K. and Thorsen, T. (1977). J. Pediatr. 90: 136-139.

Ahmann, P.A., Waltonen, S.J., Olson, K.A., Theye, F.W., Van Erem, A.J., and LaPlant, R.J. (1993). Placebo-Controlled Evaluation of Ritalin Side Effects. Pediatrics. 9 (6): 1101-1106.

Akerman, P.T., Dykman, R.A. and Peters, J.E. (1977). Teenage Status of Hyperactive and Non-hyperactive Learning Disabled Boys. Am J Orthopsychiatry. 47: 577-596.

Aman, M.G. and Werry, J.S. (1975). Methylphenidate in Children: Effects Upon Cardiorespiratory Function on Exertion. Int J Ment Health. 4: 119-131.

Arnett, E.N., Battle, W.E., Russo, J.V. and Roberts, W.C. (1976). Intravenous Injection of Talc-Containing Drugs Intended for Oral Use. American Journal of Medicine. 60: 711-718.

Ballard, J.E., Boileau, R.A., Sleator, E.K., Massey, B.H., and Sprague, R.L. (1976). Cardiovascular Responses of Hyperactive Children to Methylphenidate. JAMA. 236 (25): 2870-2874.

Barkley, R.A. (1988). The Effects of Methlyphenidate on the Interactions of Preschool ADHD Children With Their Mothers. J Am Acad Child Adolesc Psychiatry. 27: 336-341.

Barkley, R.A., Karlsson, J., Strzelecki, E. and Murphy, J.V. (1984). Effects of Age and Ritalin Dosage on the Mother-Child Interactions of Hyperactive Children. J Consulting and Clin Psychol. 52: 739-749.

Barkley, R., McMurray, M., Edelbrock, C. and Robbins, K. (1990). Side Effects of Methylphenidate in Children With Attention Deficit Hyperactivity Disorder: A Systematic, Placebo-Controlled Evaluation. Pediatr. 86: 184-192.

Biederman, J., Faraone, S.V., Spencer, T., Wilens, T., Norman, D., Lapey, K.A., Mick, E., Lehman, B.K., and Doyle, A. (1993). Patterns of Psychiatric Comorbidity, Cognition, and Psychosocial Functioning Adults With Attention Deficit Hyperactivity Disorder. Am J Psychiatry. 150 (12): 1792-1798.

Borg., E. (1961). Methylphenidate Addiction. Nord. Med. 65:211-213.

Bradley, C. (1937). The Behavior of Children Receiving Benzedrine. Am J Psychiatry. 94: 577-585.

Brooks, G.F., O'Donoghue, J.M., Rissing , J.P., Soapes,K., and Smith, J.W. (1974). Eikenella Corrodens, A Recently Recognized Pathogen: Infections in Medical-Surgical Patients and In Association with Methylphenidate Abuse. Medicine. 53: 325-342.

Brown, R.T., Wynne, M.E., and Slimmer, L.W. (1984). Attention-Deficit Disorder and the Effect of Methylphenidate on Attention, Behavioral, and Cardiovascular Functioning. J. Clin Psychiatry. 45(11): 473-476.

Brown, R.T., Slimmer, L.W., and Wynne, M.E. (1984). How Much Stimulant Medication is Appropriate for Hyperactive School Children? JOSH. 54 (3): 128-130.

Brown, W.A. (1977). Psychologic and Neuroendocrine Response to Methylphenidate. Arch Gen Psychiatry. 34: 1103-1108.

Brown, W.A., Corriveau, D.P. and Ebert, M.H. (1978). Acute Psychologic and Neuroendocrine Effects of Dextroamphetamine and Methylphenidate. Psychopharmacology. 58: 189-195.

Bryan, V., Franks, L. and Torres, H. (1973). Pseudomonas Aeruginosa Cervical Diskitis With Chondro-Osteomyelitis in an Intravenous Drug Abuser. Surg Neurol. 1: 142-144.

