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Potential Adverse Effects of Amphetamine Treatment on Brain and Behavior: A Review

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Abstract

Rationale—Amphetamine stimulants have been used medically since early in the twentieth century, but they have a high abuse potential and can be neurotoxic. Although they have long been used effectively to treat attention deficit hyperactivity disorder (ADHD) in children and adolescents, amphetamines are now being prescribed increasingly as maintenance therapy for ADHD and narcolepsy in adults, considerably extending the period of potential exposure. Effects of prolonged stimulant treatment have not been fully explored, and understanding such effects is a research priority [1]. Because the pharmacokinetics of amphetamines differ between children and adults, reevaluation of the potential for adverse effects of chronic treatment of adults is essential.

Findings—Despite information on the effects of stimulants in laboratory animals, profound species differences in susceptibility to stimulant-induced neurotoxicity underscore the need for systematic studies of prolonged human exposure. Early amphetamine treatment has been linked to slowing in height and weight growth in some children. Because the number of prescriptions for amphetamines has increased several-fold over the past decade, an amphetamine-containing formulation is the most commonly prescribed stimulant in North America, and it is noteworthy that amphetamines are also the most abused prescription medications. Although early treatment does not increase risk for substance abuse, few studies have tracked the compliance and usage profiles of individuals who began amphetamine treatment as adults. Overall, there is concern about risk for slowed growth in young patients who are dosed continuously, and for substance abuse in patients first medicated in late adolescence or adulthood.

Although most adult patients also use amphetamines effectively and safely, occasional case reports indicate that prescription use can produce marked psychological adverse events, including stimulant-induced psychosis. Assessments of central toxicity and adverse psychological effects during late adulthood and senescence of adults who receive prolonged courses of amphetamine treatment are warranted. Finally, identification of the biological factors that confer risk and those that offer protection are also needed to better specify the parameters of safe, long-term, therapeutic administration of amphetamines to adults.

Keywords

amphetamine; methamphetamine; stimulant; ADHD; narcolepsy; drug abuse

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Therapeutic use of amphetamine

Description and history

Amphetamine was initially synthesized in Berlin in 1887 as 1-methyl-2-phenethylamine. It was the first of several chemicals, including methamphetamine and methylenedioxymethamphetamine, which have similar structures and biological properties, and are referred to collectively as "amphetamines" [2]. For 110 years, amphetamine was thought to be a human invention, but the compound was found in 1997, along with methamphetamine, nicotine and mescaline, within two species of Texas acacia bushes [3, 4].

Amphetamine is one of the most potent sympathomimetic drugs, producing its effects by increasing synaptic levels of the biogenic amines, dopamine, norepinephrine and serotonin, through multiple mechanisms [5, 6]. Although amphetamine binds to all monoamine transporters, its behavioral stimulant effects are mediated primarily through dopamine and depend on the dopamine transporter (DAT) [7]. Amphetamine blocks the ability of DAT to clear the neurotransmitter from the synapse and facilitates reverse movement of dopamine across the cell membrane (i.e., cytoplasmic dopamine is transported into the synapse and extracellular space). Amphetamine also disrupts vesicular storage of dopamine, allowing it to accumulate in the cytoplasm, and inhibits the degradative enzymes monoamine oxidase A and B (MAO-A, MAO-B). These actions further promote cytoplasmic accumulation of monoamines, which can then be transported into the synapse.

Other molecular mechanisms by which amphetamine mediates monoamine release have also been implicated. These include amphetamine-induced exchange diffusion, channel-like transport, disruption of vesicular storage by the weak base properties of amphetamine, phosphorylation, and transporter trafficking [2]. Amphetamine is presumed to amplify both tonic and phasic dopamine release through such mechanisms. Noradrenergic effects of amphetamine are less well studied, but are also believed to exist at clinically relevant plasma levels of the drug [8].

Amphetamine exists as two stereoisomers that differ in effects [5]. The *l*- enantiomer (levoamphetamine) produces more cardiovascular and peripheral effects than the *d*-enantiomer (dextroamphetamine). At low doses, levoamphetamine produces greater arousal than dextroamphetamine, acting primarily on norepinephrine. At higher doses, dextroamphetamine has stimulant properties that are three- to four times as strong as those of levoamphetamine, and acts primarily on dopamine. Few clinical studies of ADHD, however, have documented differences among *d*-, *l*- and racemic amphetamine. Just as dextroamphetamine has more central and less peripheral action than levoamphetamine, methamphetamine, which is equipotent to dextroamphetamine in producing behavioral stimulant effects [9], has even fewer peripheral effects than dextroamphetamine [5].

Although primarily valued for their use in the treatment of ADHD, amphetamines are also effective in combating the excessive daytime sleepiness associated with narcolepsy. It was first noted in the 1930s that amphetamines can produce a "paradoxical" relaxing effect in severely disruptive, institutionalized, hyperactive boys [10], paving the way for their more common medical use in ADHD. It was also noted in the 1930s that amphetamines had reinforcing properties, leading to widespread prescription drug abuse (see below). Therefore, by 1980 most countries that regulate drug use had severely restricted legal use of amphetamines, but the number of prescriptions, and prescription abuse, continued to grows, particularly in North America. During 1973 there were eight billion amphetamine-containing tablets manufactured in the United States; and both licit and illicit use of amphetamines increased greatly in subsequent years. In the United States and internationally, under the Convention on Psychotropic Substances [11], amphetamine is classified as a Schedule II drug. Schedule II drugs

have an accepted medical use, but are tightly monitored due to a potential for abuse that can lead to severe psychological and physiological dependence.

Despite recommendations that amphetamines be restricted to use for narcolepsy and ADHD, with very limited use for obesity, some physicians have continued to write off-label prescriptions for other medical uses, such as adjuvant medications in treatment of depression and post-stroke cognitive impairment. In 1991, there were still fewer than 500,000 annual prescriptions written for amphetamine in the US. Over the ensuing decade and a half, however, the amount of amphetamine produced and the number of prescriptions written in the United States increased dramatically.

Events in the early 1990's likely influenced the utilization of amphetamine as a prescribed treatment. In 1991, the United States Federal Education Department began classifying ADHD as an educational disability in terms of the Individuals with Disabilities Education Act. This act mandates a comprehensive behavioral, educational and medical evaluation of children suspected of having an educational disability. A physician visit is not required, but the school district is obligated to provide any diagnostic services that are needed at no cost to parents [12]. Over the next 2 years, ADHD diagnoses tripled, from one to three million.

Other concurrent factors included heightened awareness of the biological basis of ADHD [13], reports supporting the view that the disorder was a neuropsychiatric syndrome [14], books about ADHD in the lay press, and a variety of reports on its persistence and associated impairment. Newer formulations of amphetamine also reached the market. Among these was the mixture of amphetamine salts (Adderall™), with a longer duration of action than other available stimulant preparations.

In 2000, the number of prescriptions for amphetamine exceeded eight million, a 1600% increase over nine years. That same year, US annual manufacture of amphetamine reached 30,000 kg (40 % *d*-amphetamine, 60% mixed *d*/*l* salts). In addition, 1,306 kg of methamphetamine was used primarily for treatment of obesity, although it was also approved for treatment of ADHD [11]. Since over 95% of pharmaceutical amphetamines are either *d*-amphetamine or a mixture of *d*- and *l*-amphetamine salts, this review concentrates on these compounds. Methamphetamine is less frequently used in clinical preparations, and is primarily discussed as a comparative drug.

Preparations & Indications

Pharmaceutical drugs classed as amphetamines include formulations from salts of *d*-amphetamine (DextroStat, Dexedrine), mixed *d*- and *l*-amphetamine (Adderall™), *d*-methamphetamine (Desoxyn), and an amphetamine pro-drug compound, lisdexamfetamine dimesylate (Vyvanse™). Methylenedioxymethamphetamine, commonly known as “ecstasy”, belongs to the amphetamine family; it is illicitly manufactured and widely abused but not contained in any medicinally used pharmaceutical. Methylphenidate, an amphetamine-like phenethylamine stimulant and catecholamine reuptake inhibitor, is the most common alternative to treatment with amphetamine, both for ADHD and for narcolepsy.

