DEVELOPMENT OF A REFERENCE DOSE (RfD) FOR METHAMPHETAMINE

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Integrated Risk Assessment Branch
Office of Environmental Health Hazard Assessment
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Introduction

The clandestine synthesis of methamphetamine is a growing public health and environmental concern. It is estimated that for every pound of methamphetamine synthesized there are six or more pounds of hazardous materials or chemicals produced. These are often left on the premises, dumped down local septic systems or illegally dumped in backyards, open spaces, in ditches along roadways or down municipal sewer systems. In addition to concerns over the health and well being of peace officers and public health officials, there is increasing concern about potential health impacts on the public and unknowing inhabitants, including children and the elderly, who subsequently occupy dwellings where illegal drug labs have been located.

Under the provisions of Senate Bill 536 (Bowen, Chapter 587, Statutes of 2005), the Office of Environmental Health Hazard Assessment (OEHHA) is required to develop guidance for risk-based target remediation standards for methamphetamine, methyl iodide, phenyl-2-propanone and phosphine to ensure protection of the health of all persons who subsequently occupy a former clandestine methamphetamine lab. The Department of Toxic Substances Control (DTSC) will use this guidance to develop the standards. Senate Bill 536 requires that guidance be developed first for methamphetamine.

Strategy for Developing a Risk-Based Remediation Standard for Methamphetamine

To develop a risk-based remediation standard, the toxicity of a chemical – its adverse health effects and the doses that are required to elicit them – must be well characterized. In addition, the pathways of exposure to the chemical must be identified, algorithms to quantitatively estimate the magnitude of exposure via each pathway must be developed, and appropriate parameters for each of the exposure algorithms must be researched and justified.

This report describes the toxicity of methamphetamine and provides justification for a sub-chronic *reference dose (RfD)* for the drug.[1] RfDs are concentrations or doses at or below which adverse health effects are not likely to occur. A central assumption is that a population threshold exists below which adverse effects will not occur in a population; however, such a threshold is not observable and can only be estimated. Areas of uncertainty in estimating effects among a diverse human population are addressed using

[1] The model that was adopted to estimate the magnitude of exposure to methamphetamine in a former clandestine lab is described in a separate document.

extrapolation and uncertainty factors. Therefore, an RfD for methamphetamine is an estimate of its toxicity threshold in humans.

To develop an RfD for methamphetamine, the critical effect(s) of the drug must be identified. According to the United States Environmental Protection Agency (U.S. EPA), *critical effect* is the first adverse effect, or its known precursor, that occurs to the most sensitive species as the dose rate of an agent increases. Therefore, if an exposure standard (i.e., a cleanup level) for a chemical is set low enough to prevent the occurrence of its critical effect, then the standard will prevent the occurrence of any other toxic effect as well.

For methamphetamine, we have taken a health-protective position that *any* effect induced by the drug is an adverse effect and, potentially, a critical effect. Characteristic signs and symptoms of methamphetamine toxicity in humans include general sympathomimetic effects such as stimulation of the central nervous system (CNS), dyspnea (shortness of breath or labored breathing), mydriasis (dilation of the pupils), hyperpyrexia (exceptionally high fever), diaphoresis (profuse perspiration) and anorexia (loss of appetite), and cardiovascular effects such as tachycardia (rapid heart rate), palpitations (irregular and/or forceful heart beats), and hypertension. Higher doses and/or repeated exposure can lead to cardiomyopathy, myocardial infarction, rhabdomyolysis (destruction of skeletal muscle cells), intracerebral bleeding and stroke, seizure and coma. In a report of 18 cases of methamphetamine poisoning in pediatric patients (Kolecki, 1998), the most common presenting symptom was agitation, and the most common presenting signs were tachycardia, inconsolable irritability and crying, and protracted vomiting. Less commonly observed were hyperthermia, ataxia (loss of muscle coordination), nystagmus (roving eye movements), and seizure. Based on this brief summary of adverse effects, candidates for the critical effect of methamphetamine include CNS stimulation, mydriasis, anorexia, tachycardia and hypertension. More severe effects such as seizure and myocardial infarction would be expected to occur at higher doses and therefore would not be regarded as critical effects.

Scope of the Literature Review: Emphasis on Research in Human Subjects

Approximately 160 published research reports were critically reviewed to characterize the toxicity of methamphetamine. In general, the literature review was limited to studies of the effects of methamphetamine in humans. Human studies were preferred for the following reasons:

- Since the late 1930s, more than 100 peer-reviewed reports characterizing the effects of methamphetamine in humans under controlled conditions have been published.
- Toxic effects have been described following multiple routes of exposure, including intravenous injection, subcutaneous injection, intramuscular injection, ingestion, and inhalation.
- Several studies have been conducted characterizing adverse effects in potentially sensitive sub-populations, including children, pregnant women and the elderly.