Carter, H.S. and Watson, W. A. (1994). IV Pentazocine/Methylphenidate Abuse – The Clinical Toxicity of Another Ts and Blues Combination. Clin Tox. 32(5): 541-547.

Chait, L.D. (1994). Reinforcing and Subjective Effects of Methylphenidate in Humans. Behav Pharmacology. 5: 281-288.

Chillar, R.K., Jackson, A.L. and Alaan, L. (1982). Hemiplegia After Intracarotid Injection of Methylphenidate. Arch. Neurol. 39: 598-599.

Conners, C.K. (1975). Controlled Trial of Methylphenidate in Preschool Children With Minimal Brain Dysfunction. In: Gittleman-Klein (Ed): Recent Advances in Child Psychopharmacology. New York, Human Sciences Press. Pp 65-78.

Cottler, L.B., Shillington, A.M., Compton III, W.M., Mager, D., and Spitznagel, E.L. (1993). Subjective Reports of Withdrawal Among Cocaine Users: Recommendations for DSM-IV. Drug and Alcohol Dependence. 33: 97-104.

Dackis, C.A. and Gold, M.S. (1990). Addictiveness of Central Stimulants. Addictive Potential of Abused Drugs and Drug Classes. pp. 9-26.

Davidson, E.S., Lambert, N., Hartsough, C., and Schenk, S. (submitted). Higher Incidence of Cocaine Use and Abuse in Adult Subjects Exposed to Methylphenidate (Ritalin) as Children for the Treatment for ADHD. (submitted).

Davy, T., and Rodgers, C.L. (1989). Stimulant Medication and Short Attention Span: A Clinical Approach. Developmental and Behavioral Pediatrics. 10(6) 313-318.

Elenbaas, R.M., Waeckerle, J.F. and McNabney, W.K. (1976). Abscess Formation as a Complication of Parenteral Methylphenidate Abuse. JACEP. 5: 977-980.

Emmett-Oglesby, M.W., and Taylor, K.E. (1981). Role of dose interval in the acquisition of tolerance to methylphenidate. Neuropharmacology. 20: 995-1002.

Evans, S.E. and Johanson, C.E. (1987). Amphetamine-like effects of anorectic and related compounds in pigeons. J Pharmacol Exp Ther. 241: 817-825.

Foot Notes:

1 (Jaffe, 1990)

2 Physicians Desk Reference, 1994

3 [DEA found only four studies that addressed the use of methylphenidate in children under the age of six and only about 130 children were involved in the combined studies (Barkley, 1988; Barkley et al., 1984; Conners, 1975; Schliefer et al., 1975)].

4 Brain imaging studies initially showed clear-cut reductions in glucose utilization in the premotor and prefrontal cortex, areas believed to be important in motor control and attentional processes, in hyperactive parents of hyperactive children (Zametkin et al., 1990). Subsequent studies, however, could not show the same deficits in hyperactive male adolescents (Zametkin et al, 1993) and no changes were observed in the global rate of glucose utilization after an acute dose of methylphenidate in hyperactive adults (Matochik et al., 1993).

5 The Merck Manual of Diagnosis and Therapy, Sixteenth Edition, Merck & Company, Inc., Rahway, N.J. 1992

6 American Psychiatric Association Diagnostic Criteria from DSM-IV, May 1994.

7 Bradley (1937)

8 (AMA Drug Evaluations, 1993)

9 (Safer et al., 1972; 1975)

10 (Stevenson and Wolraich, 1989)

11 Physicians Desk Reference, 1994

12 United Nations Statistical Report on Psychotropics 1993

13 United Nations Statistical Report on Psychotropics 1993

14 (Kelleher et al., 1989; Wolraich et al., 1990).