In the 1990s, longer acting forms of amphetamine were developed using capsules of mixed *d*- and *l*- salts in both immediate release pellets and enteric-coated, delayed-release beads. The different salts and beads are metabolized at different rates, resulting in a less dramatic onset and termination of therapeutic action. Amphetamine is most often administered twice daily in immediate-release formulations (Dexedrine, DextroStat, or Adderall IR tablets), or once a day in sustained-release formulations (Dexedrine or Adderal XR capsules, Vyvanse tablets). The therapeutic effects begin within 45−60 min after ingestion of an immediate-release tablet, with peak effect in 2 to 3 hours, and a total duration of 4−6 h. Effects peak about 4−7 h after ingestion

of extended-release doses, and last about 12 h, depending on the endpoint and dose. Plasma profiles of *d*- and *l*- amphetamine are similar after a single dose of 20 mg Adderall XR or two 10-mg doses of Adderal IR, given 4 h apart. Maximum plasma concentration for Adderall XR is achieved about 6 h after ingestion [15].

Amphetamine is currently FDA-approved for treatment of ADHD and narcolepsy, and methamphetamine is approved for treatment of ADHD and obesity. Amphetamine is approved for ADHD in doses of 2.5 mg/day for children ages 3 to 6, and between 5 and 40 mg/day for amphetamine in an immediate-release (IR) formulation, for school-age children. Amphetamine in an extended-release (XR) formulation has a maximum approved dosage of 30 mg per day for children. Vyvanse contains a conditionally bioreversible derivative of dextroamphetamine, which has lower pharmacokinetic variability and slightly longer duration than other delayed-release amphetamine medications, but requires higher doses. It is manufactured in tablets ranging in dose from 20 mg to 70 mg, and is approved for up to 70 mg per day for school-age children [16]

For adults, Adderall XR is approved at doses up to 20 mg per day, due to lack of evidence for clearly superior benefits from higher doses. After a report that daily Vyvanse dosages of 30 mg, 50 mg and 70 mg all improved ADHD symptoms in a sample of 414 adults [17], the FDA approved the drug for adult treatment in April 2008. There is evidence suggesting that some adults require higher doses of stimulant medications than the approved maximum levels to achieve maximal benefit [18-20]. Effects of prolonged stimulant treatment in adults, however, have not been fully explored, and this is a current research priority [1].

For narcolepsy, amphetamine is recommended at a dose of 5 mg/day for children aged 6 to 12, and between 10 and 60 mg/day over the age of 11. Although it is rarely used, methamphetamine is approved for ADHD at doses between 5 and 25 mg/day for patients over age 6. Methamphetamine is approved for obesity at a dose of 5 mg taken before meals for patients at age 12 and over. Some physicians continue to write off-label prescriptions for other uses of these drugs.

Most pharmaceutical amphetamine is used in treatment of ADHD. Although the therapeutic mode of action is not fully known, amphetamine is highly efficacious for the reduction of core ADHD symptoms in children, adolescents, and adults. In controlled clinical trials, between 55 −70% of ADHD subjects manifest “clinically significant” improvement lasting up to 4−6 weeks. In the very few studies that have compared the efficacy and safety of amphetamine directly to those of methylphenidate, amphetamine was equivalent or superior to methylphenidate on standard efficacy endpoints. Some research also suggests that a few individuals who do not respond to methylphenidate treatment for ADHD experience significant benefit from amphetamine (and vice versa) [8].

Amphetamines produce objective improvement in 65%-85% of patients with narcolepsy [21]. Many physicians prefer more recently developed medicines with less abuse potential, most notably methylphenidate and modafinil, a stimulant-like drug which increases monoamine release but also has other effects, and is primarily used as a “wakefulness promoting agent” in treatment of sleep disorders. However, while clinical comparison trials have not been conducted, meta-analysis suggests that daytime wakefulness is improved in more narcoleptic patients by amphetamines (80%) than by either modafinil (55%) or methylphenidate (70%) [22].

Amphetamines remain among the most effective appetite suppressants. However, by the 1990s, the United States Pharmacopoeia's resource, “Drug Info for the Health Care Professional”, no longer recommended amphetamine for treatment of obesity due to the high abuse potential and availability of equally effective appetite-suppressants with lower abuse potential.

CNS Side effects

Amphetamines readily cross the blood-brain barrier to reach their primary sites of action in the brain. The acute administration of amphetamine produces a wide range of dose-dependent behavioral changes, including increased arousal or wakefulness, anorexia, hyperactivity, perseverative movements, and, in particular, a state of pleasurable affect, elation, and euphoria, which can lead to the abuse of the drug.

Adverse effects listed in drug labels of prescription amphetamines include disturbances of mood and behavior in addition to cardiac and gastrointestinal effects. Most of these adverse events are considered "time-limited", resolving rapidly after discontinuation of stimulant exposure. The most common drug-related effects are loss of appetite, insomnia, emotional lability, nervousness and fever [23]. The American Academy of Pediatrics [24] also lists jitteriness and social withdrawal as common side-effects of amphetamines in children. Clonidine is increasingly administered in conjunction with stimulants to reduce ADHD-associated impulsive/oppositional behaviors or tics, and to combat insomnia. Although limited in scope, a few studies have compared the types and rates of adverse events associated with administration of amphetamine and methylphenidate to children with ADHD. In general, these studies found similar side effect profiles for the two drugs. One of the larger and best controlled studies noted that the severity of adverse events may be greater for amphetamine, especially with respect to insomnia, negative affect, irritability, proneness to crying, anxiety, sadness/unhappiness, and nightmares [25]. However, tolerability as assessed by drop-out rates due to adverse events, was low (≤2%) and did not differ between medications.

Unfortunately, the extant studies on side effect risk of the stimulants used for ADHD treatment have many limitations. All have been restricted to relatively short durations of exposure; and most are based on an assumption that a dose of methylphenidate is equivalent to half of an equal dose of amphetamine. Therefore, amphetamine is administered at 50% of the methylphenidate dose using fixed-dose designs, rather than titrating to a pre-determined efficacy endpoint before comparing adverse events. Most studies have not incorporated measurement of plasma drug level achieved although few relationships between these common adverse events and plasma levels have been noted [15]. Nevertheless, it is potentially important that treatment within approved dose ranges with amphetamines, especially newer extended-release formulations, have produced residual low, but detectable, steady-state blood levels up to 24 h after administration. Thus many individuals experience some degree of continuous drug exposure. Although not tested, this finding suggests that cardiovascular complications, which have been associated with both normal aging and amphetamine abuse in young addicts, may appear earlier in older adults receiving maintenance amphetamine treatment [26]. Regarding the detection of risk for uncommon or rare severe psychological or behavioral reactions to stimulants, controlled studies have not been large enough to pinpoint risk factors or determine differential risk by treatment assignment. Finally, a common observation across studies of the pharmacokinetics, pharmacodynamics, and safety profiles of amphetamine is the high degree of interindividual variability across most measures and endpoints. This variability calls for additional caution in application of the increasingly common practice of prescribing stimulants concurrent with use of other psychotropic medications [27, 28].

Prevalence

ADHD is the most common reason for mental health, special education or behavioral referral in pediatric medicine, and community studies yield prevalence rates from 1.7% to16% of school age children [14, 29], and 1%-5% of adults. Adoption and twin studies estimate that 60 −80% of the risk for ADHD is heritable, likely reflecting a polygenic or oligogenic risk mechanism [30]. The prescription of chronic stimulant medication for maintenance therapy has long been the most effective treatment for ADHD [31], and stimulant use has continued to

increase over the last decade. Despite this increase, estimates suggest that roughly half of children and adolescents with ADHD do not receive medical treatment for the disorder [29], and even fewer adults with ADHD receive any intervention directed at its amelioration.

ADHD treatment forms the bulk of the total prescriptions for pharmaceutical amphetamines. A study of children receiving licit stimulants in the Netherlands found that 90% of them were diagnosed with ADHD [32]. Medical use of stimulants is highest in North America (1 to 2 % of the population), and Australia, particularly the state of Western Australia (2.4%), with somewhat lower values in Europe (0.8 to 1.7%). This frequency of amphetamine use parallels regional differences in the prevalence estimates of ADHD [33]. In 2004, 70% of the stimulant prescriptions for children in Western Australia were for *d*- amphetamine. However, as methylphenidate was approved for government subsidies in late 2005, its use has probably since increased [33].

