USE OF D-AMPHETAMINE AND RELATED CENTRAL NERVOUS SYSTEM STIMULANTS IN CHILDREN

The abuse of amphetamines has become a problem of international significance. Japan was the first country to recognize this problem, and by 1954 there were an estimated 500,000 to 600,000 abusers in Japan. More than ten years ago Japan banned the use of amphetamines. The United Kingdom restricted distribution of amphetamines to hospital pharmacies in 1968. Sweden categorized amphetamine as a narcotic in 1944 because of abuse; and in 1965 phenmetrazine (Preludin) and in 1968 methylphenidate (Ritalin) were removed from the market. Patients now requiring amphetamines are registered with the government. Sweden has about 10,000 drug addicts (almost all between 15 and 30 years of age) using central stimulants intravenously; this is about the same percentage of their population as the estimated percentage of heroin addicts in New York City. In contrast, the number of heroin and opiate addicts in Sweden is estimated to be less than 500.

In 1970, the Food and Drug Administration (FDA) responded to the problem of amphetamine abuse in the United States by limiting the package insert labeling for amphetamines to three indications: narcolepsy, hyperkinesis in children, and the short-term treatment of obesity. Currently, the latter indication is being reviewed and may no longer be valid.

Among the related agents there is some specificity in labeling, e.g., methylphenidate is approved for use in adults with mild depression, narcolepsy at any age, and children with minimal brain dysfunction but not obesity; phenmetrazine for use only in obesity, etc. However, in the broad view there is a similarity in the pharmacologic properties, side effects, and abuse liability of dextro-amphetamine, methamphetamine, methylphenidate, and phenmetrazine. Since the latter two drugs are available only through a single company as a trademarked product, control has been strict and large scale diversion to illicit channels has not been a problem in the United States.

The FDA also has limited the amount of amphetamine which can be manufactured. In 1972 procurement of methylphenidate was cut in half (from 2,854 kg produced in 1971), and that of phenmetrazine was reduced from 4,638 kg to 2,672 kg.

In addition, amphetamine, phenmetrazine, methamphetamine, and methylphenidate were elevated to Schedule II substances, the same category as opium, codeine, and morphine. Schedule II drugs are those considered to have a high potential for abuse, and such abuse may lead to severe psychologic or physical dependence. The Health Protection Branch of the Department of National Health and Welfare of Canada, with the endorsement of the Canadian Medical Association and l'Association des médecins de langue française du Canada, has moved to prohibit the use of amphetamines and related compounds for weight reduction purposes as of September 1, 1972.

The actions by governmental agencies prompted this review of the medical indications for the use of amphetamine in the pediatric age group. The Committee will also consider ways in which these agents become diverted to illegal usage.

At present there are only two valid indications for the use of amphetamines in childhood: (1) the hyperkinetic syndrome, (2) obesity.

The statements presented herein do not preclude alternatives which may be more appropriate, taking into account local situations and all other relevant facts.

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and (2) the rare condition of narcolepsy. Although adequate studies are not available, the usefulness of amphetamines for the treatment of obesity appears to have short-term value without a lasting effect on weight gain attained during adulthood. The use of amphetamines for cramming for examinations and improving athletic performance cannot be condoned.

The hyperkinetic syndrome is characterized by motor restlessness, short attention span, poor impulse control, learning difficulties, and emotional lability. It affects an estimated 3% of grade school children, and apparently resolves spontaneously in most instances by puberty. Carefully selected patients respond favorably to long-term medication with d-amphetamine or methylphenidate in about 65% of patients. The mechanism of drug action is unknown, although certain inhibitory centers in the brain may be activated. Children responding to medication promptly and unequivocally exhibit increased attention span and control over spontaneous motor activity. Omission of a single dose may result in return of the hyperactivity. Also, academic and behavioral performance may become more productive because treatment may break the vicious cycle caused by the effects of the disturbing restless, impulsive behavior on the family and on the school situation.

In a 12-year follow-up study of 340 hyperkinetic patients, no major problems resulting from drug toxicity were found. Similarly, follow-up studies on patients treated during childhood give no indication of increased use of amphetamines or other drugs in later years. In fact, there has been a lack of willful increase in dosage, presumably resulting from the lack of euphoric effect from amphetamine in these patients. A recent paper documents lesser weight gains in nine children on medication (d-amphetamine, 10 to 15 mg, or methylphenidate, 30 to 40 mg/day) for two years. Although there was a correlation between depression of weight gain with linear growth, further studies will be needed to ascertain if adult height is compromised by long-term therapy.