15 Using a 1985 National Ambulatory Medical Care Survey, Kelleher et al (1989) investigated the frequency of follow up arrangements and concurrent psychotherapy among U.S. children. They found that few providers reported referral or concurrent psychotherapy for patients receiving psychostimulants. Wolraich et al. (1990) reported a serious underuse of systematic behavior treatment in primary care practices. Wolraich and colleagues surveyed a random national sample of primary care physicians (the principal doctors to diagnose and treat ADHD children) and then directly screened 457 patients of 10 pediatricians and family practitioners in two small Midwestern cities. They found that few other forms of therapy, such as behavior modification, were actually used by primary care physicians despite the fact that the majority of physicians in the national surveys and in the midwestern cities reported using behavior treatments. The authors concluded that, while efficacious, behavior modification usually requires a rigorous program to achieve significant benefits and that casual advice by the physician is not likely to be effective or be perceived by the patients as a behavior modification program. "The paucity of non-drug therapies used with children with a diagnosis of ADHD is of concern given the findings that suggest the importance of multimodality therapy for long-term beneficial outcomes" (Wolraich et al., 1990)

16 (Kelleher et al., 1989; Wolraich et al., 1990)

17 (for example: Akerman et al., 1977; Barkley, 1977; Blounin et al., 1978; Satterfield et al., 1987)

18 .For example, Satterfield et al., (1987) described the results of two prospective longitudinal studies of predeliquent hyperactive boys. One group of 80 boys was treated with methylphenidate alone (DTO group) and a second group of 50 boys received methylphenidate in addition to intensive psychological treatments (MMT group). The MMT group received individualized therapy for an average of 3.5 visits per month for 35 months. MMT mean follow up was 9.3 years or at 17.4 years of age. DTO mean follow up was 8.7 years or 17.6 years of age. The MMT group had significantly less delinquency and teenage antisocial behavior, they were more attentive in school and better adjusted at home and more globally improved compared to the DTO group. The authors concluded that medication may be necessary to facilitate impulse control so that the child can better apply what is learned in psychotherapy. While most clinicians ascribe to this theory and indications for use of methylphenidate in the PDR recommends a multimodal approach to therapy, few ADHD children are treated with anything other than psychostimulants.

19 (Kelleher et al., 1989; Wolraich et al., 1990)

20 Rappley, 1995

21 Physicians Desk Reference, 1994

22 [DEA found only four studies that addressed the use of methylphenidate in children under the age of six and only about 130 children were involved in the combined studies (Barkley, 1988; Barkley et al., 1984; Conners, 1975; Schliefer et al., 1975)].

23 (for example: Davy and Rogers, 1989; Rostain, 1991; Stevenson and Wolraich, 1989). On laboratory measures of attention, impulsivity and learning, methylphenidate administration has routinely been found to improve ADHD children's performance on the order of about 25% compared to placebo levels of performance (Pelham, 1986; Swanson and Kinsbourne, 1979). Improvement is shown most clearly as a reduction in classroom disruptiveness and an increase in on-task behavior. Task irrelevant activities such as fidgetiness, finger tapping, and fine motor movements are reduced. In general, medicated children are less disruptive and more compliant than non-medicated children (Barkley et al., 1984).

24 (Rapoport et al.,1978; Gittelman and Kanner,1986)

25 (Jaffe, 1990)

26 ($100,000 in 1991, $50,000 in 1992, $200,000 in 1993 and $398,000 in 1994).

27 Jaffe, 1990

28 McCormick McNeel, 1963; Spensley and Rockwell, 1972

29 Hahn et al., 1969; Jaffe and Koschmann, 1970

30 Wilson et al., 1971; Johanson and Schuster, 1975; Risner and Jones, 1975; Griffiths et al., 1975; Spealman et al., 1989

31 Preston et al., 1995

32 Huang and Ho, 1974; Evans and Johanson, 1987; Wood and Emmett-Oglesby, 1988

33 Emmett-Oglesby and Taylor, 1981; Wood and Emmett-Oglesby, 1988; Leith and Barrett, 1981

34 Johanson et al., 1976; Nielsen et al., 1983; Griffiths et al., 1976; Dackis and Gold, 1990; Wesson and Smith, 1978; Lamb and Griffiths, 1987; Sannerud et al., 1995