Boys are diagnosed with ADHD 2−4 times as frequently as girls. The frequency of diagnoses increases steeply from age 3 to about age 8, and increases at a slower rate or plateaus through the teen years. In a study of almost 10,000 Australian children taking medicinal stimulants, the highest prevalence of ADHD was 5.5%, and was found in 14 year-old boys [33].

The proportion of total stimulant prescriptions written for adults has not been documented, but adult diagnosis of ADHD has increased over recent years, attaining a census-adjusted visit rate of 0.4% in the US by 2003 [34]. In 4,569 adults diagnosed with ADD/ADHD from 1999−2004 in the US, and who received mixed amphetamine salts, methlyphenidate, or atomoxetine (a selective norepinephrine transporter inhibitor), 34% were given amphetamine [35]. Amphetamine treatment lasted for a median of 128 days, longer than treatment periods associated with methylphenidate (99 days), or atomoxetine (86 days). Adults can receive higher amphetamine doses than children, with evidence that doses of up to 0.9 mg/kg/day are required to attain maximal benefits [18-20]. In addition, the elimination half-life of amphetamine in adults is two to three times as long as that observed in children [36]. Because the treatment of adult ADHD could theoretically be quite prolonged if symptoms persist, the careful evaluation of the potential for adverse effects of cumulative amphetamines in adults is needed.

Narcolepsy is a less common disorder than attention deficit disorder, with prevalence estimates ranging from 0.005 % in the US, to 0.05% in five European countries, to 0.15% in Japan [37]. It is characterized by excessive daytime sleepiness, cataplexy, and hypnagogic hallucinations. Narcolepsy is most typically diagnosed in the second or third decade of life. As it is a chronic disorder, treatment needs are essentially life-long.

It is remarkable that the prevalence of problematic use of amphetamine has been rising in the elderly, and that prescription substance abuse in this population may augment associated risks and require unique considerations for diagnosis and treatment [38]. The number of emergency department mentions of amphetamine for illicit substances among patients 55 years and older increased 700% from 1995 to 2002 [39], and it is estimated that the number of adults of this age in need of substance abuse treatment will increase from 1.7 million in 2000 and 2001 to 4.4 million in 2020 [40]. The increased use of amphetamines as maintenance medications in adults, the longer elimination half-life in adults compared with children or adolescents, the larger dosages and treatment durations applied to adults, and the increased prevalence of problematic use in adults all underscore the need for careful evaluation of the potential for adverse effects of cumulative amphetamine administration in adulthood.

Animal studies - Neurotoxicity and implications for therapeutic treatment

Many of the behavioral effects of amphetamines that have been observed in humans can be demonstrated in experimental animals. These include arousal, hyperactivity, stereotypic

perseverative movements, psychomotor depression, cognitive impairment, hallucinatory-like behaviors, and chronic self-administration. Evidence indicates that the effects of amphetamine on the neurotransmitters dopamine and norepinephrine play critical roles in eliciting these effects. After chronic exposure to amphetamines, animals exhibit either tolerance (an attenuated response) or sensitization (an augmented response) during subsequent drug administration, indicating that adaptations in the neurobiological substrates of these behaviors.

Concerns have been voiced that, in addition to neurobiological adaptations, prolonged exposure to amphetamine could damage components of the central nervous system. These concerns arise, in part, from evidence that exposure of experimental animals to acute, high doses of amphetamine or methamphetamine produces damage, generally referred to as "neurotoxicity", to dopaminergic neurons innervating the dorsal striatum (caudate-putamen). The evidence for neurotoxicity in rodents derives almost exclusively from studies utilizing very high parenterally administered doses of the drugs, typically administered in a "binge" pattern; i.e., four successive injections at 2-hr intervals [41, 42]. The damage is evident as deficits in phenotypic markers for dopaminergic nerve terminals, including dopamine, its biosynthetic enzymes tyrosine hydroxylase and aromatic amino acid decarboxylase, and both the plasma membrane dopamine transporter (DAT) as well as the vesicular monoamine transporter. High doses of amphetamines have produced enlarged chromatolytic medulla neurons in cats [43], and parenteral dosing in rodents can also produce swollen or reduced dopaminergic axons, and serotonin deficits. The deficits in dopaminergic nerve terminals are not accompanied by apparent damage to the dopamine-containing cell bodies within the substantia nigra. Nevertheless, they can persist for years following cessation of drug exposure [44]. Although the relevance of these data to the consequences of low dose, prescription use of amphetamines in humans is not entirely clear, the potential for similar damage following prolonged low dose exposure merits some consideration.

The mechanisms responsible for amphetamine-induced neurotoxicity have not been fully identified. However, accumulated evidence suggest that the high levels of cytoplasmic dopamine associated with amphetamine-mediated disruption of vesicular storage lead to accumulation of reactive oxygen species and severe oxidative stress [45], which contribute to the damage to dopamine nerve terminals. Efforts to detect similar stimulant-induced neurotoxicity with high-dose exposure to methylphenidate have produced negative findings [46, 47]. It has been speculated that the absence of such damage reflects the mechanism of action of methylphenidate, which is strictly to block dopamine reuptake at the dopamine transporter in the absence of disruption to the vesicular storage pool. In contrast, amphetamine and methamphetamine appear to have similar potency across a range of acute and chronic neurochemical and behavioral actions [9, 48-50], including their ability to induce neurotoxicity [50, 51], and to disrupt vesicular storage of dopamine. Although unrelated to neurotoxicity, it is remarkable that methylphenidate given to juvenile rats did produce striatal dopamine transporter downregulation that persisted into adulthood [52].

Although evidence for neurotoxicity in rodents derives from studies utilizing very high amphetamine doses, and repeated exposure to lower doses equivalent to the human therapeutic range do not produce toxicity in rodents (e.g., 50), a similar study of non-human primates produced very different results. Adult baboons and squirrel monkeys were treated with a 3:1 mixture of *d/l* –amphetamine similar to the pharmaceutical Adderal for 4 weeks [53]. Plasma concentrations of amphetamine (136 +/− 21 ng/ml) matched the levels reported in human ADHD patients after amphetamine treatment lasting 3 weeks (120 to 140 ng/ml) [54] or 6 weeks in the highest dose (30 mg/day) condition (120 ng/ml) [15]. When the animals were sacrificed 2-weeks after the 4 week amphetamine treatment period, both nonhuman primate species showed a 30−50% reduction in striatal dopamine, its major metabolite 3,4-Dihydroxy-Phenylacetic Acid (DOPAC), its rate-limiting enzyme (tyrosine hydroxylase), its membrane

transporter, and its vesicular transporter. These consequences are similar, if not identical to the effects of neurotoxic doses in rodents.

Though the paradigm used by Ricaurte et al. [53] arguably still incorporates amphetamine exposure at a level above much clinical use [15, 55], it raises important unanswered questions. Is there a threshold of amphetamine exposure above which persistent changes in the dopamine system are induced? One study in rodents reported that 15 daily "binges" with 4 mg/kg amphetamine significantly compromised striatal dopamine integrity, whereas an identical treatment with 2.5 mg/kg did not [50]. What factors influence individual differences in vulnerability to persistent neurochemical changes following exposure to amphetamine? For example, stress augments the neurotoxic effects of the amphetamines (see, for example, [45]), and hormone levels differentially affect methamphetamine neurotoxicity in female and male mice [56]. Does the cumulative exposure consistent with lifelong maintenance medication produce persistent dopaminergic changes associated with behavioral deficits that increase at advanced ages? Older rats, mice and gerbils developed greater methamphetamine neurotoxicity than younger animals, as indicated by striatal dopamine reduction, structural deficits and increased levels of glial fibrillary acid protein [57-59]. In addition, brain amphetamine levels at both 20 and 65 min after intraperitoneal administration of 2.5 mg/kg of amphetamine were twice as high in the brains of old rats as in young rats [60]. On the other hand, prior exposure of rats to progressively increasing nontoxic doses of amphetamine or methamphetamine markedly protects against the neurotoxic effects of subsequent high-dose stimulant exposure [61, 62].