- Studies have been conducted characterizing adverse effects in normal, drug-naïve individuals; persons with limited "recreational" experience with methamphetamine, persons with pre-existing health problems (e.g., narcolepsy), and persons with pre-existing psychiatric illness (e.g., depression).
- Multiple doses of methamphetamine have been evaluated.
- Studies characterizing the effects of acute, sub-acute and sub-chronic daily exposure to methamphetamine have been conducted. Exposure durations as long as 20 weeks have been evaluated.
- Several studies have been conducted under placebo-controlled, double blind conditions.
- Studies examining the effects of sustained-release formulations of methamphetamine have been conducted. This mode of dosing more closely mimics the long-term, low level exposure that is anticipated to occur in humans residing in a former clandestine methamphetamine lab.

Conversely, there were several reasons why an intensive review of the animal toxicity literature was not conducted. Foremost among these is the large species-dependent disparity in sensitivity to the drug, with laboratory animals (particularly rats and mice) generally being much less sensitive to methamphetamine than humans. For example, in characterizing the cognitive effects of postnatal exposure to methamphetamine in mice, Acevedo et al. (2007) utilized a daily dose of 5 mg/kg. In an adult human, this would be equivalent to a total dose of 300-350 mg, which would be potentially life-threatening. In addition, the pharmacokinetics of methamphetamine in laboratory animals and humans differ substantially. As Cho et al. (2003) point out, the elimination half life of methamphetamine is 70 minutes in rats; in humans, the half-life is 12 hours.

Given the wealth of studies examining the effects of methamphetamine in humans and the uncertain relevance of data derived from laboratory animal studies, the literature review presented in this report focuses almost exclusively on human toxicity data.

Primary Support Studies Cited to Identify Methamphetamine's Critical Effects

The primary study used for development of an RfD for methamphetamine was a sub-chronic study of the drug's efficacy in reducing weight gain during pregnancy (Chapman, 1961). The study involved a total of 84 women who were administered a sustained-release formulation of d-methamphetamine (Desoxyn® Gradumet®). Three doses of methamphetamine were tested, and the study was conducted under placebo-controlled, double blind conditions. The duration of treatment was 15-16 weeks. Sub-chronic dosing with methamphetamine produced a dose-related decrease in weight gain over the course of pregnancy. This effect was highly statistically significant. Based on the results of this study, the critical effects of methamphetamine were identified as appetite suppression and consequent reduction in body weight gain, and the lowest observed adverse effect level (LOAEL) for methamphetamine was 0.08 mg/kg-day. The results of the Chapman study were corroborated in a smaller but similar study conducted by Bayly

(1960). A detailed summary of the Chapman study and statistical analysis of the data are provided in the next section of this report.

A large study of the efficacy of methamphetamine as an aid in the treatment of enuresis (bed wetting) in children (Young and Turner, 1965; summarized on pages 51-53) was also evaluated as a potential basis for development of the RfD. This study involved 299 children 4-15 years of age.[2] Most of the children in one treatment group of 110 children were given 5 mg of Methedrine (d-methamphetamine) each day just before bedtime. There were 105 children in the control (non-drug) group. Sleep disturbance was experienced in eight of the 110 children who received Methedrine. This effect disappeared when the dose of the drug was reduced to 2.5 mg. These results confirm the frequently reported observation that a critical effect of methamphetamine is disturbance of sleep. They suggest that the LOAEL for methamphetamine in children was 5 mg (0.2 mg/kg-day), and that the no observed adverse effect level (NOAEL) was 2.5 mg (0.1 mg/kg-day). However, the conclusion that 0.1 mg/kg-day represents a childhood NOEAL must be tempered by the fact that it is based on observations from just eight children.

The LOAELs reported by Chapman (1961) and Young and Turner (1965) were 0.08 mg/kg-day and 0.2 mg/kg-day, respectively, suggesting that adults may be more sensitive to methamphetamine than children.[3] The fact that the critical effects were weight loss in the adult study and sleep disturbance in the childhood study may account in part for this disparity.[4] Another significant difference between the two studies was the drug formulation: a slow release formulation which produces more constant blood levels over a longer duration was used in the adult study but not in the childhood study.

Young and Turner also identified a NOAEL, 0.1 mg/kg-day. The lack of an experimentally identified NOAEL in the Chapman study has a significant impact on the derivation of the RfD for methamphetamine. For the purpose of estimating an RfD, an experimentally identified NOAEL is generally incorporated into the calculation without an additional uncertainty factor. In contrast, if a LOAEL is used as a basis for the RfD, it is usually divided by a 10-fold uncertainty factor to estimate a NOAEL. Therefore, a NOAEL estimated from the data of Chapman (1961) is 0.008 mg/kg. Comparing the *experimentally determined* NOAEL from the Young and Turner study (0.1 mg/kg-day) with the *estimated* NOAEL from the Chapman study (0.008 mg/kg-day), it is clear that the choice of Chapman (1961) as the primary basis for development of a methamphetamine RfD effectively adds an additional 12.5-fold safety factor to the RfD.