35 Martin et al., 1971; Smith and Davis, 1977; Brown et al., 1978; Chait, 1994

36 Heischman and Henningfield, 1991

37 Gawin and Kleber, 1986; Gawin, 1989; Gawin and Ellinwood, 1988; Gawin et al., 1992; Weddington et al, 1990; Satel et al, 1991; Dackis and Gold 1990; Watson et al 1992; Cottier et al., 1993

38 Rioux, 1960; Spensley and Rockwell, 1972; Goyer et al., 1979; Keeley and Light, 1985; Jaffe, 1991

39 Davidson et al., submitted

40 Davidson et al., submitted

41 Goyer et al., Jaffe, 1991

42 Brooks et al., 1972; McCormick and McNeel, 1963; Rioux, 1960; Spensley and Rockwell, 1972

43 For example: Arnett et al., 1976; Brooks et al., 1972; Chillar et al., 1982; Jaffe and Koschmann, 1970; Levine et al., 1984; Lewman, 1972; Lundquest et al., 1987; Stecyk et al, 1985

44 United States Pharmacopeia, Drug Information for the Healthcare Professional

45 Methylphenidate has been shown to alter a number of neurotransmitter systems (see Factor 2, Neurotransmitter effects). Neuroendocrine (Aarskog et al., 1977; Brown, 1977; Gualtieri et al., 1982; Janowsky et al., 1978; Weizman et al., 1987) and cardiac function (Aman and Werry, 1975; Ballard et al., 1976; Brown et al., 1984; Greenberg and Yellin, 1975, Safer, 1992; Safer and Allen, 1975; Wang et al., 1994) are altered with both acute and chronic dosing of methylphenidate. Long term effects of these system disturbances have not been documented and some controversy exists about the potential harm of chronic methylphenidate administration in children especially in regard to possible tics and dyskinesias, growth retardation, cardiac function in later life and substance abuse.

46 Davidson et al., submitted; Schenk and Davidson, in press

47 Biederman et al., 1993; Gualtieri et al., 1985; Levin and Kleber, 1995; Shekim et al., 1990; Spencer et al., 1994

48 Borg, 1961; Jorgensen and Kodahl, 1961; Noriek, 1960

49 Perman, 1970

50 For example: Brooks et al., 1972; Colman, 1984; Elenbaas et al., 1976; Lewman, 1972; Levine et al., 1984; Lindel et al., 1972; Lundquest et al., 1987

51 Bryan et al., 1973; Carter and Watson, 1994; Kishorekumer et al., 1985; Lundquest et al., 1987

52 Lewman (1972) and Haglund and Howerton (1982)

53 Bradford (1975)

54 Goyer et el., 1979 and Jaffe, 1991

55 Data compiled from the United States pharmacopeia, Drug information for the healthcare professional. Rockville, MD: The United States Pharmacopeial Convention; 1990

56 Barkley et al., 1990; Jacobvitz et al., 1990, McBride, 1988; Ullmann and Sleator, 1986; Wolraich et al., 1990

57 Klein et al., 1980

58 Safer et al., 1975; Satterfield et al., 1979

59 Loney et al., 1981

60 Pharmacopeial Convention, 1990

61 Aman and Werry, 1975; Ballard et al., 1976; Brown et al., 1984; Greenberg and Yellin, 1975; Safer and Allen, 1975

62 Gualtieri et al, 1985; Shekim et al., 1990; Spencer et al., 1994; Biederman et al., 1993

63 Levin and Kleber, 1995

64 Schenk and Davidson, in press

65 Davidson et al., submitted

66 Fulton et al. (1988), Goyer et al. (1979) and Jaffe et al. (1991)

67 Biederman et al., 1993; Gualtieri et al., 1985; Levin and Kleber, 1995; Shekim et al., 1990; Spencer et al., 1994

< Home page