In humans, markers of striatal dopamine function decline with age. Nuclear medicine procedures have indicated that availability of the dopamine transporter in the striatum decline at a rate of 6 − 7% per decade [61-63], and measures of nigrostriatal neurons have indicated a loss of 70% in the putamen after the age of 55 years [64]. In addition, the age-related loss of dopamine appears to accelerate after age 60 [63, 64]. One important question is, "Does exposure to amphetamine during development and/or early adulthood accelerate and enhance the age-related decline in dopaminergic function?" In addition, are humans at increased risk from neurotoxicity when amphetamine is administered in late adulthood or senescence?

Such questions underscore the need to determine which animal paradigms best simulate relevant therapeutic exposure at different periods of the human lifespan. The mechanisms underlying neurotoxicity remain speculative, however; and some evidence suggests marked species differences in vulnerability to stimulant-induced neurotoxicity (see 65 for a review). For example, as noted above, 15 daily "binges" of 2.5 mg/kg amphetamine in rats had no deleterious effects on caudate dopaminergic integrity [50], whereas just two injections of 2 mg/kg amphetamine in vervet monkeys produced a relatively long-lasting near 90% decrease in dopamine levels within the caudate nucleus [51]. Given the potential for profound species differences in susceptibility to stimulant-induced neurotoxicity, preclinical approaches may have limited utility in addressing questions relevant to clinical practice. Rather, systematic longitudinal and cross-sectional studies of the effects of prolonged human stimulant exposure are required.

Human studies- Negative consequences of chronic amphetamine use

Effects on Growth

Amphetamines have long been shown to slow weight gain, but some studies have suggested that these effects fade over several years of exposure (see below). The effects of psychostimulants on height have also generated controversy and concern, but until recently, consensus from studies examining growth changes during stimulant treatment was lacking. Recent reports have added some clarity to the issue, and the NIH National Toxicology Program

concluded that there was concern for neurobehavioral developmental toxicity from amphetamines [23].

Poulton [66] reviewed 29 reports on growth effects. Eleven of them concluded that stimulant treatment reduced height. Negative studies were often hampered by methodological weaknesses, and few conclusions were available. Despite some observations of slowing of height velocity in school-age children, discrepancies regarding attenuation of height in studies of adolescents and adults with earlier stimulant treatment histories have led to suggestions that the long-term significance of stimulant effects on growth are minor and probably transitory. While a variety of mechanisms have been suggested to account for attenuating effects of stimulants on growth, reduced caloric intake may be the major reason, in view of the decrease in appetite associated with these drugs.

Since the 2005 review, additional research reports on growth effects have emerged. Again, some found small or no deficits [67, 68], but these studies lacked an untreated ADHD group. In one of the longest prospective studies, which included a no drug comparison, 370 ADHD children from 7.0 to 9.9 years of age, enrolled in the Multimodal Treatment Study of ADHD (MTA), were contrasted according to the use and continuity of stimulant treatment [69]. Growth deficits in predicted height and weight were noted in continuously, but not inconsistently medicated patients. The deficits were maximal in the first year of stimulant use, decelerated over the second year, and were maintained after the third and final evaluated year of treatment for both height (2.0 cm less than predicted) and weight (2.7 kg less than predicted). Notably, findings from the MTA study did not support the idea that growth deficits rebound during continuous use of stimulant medication.

The only study contrasting effects of amphetamine with those of methylphenidate on growth rate used a retrospective, case-review design, and found slightly larger effects of amphetamine on reducing weight but no differences between the drugs in affecting height [67]. After 5 years of treatment in a prospective longitudinal study, reductions in expected height were noted only after several years of exposure [70]. Estimating from the sample participating, the average reduction in height for a 9-year-old treated for 4 years would amount to 1.9 cm. The study did, however, assess the relationship between drug dosage and growth. Significant effects on weight appeared to require average daily doses of methylphenidate that exceeded 1.5 mg/kg/day, and higher doses were associated with greater reductions in height velocity. Similarly, the MTA analyses [69] demonstrated a significant relationship between cumulative drug exposure and height slowing, and another report found the greatest height reductions occurring in the highest daily dosage quartile of 1.53 − 2.54 mg/kg/day of methylphenidate [68]. The consistency of these findings relating dose and exposure to growth effects provides greater evidence for the association of stimulants with reliable, albeit modest, effects on growth, and suggests the possibility that a threshold may exist for such adverse events. Lastly, the report from the NIMH Preschool ADHD Treatment Study, using normative data as a comparison over a 12-month period of exposure to methylphenidate, found that children between 3−5 years of age may be more vulnerable than older children to the growth-slowing effects of stimulants [71].

Studies of growth effects of stimulants have been hampered by several challenges: the need for monitoring periods of several years; the inability to include an untreated group due to ethical concerns; the high rate of non-compliance with treatment; lack of comparisons between different stimulants; and effects of attrition on statistical power. Furthermore, most samples studied have been limited in the age range and have demonstrated substantial variability in the effects. Some children were unaffected, while others showed strong growth suppression. Study of this interindividual variability may help identify factors that confer risk and/or protection. Overall, it appears that some young patients are at risk for neurobehavioral developmental growth suppression from medical stimulants [23], and concern is heightened for patients from

3 to 5 years of age, patients who receive high doses of stimulant medications for over a year, and patients who are medicated continuously, without drug holidays.

Amphetamine abuse: brief history

The mesolimbic dopamine system, especially the portion terminating within the nucleus accumbens in the ventral portion of the basal ganglia, is the anatomical system most highly implicated in mediating both the stimulant properties and reinforcing properties of amphetamines. Since amphetamines were first used medically, there have been reports of prescription abuse by individuals seeking weight loss, enhanced energy, sleep postponement (student "cramming", long-distance driving), improved athletic performance, or simply enhancement of recreational social activities. Regardless of the original reason for using amphetamines, regular use of these drugs has motivated some to continue their ingestion in order to self-medicate the discomforts associated with withdrawal of an addictive substance [72, 73]. Abuse of amphetamine is associated with tolerance and psychological dependence and is difficult to treat [72, 73]. Withdrawal generally produces fatigue, depression and social disability [72, 73].

Widespread abuse caused Sweden to categorize amphetamine as a "narcotic" in 1944. By 1954, there were over half a million amphetamine abusers in Japan. During the 1960s and early 70s, Japan, the United Kingdom, United States, Canada, and most other countries that regulate pharmaceuticals banned or severely restricted legal use of amphetamines. Despite this legislation, and medical recommendations to limit amphetamine use, some physicians continued to write off-label prescriptions, often with insufficient follow-up monitoring, and abuse continued to grow. In a 1971 survey, 30% of college students reported using amphetamines without a prescription [74]. Aggressive law enforcement and media campaigns succeeded in reducing illicit amphetamine use in the 1980s, but use increased again in the next decade and has continued to rise in young adults. Although there are indications that illicit amphetamine use may have peaked in a 2006 survey from the United States [75], a disturbingly large number of 8th grade students (7.3%) report taking prescription amphetamines without medical instruction.

The steep increase in the diagnosis of ADHD during the 1990's in the United States led to a parallel increase in production and societal exposure to legally distributed amphetamine. This change contributed to the surge in illicit use of pharmaceutical amphetamine, and the illegal manufacture and use of methamphetamine and methylenedioxymethamphetamine that continued to accelerate through the 1990s. Detailed discussion of these epidemics goes beyond the scope of this review, but they continue to be a substantial international public health problem, as detailed in a recent supplement of the journal "Addiction" [76].

Amphetamine abuse: sources and extent

Resale of prescribed amphetamines constitutes one source of illicit stimulants available for abuse. In addition, licit dextroamphetamine is a substrate for manufacture of illicit methamphetamine, which can then be smoked or injected. One of the easiest ways to make methamphetamine is by addition of a single methyl group to the amino group on the middle carbon atom of amphetamine. Conversely, smoked methamphetamine thermally degrades to yield amphetamine by N-demethylation [23, 77].