Narcolepsy is a lifelong disorder characterized by excessive daytime sleep patterns (narcolepsy proper); in some patients it is accompanied by emotion-induced muscular weakness (cataplexy, 66%), sleep paralysis (20%), and presleep-hypnagogic hallucinations (30%). The exact incidence of this disease in the pediatric-aged population is unknown, although it is a rare condition. In a report from the Mayo Clinic, 400 narcoleptic patients were seen in a seven-year period. Sixty percent had onset of symptoms before the age of 15, although only 16 of the 400 requiring treatment were under age 15. d-Amphetamine and similar agents provide symptomatic relief of narcolepsy proper and a 50% reduction in cataplexy. The dosage required is in the low range (5 to 10 mg, two or three times a day), similar to that used for the hyperkinetic child. Caffeine is also effective, and the dose of d-amphetamine can be tapered if caffeine is coadministered; caffeine can be given in tablet form, as coffee, or as a cola beverage.

Amphetamines are popularly promoted for the treatment of obesity without proof of lasting benefit; therefore, their use in weight reduction programs cannot be endorsed. Regardless of initiating cause or causes, obesity results from caloric intake exceeding metabolic expenditure. The problem of obesity in childhood is important because 80% of these children become even more obese during childhood. The relatively few double-blind control studies in adolescents treated with various amphetamines and amphetamine-type drugs have shown that any beneficial effect on weight loss is generally evanescent, lasting four to eight weeks. Studies purporting to show beneficial effects are almost all of short duration. A familiar pattern is that weight loss occurs during the first few weeks of the trial; the patient then becomes refractory, an increase in dosage is necessary, and this increase causes side effects. No well con-
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trolled study has demonstrated a long-term beneficial effect on body weight of obese adolescents. Reports in the literature concerning adults who abuse drugs frequently indicate that their first exposure to stimulant drugs was through a physician prescribing amphetamines for weight reduction. Moreover, a fair percentage of adolescents are over-weight and this age group is particularly vulnerable to becoming abusers, in contrast to the young child who receives medication for hyperkinesis.

The availability and use of amphetamines is commonplace among teenagers. In a study of 1,300 students in five San Francisco area colleges, only 8% reported having any difficulty in obtaining a supply of amphetamines. In the 1971 Playboy survey of 3,000 college students, use of amphetamines while in college was registered at 30% and was exceeded only by use of alcohol and marijuana. Over 60% of those who used amphetamines denied chronic use; most used them when “cramming” for examinations, attempting to lose weight, or hoping to excel in athletic competition. These patterns of abuse probably should be considered as distinct from the abuse by intravenous administration of high doses in a chronic manner. A physician prescribing the drug is frequently the initial source of supply; its use can then be continued by its easy availability from peers. The abuse of stimulants is frequently concurrent with sequential abuse of depressive drugs, particularly barbiturates and alcohol. Thus, the signs and symptoms of abuse may range from undetectable to those of paranoid delusions and wildly destructive behavior associated with heavy use of intravenous methamphetamine in so-called runs, i.e., the administration every few hours for as long as several days.

The misuse of these agents frequently can be traced to mistaken ideas about their usefulness as therapeutic agents. Pediatricians have had unduly optimistic expectations of therapeutic responses for the child with poor school performance, the overweight child, or the teen-ager with mild depression. School and team physicians have allowed or overlooked the use of amphetamines and similar agents in athletic contests. Pediatricians are also under pressure from educators and parents who are concerned regarding children who act out in school or are difficult to manage.

Agents such as methylphenidate (Ritalin), phenmetrazine (Preludin), methamphetamine (Desoxyn), and chlorphenetermine (Pre-Sate) have properties similar to d-amphetamine. When tested in a randomized, double-blind fashion under carefully controlled conditions, experienced abusers did not distinguish among intravenous amphetamine, methamphetamine, phenmetrazine, and methylphenidate.

An estimated 8 billion amphetamine-containing tablets are manufactured annually in the United States; this is enough to give every man, woman, and child in the nation 35 substantial doses. This indicates a widespread misuse of an agent having extremely limited therapeutic value. Pediatricians must reflect on their role in introducing patients to these agents; they must not unwittingly contribute to the current problem of overuse, misuse, and abuse. Moreover, physicians must be aware of the widespread use of these agents by some of their patients so they can accurately diagnose illnesses ranging from mild problems of insomnia, nervousness, and depression to such severe conditions as hepatitis, septicemia, and psychotic reactions which may result from intravenous abuse.

The Committee on Drugs recommends that:

1. the use of d-amphetamine and similar agents be limited to children with a clearly defined hyperkinetic syndrome or narcolepsy;
2. d-amphetamine and related agents should not be used in the treatment of obesity;
3. pediatricians become familiar with the wide variety of signs and symptoms that may result from use and abuse of amphetamine-like drugs;
4. the use of central nervous system stimulants in athletics be condemned.

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