The proportion of students taking prescription stimulants who are approached to sell, give or barter their drugs has been reported to be 16% in rural Midwestern schools [78], 23% in a racially diverse sample of secondary school students [79], and 54% in Midwestern college undergraduates [80, 81]. Another study found that a disturbing 22% of the Canadian secondary school students who took licit amphetamines either sold or gave away their drugs [82]. Legal

amphetamines can also be diverted to illicit use without the consent of the patients. Secondary school officials responsible for dispensing medication in Iowa reported drug theft from 15% of the school medication storage areas [83]. The Los Angeles Times [84] recently reported that abuse of prescription drugs has actually supplanted illegal substances as the preferred drugs of substance abusers, citing a March 2008 statement to congress by Dr. Nora Volkow, Director of the National Institute on Drug Abuse, that "Unlike illicit drug use, which shows a continuing downward trend, prescription drug abuse . . . has seen a continual rise through the 1990s and has remained stubbornly steady . . . during recent years."

Insufficient physician follow-up care for stimulant-treated children contributes to the problem. A recent study in the Netherlands suggested that such care was deficient, with 1 of 5 patients receiving no follow-up care, and those who did receive care averaging only two physician visits per year [32]. In addition to the risk of stimulant abuse associated with ADHD treatment, clinical reports estimate the risk of addiction from amphetamines prescribed for sleep disorders at 1 −3% [37]. Additional risk accrues in patients prescribed higher amphetamine dosages for longer periods, and those with comorbid psychiatric disease [85].

Some alternative drugs have been marketed as having lower abuse potential than amphetamine. For example, in a direct comparison, methylphenidate scored below amphetamine in ratings of "Willing to Take Again", perhaps the closest subject-rated approximation of the reinforcing effects of a drug [86]. It has been suggested that methylphenidate has pharmacological properties that render it of lower abuse potential than other stimulants, especially for ADHD patients [87]. However, some authors have concluded that the abuse potential of methylphenidate is equivalent to that of amphetamine, on the basis of findings in animal models and human research [88]. The lower frequency of the abuse of methylphenidate, as compared with amphetamines, might reflect lack of availability of intravenous or inhaled forms which provide fast delivery of the drug to the brain, in order to produce the intense pleasurable sensations often described as a "rush".

On a positive note, just as oral administration produces slower dopamine release and is less reinforcing than parenteral routes, the new delayed delivery formulations release drug more slowly than immediate release formulations, and also appear to have less abuse potential. An oral once-a-day osmotic delayed-release formulation of methylphenidate produced lower subject ratings of both detectability and likeability than an immediate-release formulation that was associated with equivalent plasma concentration and dopamine transporter occupancy [89]. Lisdexamfetamine dimesylate (Vyvanse), the delayed release prodrug which is converted into d-amphetamine in the body, produced lower subjective ratings of drug-liking in adult substance abusers than dose-equivalent immediate-release d-amphetamine administered both orally and intravenously [90, 91]. These studies suggest that the abuse potential of stimulants decreases with the rate of delivery to sites of brain action. It remains possible, however, that some individuals may increase their ingestion of delayed-release formulations to titrate their enjoyment of the drug to the levels associated with immediate release formulations.

Amphetamine abuse: developmental stage influences risk

An association between childhood ADHD and increased risk for substance abuse has been described, although some argue that the relationship may reflect the common comorbid problems of oppositional defiant disorder, conduct disorder, or antisocial personality disorder, rather than ADHD *per se*. A recent review concluded that 20% of adults with substance abuse disorders have ADHD, and that ADHD both alone and in combination with co-occurring psychopathology increases risk for the development of substance abuse disorders in adulthood [92]. A case-control family study found that adolescents and young adults (ages 15 − 25) with ADHD reported more cigarette, alcohol, and illicit stimulant use than age-matched without ADHD [93]. It is notable that the motivation for ingesting these substances was reported as

"getting high" in only 22% of ADHD patients, but more often reported as self-medication for tiredness resulting from disturbed sleep (38% of ADHD patients) or self-medication of impaired mood (most ADHD patients).

Concern has been raised over the question of whether stimulant treatment of ADHD might increase the risk of later substance abuse beyond the risk from the diagnosis of ADHD alone. Some reports have supported this idea [94-97]. Most of the studies examining this issue, however, including a meta-analysis, found that stimulant treatment had no effect on the risk for subsequent substance abuse or lowered the risk by as much as 50%, although this protection did not extend to nicotine dependence [92, 98].

A survey of over 9,000 Midwestern college students found that those who initiated prescribed use of stimulant medication for ADHD in secondary school were three times as likely as students never prescribed stimulant medication to report illicit use of prescription stimulants, and that those who initiated such medication in college were seven times as likely to report illicit use [80]. Both groups also reported more use of alcohol, marijuana, cocaine, and all illicit drugs than students never prescribed stimulant medication. Although these results can be explained by an increased risk for substance abuse associated with ADHD, college students who initiated prescribed use of stimulants for ADHD in elementary school did not report more illicit use of prescription stimulants, or more use of any other abused substances, as compared to students never prescribed stimulant medication [80]. This finding supports the idea that stimulant treatment for ADHD can protect against the illicit drug use otherwise associated with an ADHD diagnosis, but suggests that such protection is maximal when stimulant treatment is initiated prior to secondary school. The notion that early stimulant treatment might lower the risk for subsequent stimulant abuse is supported by some [99-101] though not all [102] preclinical studies of administration of low doses of methylphenidate during the equivalent of human adolescence. In supportive studies, methylphenidate decreased subsequent measures that have been linked to drug abuse liability.

Unfortunately, preclinical and clinical data suggesting that early stimulant treatment for ADHD reduces risk for later substance abuse does not eliminate the possibility that prescription stimulants initiated during later developmental periods of high risk, might act as "gateway" drugs and thus increase risk of substance abuse. Given the frequency of substance abuse in high school and college-age samples, the number of students who seek and receive stimulant treatment for ADHD primarily for purposes unrelated to their ADHD symptoms (i.e., weight loss, "cramming", improved athletic or social performance, etc.) is likely to increase during late adolescence and early adulthood. Higher rates of substance use in students initiating licit medical stimulant treatment during these years, and a recent finding of positive correlation between age at initiation of stimulant medication and later substance abuse [103] underscore the need for especially careful monitoring of late initiated stimulant medication.

The idea that risks as well as benefits of stimulant exposure depend on developmental timing is also supported by preclinical studies. The adolescent brain has been described as being in flux [104], undergoing numerous regressive (e.g., pruning of neocortical synapses [105], decreases in receptors of different neurotransmitter systems [106, 107]) and progressive changes [108, 109]. Preclinical investigations suggest there are notable ontogenic alterations during the adolescent transition from childhood to adulthood, including substantial reorganization of mesocorticolimbic dopaminergic neural circuits [110-115]. It has been proposed [104] that these dopaminergic alterations may represent a shift in the relative balance between subcortical and cortical dopamine systems, especially during early adolescence, towards a predominance of cortical dopamine and enhanced dopaminergic tone in the prefrontal cortex. Studies on the ontogeny of drug sensitivity have shown that adolescent rodents are less sensitive than younger animals and adults to the locomotor and stereotypy-inducing effects of amphetamine

116-124. Furthermore, most evidence indicates that methamphetamine treatment of pre-weanling rats produces fewer and/or less marked neurotoxic effects than the results from adult preclinical and clinical studies 125-129.

On the basis of these observations, it has been widely concluded that monoamine systems may be less vulnerable to the neurotoxic effects of methamphetamine in very young as compared to older rats. A few animal studies have specifically examined the effects of methamphetamine exposure during the equivalent of human adolescence. Rats at postnatal day (PND) 35−55 are alleged to be developmentally comparable to humans of about 12−18 years 130. Some of the evidence derived from these studies in rats suggests a transition in susceptibility to methamphetamine-induced neurotoxicity occurring around PND-40 128. Rats treated with methamphetamine at PND-90, but not PND-40, exhibited deficits in striatal dopamine parameters seven days after treatment 131. One hour after treatment, plasma and striatal levels of methamphetamine in the PND-90 group were approximately double the levels in the PND-40 group, suggesting that pharmacokinetic factors represent a potential confound in interpretation of the effects of age.

In another study, methamphetamine pretreatment through much of adolescence and early adulthood; i.e., six biweekly injections of 15 mg/kg, beginning at PND-40, blocked the neurotoxic effects produced by a methamphetamine binge (10 mg/kg × 4, at 2-hr intervals) at PND-90 132. This neuroprotective effect could not be attributed to pharmacokinetic factors, but as commonly observed for stimulant-induced behavioral and neurochemical alterations, the pattern of drug exposure was critical. Neither PND-40 pretreatment with a single methamphetamine binge (10 mg/kg × 4, at 2-hr intervals), nor single weekly injections, produced the neuroprotective effects of the biweekly injections. Clearly, valid extrapolations to human drug users from rodent models rest on the translational utility of the stimulant treatment paradigm that is employed.

Two recent prospective studies have evaluated the relationship of stimulant treatment for ADHD to later substance abuse in humans. In 112 6−17 year old male Caucasians with ADHD, stimulant treatment neither increased nor decreased the frequency of substance use disorders ten years later (mean age = 22) as compared to the ADHD patients not treated with stimulants 133. Among those with alcohol abuse, however, stimulant treatment was associated with a longer duration of abuse by 1.6 years ($p = 0.04$).

The 2nd study assessed 176 methylphenidate-treated 6−12 year old male Caucasians with ADHD (but without conduct disorder), and 178 non-ADHD control subjects, with reassessment during late adolescence (mean age = 18.4) and early adulthood (mean age = 25.3) 103. There was a direct relationship between age at initiation of stimulant treatment and the frequency of both substance use disorder and antisocial personality disorder. Lifetime rates of substance abuse disorder were greater among ADHD patients who initiated treatment after age 7 (44%), as compared to patients who initiated treatment before age 8 (27%), or non-ADHD patients (29%). The authors conclude that early initiation of methylphenidate treatment does not increase risk for negative outcomes and may have protective long-term effects. Because 98% of the sample initiated stimulant treatment by age 11, however, this study can not address the possibility that the increasingly common practice of initiating stimulant medication during the high-risk years of secondary school or college may increase risk for substance abuse. We are unaware of any studies that specifically address this important question.

In summation, abuse of both licit and illicit amphetamines constitutes a serious public health concern. Illicit amphetamines are second only to marijuana as a form of illicit drug abuse in young adults, with a prevalence of 8.1% among 12th grade students 75. Illicit use of prescription medications is currently at its highest level in decades, and amphetamines are the prescription

drugs most commonly abused by adolescents and young adults. Licit amphetamines contribute to amphetamine abuse through multiple mechanisms, including their distribution to individuals who were not given medical prescriptions through sale or theft, and their use as substrates for synthesis of more dangerous drugs. Although stimulant medication for ADHD reduces the frequency of later substance abuse when it begins during early childhood, the effect of initiating stimulant medication in late adolescence or adulthood is currently unknown, and there are indications that there may be neurobehavioral risks associated with this practice.

Brain damage from abuse

Most of the evidence for amphetamine-induced human brain damage comes from examination of current and former amphetamine abusers. Because of the paucity of studies of brain integrity after use of prescription amphetamines, speculation regarding the potential for damage due to prescription amphetamines draws primarily from the consequences of the abuse of these drugs. Almost all reports of brain abnormalities in stimulant abusers have employed retrospective self-reports of abuse history. Highly variable patterns of abuse have been reported across studies of methamphetamine abusers, with minimal durations of abuse ranging from 1 to 7 years, average lifetime use ranging from 276 g to 4930 g, and the duration of abstinence from methamphetamine at time of testing ranging from 0 to 730 days [134]. Estimates of typical human methamphetamine doses in moderate-high abusers range from 15 − 100 mg, corresponding to about 0.25 − 1.5 mg/kg per administration, and 3 − 8 hits/day [135-140]. Drug use reported in some brain imaging studies has been at the higher end of these ranges (e.g., mean daily use of 1.6 g/day [141]. Perhaps of more direct relevance, blood samples obtained from individuals detained by police for possible criminal activity and testing positive for methamphetamine revealed concentrations in the low micromolar range, with a mean value of 2 μM (300 ng/l) [142]. This is several-fold higher than typical therapeutic levels of 25 − 50 ng/ml.

Chronic users of methamphetamine have multiple abnormalities in brain chemistry, function, and structure, particularly in the striatum of the basal ganglia, the brain region with the highest dopamine concentrations. Evidence consistent with the notion that the neurotoxicity demonstrated in animals (discussed earlier) also occurs in humans taking methamphetamine has accrued from neuroimaging findings of reduced availability of transporters for dopamine, serotonin, and vesicular monoamines [143]. Autopsy data, which have demonstrated deficits in dopamine, the dopamine transporter, and tyrosine hydroxylase, can be interpreted as consistent with dopaminergic damage, but little if any deficit in the vesicular monoamine transporter ($VMAT_2$) [43, 144, 145] . In contrast, administration of high stimulant doses to rodents or nonhuman primates promotes a profound decrement in $VMAT_2$ as well as in the other markers for dopaminergic nerve terminals [146-149]. Notably, a decrease in $VMAT_2$ has been considered by some to indicate a decline in intact monoamine nerve terminals [146, 150-152]. In view of these findings, some investigators have suggested that decrements in the dopamine transporter without parallel decrements in $VMAT_2$ may represent neuroadaptational downregulation in dopamine transmission rather than degeneration of dopamine terminals [145].

Proton MR spectroscopy measures of metabolites in the cerebral cortex and basal ganglia have consistently identified reduced markers of neuronal integrity, and increased markers of glial content, suggesting that glial proliferation may follow neural damage [143]. Using cerebral glucose metabolism as an index of functional neural activity, study of methamphetamine abusers during early abstinence from the drug revealed abnormally high activity in amygdala, ventral striatum and lateral orbitofrontal cortex but abnormally low activity in medial prefrontal, and particularly cingulate cortex [153]. With continued abstinence from the drug, there is abnormally high global and cortical glucose metabolism, particularly in the parietal lobe [154, 155], and relatively lower activity, after scaling to global mean activity, in striatal and thalamic regions [155, 156]. Finally, structural magnetic resonance imaging (MRI) studies have

noted abnormalities including apparent reduction of gray matter volume in cingulate cortex and the hippocampus during early abstinence from methamphetamine [157], and later enlargement of the parietal lobe and of portions of the basal ganglia [158, 159]. Size deficits have generally been interpreted as representing cell loss and enlarged areas thought to result from inflammation and possible reactive gliosis, although it has been suggested that volume increases in striatal volume may be compensatory [134, 158].

The dopamine transporter and spectroscopic abnormalities have been positively related to total methamphetamine use, residual psychiatric symptoms [160-166], and motor or memory deficits [167]. Increased parietal glucose metabolism was associated with cognitive deficits [154, 155], and abnormalities in relative glucose metabolism were associated with impaired mood [153] and impaired vigilance [168]. While the enlargement in parietal volume and the deficit in hippocampal volume were also associated with cognitive deficits in the above-cited studies, one report of basal ganglia volume being greater than in a comparison group found the volumetric measure to be positively correlated with verbal fluency and fine motor performance, but negatively associated with duration of methamphetamine use [158]. Striatal enlargement may thus constitute an initially adaptive response to methamphetamine toxicity that fails to maintain either function or structural integrity after prolonged abuse.

More research is needed to characterize the “dose-response” relationship between exposure and brain abnormalities, and the extent and time-course of recovery and normalization of these abnormalities during abstinence from chronic methamphetamine. Postmortem studies of animals and humans suggest that the primary dopaminergic damage involves terminals and processes rather than cell bodies. Some degree of recovery after protracted abstinence has been noted in perfusion of the cingulate cortex [169] and in striatal dopamine transporters [170]. These studies compared subjects tested once during broad periods of early abstinence (< 6 months) with other subjects tested during even broader ranges of prolonged abstinence.

Two additional studies repeated assessments of cerebral glucose metabolism in the same individuals during abstinence from chronic methamphetamine. Wang and associates [156] compared five subjects tested at < 6 months abstinence and again between 12 and 17 months. They noted recovery in thalamic but not striatal deficits in relative glucose metabolism. We recently compared 12 healthy control subjects to 10 methamphetamine abusers who were abstinent only 5−9 days, and then reassessed both groups a month later [154]. Glucose metabolism did not change over the month in subcortical regions of either group or in the cortex of healthy subjects, but increased in the neocortex of the abstinent methamphetamine users, with a maximal increase exceeding 20% in the parietal lobes. Changes in both absolute parietal and relative striatal glucose metabolism were correlated with changes in vigilance performance and depressive symptoms in methamphetamine users but not control subjects. Increased cortical activity was interpreted as reflecting either compensatory processes during early abstinence, unmasking of damage from chronic methamphetamine abuse that is obscured by suppression of cortical glucose metabolism for at least 5 days after cessation of drug use, or new damage after the initial week of abstinence.

The provocative possibility of additional damage during early abstinence from amphetamine is consistent with observations of a methamphetamine abstinence syndrome where symptoms are maximal only after several days of abstinence [171, 172], and a study where a treatment of three daily exposures of rats to methamphetamine was sufficient to induce reactive gliosis that continued for over two weeks after the final exposure [173]. In addition, the P300 event-related potential recorded from the human scalp is modulated by catecholaminergic neurotransmission [174, 175], and it exhibits reduced amplitude during early abstinence from chronic methamphetamine abuse. A rat model reported 15 days of methamphetamine reduced P300

after 7−10 days of abstinence, indicating that the deficit was not an acute effect of methamphetamine [176].

Brain damage from licit amphetamines

It is not known if there are similar alterations in the dopaminergic system of humans receiving long courses of prescription amphetamines [23]. However, in the most relevant animal model, 4 weeks of treatment with an amphetamine similar to the pharmaceutical Adderal produced plasma concentrations in adult baboons and squirrel monkeys that matched human ADHD patients after clinical treatment, and both species showed a 30−50% reduction in striatal dopamine, its major metabolite, its rate-limiting enzyme, its membrane transporter, and its vesicular transporter [53]. Although Parkinsonian symptoms generally require about twice as much dopamine reduction (80−90%), aging itself produces cumulative decrements in dopaminergic cells, dopamine metabolites and dopamine receptor binding [38]. These changes have been associated with modest cognitive and motor losses [177], and age-linked reductions in frontal cortex metabolism [178] similar to those characteristic of cocaine abusers [179]. Therefore, it would be of interest to explore whether there are any indications of delayed adverse motor or cognitive outcomes associated with very prolonged and high-dose stimulant exposure in older adults taking maintenance amphetamines, similar to what has been shown for aging boxers who accrued dopamine loss as a consequence of repeated closed head concussive trauma in their youth [180]. The finding that dopamine levels in autopsied chronic methamphetamine users were reduced more in the caudate (mean = −61%, but maximum reduction = −97%) than in the putamen (mean = −50%), whereas Parkinson's disease shows the opposite pattern, led to the suggestion that chronic amphetamine use may increase risk for cognitive deficits more than for motor deficits [144]. One way to explore the hypothesis of accelerated aging would be to compare functional and structural neuroimaging indices of cerebral integrity during normal aging, which have undergone extensive development in recent years [181], to patients receiving maintenance treatment with amphetamines.

In contrast to concerns about potential adverse effects of amphetamine on the brain during aging, it is remarkable that the reduction of the heightened risk for substance abuse that is otherwise associated with ADHD by the initiation of stimulant treatment during childhood appears to be accompanied by a congruent reduction in structural brain pathology. Unmedicated children with ADHD had smaller brain white matter volume than medicated children with ADHD (−8.9%, P<.001) or children without ADHD (−10.7%, P<.001), suggesting that early stimulant treatment may normalize brain white matter volume in ADHD [182].

Stimulant medication for childhood ADHD, however, has been associated with adverse as well as with beneficial effects. The longest controlled clinical trial of stimulant medication effects followed 579 children age 7− 9.9 years during 14 months of randomized ADHD treatment [183]. Stimulant treatment was superior to behavioral treatment or routine community care. However, undesirable side-effects were reported by 64% of participants, and moderate to severe side-effects by 14%. Only 10% of participants were treated with amphetamine (most children used methylphenidate), and side-effects were not cross-tabulated by the medication received, so it is unclear if amphetamine produced a disproportionate fraction of the unwanted effects, as previously reported when comparing 2-weeks of amphetamine with methylphenidate treatment in 125 ADHD children [25]. In addition, only standard clinical measures were employed, so the association of adverse effects with neurotoxicity could not be assessed. In animals, doses of amphetamine with behavioral effects equivalent to those of methylphenidate produce the same synaptic accumulation of dopamine as methylphenidate but 4 to 10 times the extracellular accumulation of dopamine [184, 185], suggesting the potential for long-term toxicity involving the dopaminergic system if high extracellular concentrations

of dopamine contribute to neurotoxicity. To our knowledge, no controlled studies have explored adverse behavioral, cognitive or neurobiological consequences of years, much less decades, of chronic amphetamine treatment.

Evidence has been reported for sensitization of behavioral effects in healthy adults after three identical administrations of .25 mg/kg of d-amphetamine 48 hours apart [186]. Although this dose is in the clinical range, and less than 1/3 the daily dose prescribed for some adults, vigor and euphoria ratings were maximal after the final dose, especially in women, consistent with evidence from animal studies, suggesting stronger sensitization in females [187]. More efforts are needed to determine under what circumstances sensitization occurs in humans, and to quantify the mediating effects of age and gender. Further questions relevant to clinical treatment and longer-term exposure include the following: Is sensitization maintained or associated with differences in clinical dosages or regimens, extended durations, compliance with treatment, or patterns of abuse? It is important to note, however, that there is no clear evidence for sensitization in stimulant treatment of ADHD. Furthermore, although moderate and high doses of stimulants robustly produce long lasting sensitization in experimental animals [188], preclinical studies that have utilized stimulant doses in the therapeutic range failed to produce evidence for sensitization (see 189 for review). In sum, assessment of long-term effects of prescription amphetamine administration is important for many reasons, including the recent increase in the dosages and durations of pharmaceutical amphetamine treatment for adult ADHD [34], and occasional reports of what might be amphetamine-mediated psychosis in users of prescription amphetamines.

Amphetamine psychosis

High doses of amphetamines can produce psychotic behavior indistinguishable from schizophrenia in asymptomatic schizophrenics and in some healthy human subjects [190, 191]. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) recognizes diagnoses of amphetamine-induced psychotic disorder with delusions and amphetamine-induced psychotic disorder with hallucinations. In one study of healthy volunteers, repeated administration of 5−10 mg of oral dextroamphetamine produced paranoid delusions in all subjects at cumulative dosages between 55 and 75 mg [192]. The current illicit amphetamine epidemic is increasing the incidence of this problem. Australian methamphetamine users had 11 times the prevalence of psychosis found in the general population, and methamphetamine dependence further tripled the risk for psychosis, even after adjusting for prior history of psychotic disorders [193]. A European study documented recent increases in hospital admissions for amphetamine-induced paranoid psychosis [194].

After the first occurrence, paranoid symptoms can be invoked by psychosocial stress, but also readily reappear after amphetamine injection. This behavioral sensitization is thought to be mediated by catecholaminergic supersensitivity. It has been argued that the behavioral sensitization produced by repeated administration of lower doses of amphetamine to non-human animals is a better model of amphetamine psychosis than the neurotoxicity produced by higher doses, and that this sensitization is at least partially mediated by enhanced mesotelencephalic dopamine release upon re-exposure to the drug [188]. In humans, spontaneous occurrence of amphetamine-induced hallucinatory psychosis (i.e., flashbacks) are accompanied by concurrent increases in plasma norepinephrine and 3-methoxytyramine, a major metabolite of released dopamine in frontal cortex [195, 196] Several genetic studies also implicate dopamine in amphetamine-mediated psychosis, including an association of nine or fewer repeat alleles of the dopamine transporter gene hDAT1 with increased severity of amphetamine-mediated psychosis [197] and a report that the Taq1A A1/A1 polymorphism, which codes for reduced density of dopamine D2 receptors, also reduces the risk for development of flashbacks [198].

Amphetamine prescription labels state that psychotic episodes are rare at recommended doses, but that behavioral disturbance and thought disorder may be exacerbated in presence of pre-existing psychoses. A recent review of 54 scientific studies concluded that a single stimulant dose can produce a psychotic response in 50−70% of patients with schizophrenia and pre-existing acute psychotic symptoms and 30% of schizophrenics without acute symptoms [191]. The authors present evidence, however, that low-dose antipsychotic treatment may reduce or prevent sensitization in chronic stimulant users. As a side note, amphetamine abuse has occasionally been clinically linked to choreoathetoid-type involuntary movement disorders, and neuroleptics are thought to effectively treat these disorders by normalizing an excessive ratio of dopamine to acetylcholine in the corpus striatum [199] (but for another possible mechanism see [134]).

About 30−40 % of amphetamines are excreted unchanged. The rest of the parent drug is converted to metabolites. The proportions of amphetamines that are metabolized are strongly affected by urinary pH [23]. Ingestion of acidic substances causes an accelerated excretion of *d*-amphetamine while alkaline agents (e,g., antacids) markedly increase both retention and absorption of amphetamines, sometimes resulting in dangerously high amphetamine levels. It has been suggested that the accumulation of metabolites may contribute to generation of psychotic symptoms [200] and to general amphetamine neurotoxicity [201].

Clinical case reports of the induction of psychotic states by prescription stimulants have appeared occasionally [202-206]. For example, one paper concluded that 10 mg of daily Adderal taken over five weeks for ADHD induced classic psychotic symptoms in a formerly drug-naive adolescent with no personal or family history of psychiatric disorders other than ADHD. Symptoms abated after 7 days (5 half lives) without drug. Recently, the FDA attempted to better appreciate the frequency of any psychotic or manic-like reactions to stimulants in individuals with ADHD receiving psychostimulants. Pooling data from both placebo-controlled trials (5,717 subjects) and open-label studies (15,999 subjects), an average rate of 0.25% or 1 out of 400 subjects was observed [207]. Although the rate was uncommon to rare, the appearance of such adverse events certainly highlights the need to explore predictors of such worrisome effects, such as the dopaminergic genetic risk and protective factors discussed above [197, 198].

In treatment of narcolepsy, use of amphetamine doses greater than 120% the maximum level recommended by the American Academy of Sleep Medicine have been associated with psychosis, psychiatric hospitalizations, substance abuse, and suicide [208]. Although one paper reported that two of eleven adults taking high doses of methylphenidate for narcolepsy developed acute psychotic symptoms [209], we are not aware of any comparable study quantifying such symptoms as a consequence of amphetamine treatment for narcolepsy.

Heritability

Although the mechanisms whereby amphetamines produce adverse effects in humans are largely unknown, it is clear that in contrast to low heritability estimates for abuse of depressant drugs, stimulant abuse is much more heritable. It seems likely that adverse developmental effects and neurotoxicity are also genetically mediated. Amphetamines had the highest heritability of any category of DSM-III drug abuse in twin samples serving in Vietnam [210], and in Minnesota drug abuse treatment programs [211]. In the latter, genetic influences accounted for 78% of variance in amphetamine abuse/dependence in men and 73% in women. Studies of specific genes have focused on regulators of synaptic dopamine activity, the primary mechanism of biological action of the amphetamines. As noted above, a polymorphism associated with reduced density of dopamine D2 receptors also reduced the frequency of flashbacks [198], and presence of a 9- or fewer repeat allele of the dopamine transporter gene was associated with prolonged amphetamine psychosis [197]. The latter paper postulated that

reduced inactivation of dopamine due to lower density of dopamine transporters increased susceptibility to amphetamine neurotoxicity. A study of the gene for catechol-O-methyl transferase reported that the allele which carries lower activity for inactivating dopamine (*met*), was associated with both methamphetamine-triggered psychosis and with spontaneous symptom relapse not triggered by drug use [212]. A third Japanese study identified similar associations for the PICK1 gene, which codes for a protein associated both with schizophrenia and with the dopamine transporter [213]. Although studies of drug abusers involve higher than clinical exposures to amphetamines, the psychotic episodes occasionally reported after licit use of amphetamines may also have been promoted by genetic factors, particularly those that increase synaptic dopamine.

Recommendations

More than 100 studies involving tens of thousands of subjects have demonstrated that stimulants are efficacious and well-tolerated by most patients when taken for up to several years. We know much less than we should, however, about the biological and cognitive effects of more protracted courses of therapeutic stimulants on adult human brains and adult behavior [214]. In cell lines transfected with human catecholamine transporters, amphetamine tripled the expression of the early intermediate gene c-*fos*, which is thought to play an important role in neural plasticity [215]. A growing body of literature suggests that the consequences of modifying neural plasticity with amphetamine vary greatly with both individual and developmental factors. The increased use of amphetamine stimulants as life-long maintenance medications combines with the longer elimination half-life in adulthood to underscore the importance of quantifying the safety and adverse effects associated with such practices. Dose-relevant preclinical investigations of the effects of protracted exposure, particularly in nonhuman primates, and longitudinal studies of markers for brain aging in the adults who have the longest exposure to medical amphetamines, are important initial steps.

Beyond the characterization of generally safe treatment protocols, it is important to identify protective factors. As noted above, a genotype that codes for lower density of dopamine D2 receptors (compared to a parallel functional polymorphism), protects against amphetamine-induced psychosis [198]. Treatment with either lithium or valproate reportedly protect against dextroamphetamine-induced alterations of brain choline concentration in patients with bipolar disorder [216]. Recent studies in animals have produced evidence for neuroprotection against amphetamine-mediated toxicity by several substances, including nomifensine [217], methyllycaconitine [218], coenzyme Q10 [219], baicalein [220] and melatonin [221]. In addition, impairment of learned place preference consolidation by amphetamine-induced neurotoxicity was ameliorated by administration of a glutathione precursor [222].

For clinical safety, it is perhaps even more essential to identify individual risk factors for adverse effects of amphetamines. Cognitive, genetic, and other biological markers associated with risk for adverse events from stimulant exposure should be explored. For example, individuals who are homozygous for the 9- repeat allele of the dopamine transporter protein gene, SLC6A, experience virtually no subjective euphoria or anxiety in response to amphetamines [223]. It is unclear, however, from a clinical perspective, whether possession of this genotype should contraindicate medical use of amphetamines, suggest augmenting dosing regimens, suggest combining amphetamine with other treatments or some other modification of treatment. How can we better understand the implications of such relationships for brain function and clinical practice?

As human genetics and *in vivo* neuroimaging techniques are becoming more accessible than before, combining the accumulating knowledge in these two domains may be extremely useful. Positron emission tomography (PET) ligands, which are well-developed for the dopamine

transporter [214], and magnetic resonance spectroscopy mapping of metabolites, will be useful in assessing human catecholamine adaptation during amphetamine treatment. Potential changes in dynamic connectivity can be explored with functional magnetic resonance imaging (fMRI), which has better temporal and spatial resolution than PET for the study of brain response. Functional brain response results will be informed by studies of anatomical connectivity employing diffusion tensor imaging (DTI), a form of MRI sensitive to water flow in axons [224]. Additional structural effects of amphetamine use can be investigated with other new MRI techniques which sensitively quantify changes in brain morphometry over time, including voxel-based, tensor-based, and cortical thickness mapping [225, 226]. Collecting multimodal imaging datasets and analyzing them using multiple complimentary techniques is becoming increasingly feasible. A single MRI session can incorporate sequences that assess several tissue parameters (volumes of gray and white matter, T1, T2, DTI, iron measures, etc) and also collect functional brain responses with fMRI. One ongoing study assesses drug-naïve young adults who report they will soon start using the amphetamine drug methylenedioxymethamphetamine (“ecstasy”) with proton magnetic resonance spectroscopy, perfusion-weighted imaging, DTI, and psychological questionnaires, and will continue periodic reassessments to determine the relationship of drug use to longitudinal change in these measures [227]. Longitudinal exploration of such multimodal datasets will increase understanding of both the techniques employed, and the underlying safety limits and pathophysiology associated with adverse consequences of amphetamine use.

In sum, clinicians should carefully monitor patients receiving long-term therapeutic administration of stimulant medications for signs of adverse effects on development, substance abuse, central toxicity or psychological problems. Research agencies should study effects of protracted exposure in nonhuman primates, and sponsor longitudinal studies of indices of healthy aging in adults exposed to protracted courses of medical amphetamines. As results of these studies are revealed, the relationships of *a priori* genetic factors and *a posteriori* multimodal brain responses to behavioral and neurobiological consequences of protracted amphetamine treatment must be rapidly transmitted to clinicians in order to facilitate safer use of amphetamines.

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