The decision to adopt the results of Chapman (1961) as a basis for derivation of the RfD for methamphetamine was based on the following considerations:

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[2] The average age of the children who received Methedrine was 7.1 years. For the purpose of calculating doses on a mg/kg body weight basis, the average body weight of a 7 year-old child is 25.1 kg (U.S. EPA, 1997).

[3] In assessing the relative sensitivities of adults and children with ADHD to stimulants, Dulcan (1997) suggested that adults are indeed more sensitive to both the therapeutic and side effects of these drugs.

[4] It should be noted that Chapman (1961) also identified women who experienced insomnia, and no significant differences across treatment groups were observed. [See Table 3, page 13]

(1) Chapman utilized the Gradumet® (sustained release) formulation of methamphetamine, which reduces the rate of drug absorption and produces more constant blood levels over a longer duration. This more closely mimics the long-term, low level exposure that is anticipated to occur as a result of living in a remediated methamphetamine lab.
(2) The NOAEL reported by Young and Turner was based on interviews with the parents of the children who participated in the study, not on direct observation by the researchers themselves. This endpoint is not quantitative and was observed in just eight of the 110 treated children.
(3) As noted in several authoritative reviews (discussed in the following section), children may develop tolerance to the common side effects of stimulants. Therefore, the children in the Young and Turner study who initially experienced disturbance of sleep may have simply developed tolerance to this effect. If this were the case, sleep disturbance may have disappeared even if the dose of methamphetamine had not been reduced by half.

Comprehensive Reviews of the Adverse Effects of Stimulants in Children with ADHD

A primary source of uncertainty in the RfD calculation is the potential adverse effects of methamphetamine on the psychological, social, and cognitive development of children. To address this uncertainty, three recent comprehensive reviews of the effects of stimulants in children with Attention Deficit/Hyperactivity Disorder (ADHD) were consulted. While they do not specifically address the adverse effects of methamphetamine, these reviews provide detailed, authoritative summaries on the effects of drugs whose pharmacodynamics are similar to those of methamphetamine (e.g., methylphenidate) or whose pharmacodynamics and chemical structure are similar to that of methamphetamine (e.g., amphetamine).

In 1997, the American Medical Association's Council on Scientific Affairs published a report on the diagnosis and treatment of ADHD in children and adolescents (Goldman et al., 1997). The report was based on a comprehensive literature review using a National Library of Medicine database search of reports published between 1975 and March 1997. A significant portion of this report addressed the efficacy and adverse effects of stimulants commonly used to treat ADHD, and concluded the following:

- More than 170 studies have been conducted examining the effect of stimulants in children with ADHD. A total of over 6000 school-age children were involved in these studies.
- In treating ADHD, the response rate for any single stimulant drug is over 70%, and up to 90% of children will respond to at least one stimulant without significant adverse events if the dose is carefully titrated.
- Stimulants have been "unequivocally shown (i.e., by double-blind, placebo-controlled studies) to reduce core symptoms of hyperactivity, impulsivity and inattentiveness." Contrary to popular wisdom, the effect of stimulants in children

with ADHD is not "paradoxical" because the direction of behavioral changes in children with psychological conditions other than ADHD (e.g., learning disabilities or depression) and normal controls is the same.

- Stimulants may produce adverse effects, but these are usually mild, of short duration, and controllable with adjustments in dose or the timing of dosing. The most common adverse effects are insomnia, decreased appetite, stomachache, headache, and jitteriness.
- A small percentage [not specified] of children administered a stimulant may experience cognitive impairment that requires a reduction in the dose or cessation of treatment. Rare cases of psychosis have also been reported.

A 1998 National Institutes of Health (NIH) Consensus Statement on the diagnosis and treatment of ADHD was prepared by a 13-member panel representing the fields of psychology, psychiatry, neurology, pediatrics, epidemiology, biostatistics and education. The panel developed its conclusions based on open forum presentations from 31 experts in the same fields and extensive review of the scientific literature. Two of the predefined questions the panel was tasked with addressing were, "What are the effective treatments for ADHD?" and "What are the risks of the use of stimulant medication and other treatments?" Regarding these questions, the panel concluded the following:

- In terms of short-term efficacy, few if any differences have been found among the major stimulants that are used to treat ADHD.
- Stimulants may not "normalize" the entire range of behaviors associated with ADHD, and children who are being treated with stimulants may continue to display certain behavior problems more frequently than normal children.
- While little information is available on the effects of long-term stimulant treatment, "…there is no conclusive evidence that careful therapeutic use is harmful."
- Adverse drug effects are usually related to dose. Moderate doses are most often associated with decreased appetite and insomnia, both of which occur early in treatment and may decrease with continued dosing.
- Very high doses of stimulants, particularly amphetamines, may cause central nervous system and cardiovascular damage as well as hypertension. A "rare percentage" [not specified] of children and adults treated with high doses may experience hallucinations. High doses are also associated with compulsive behaviors and movement disorders.
- There is a clear need for studies on the effects (risks and benefits) of long-term treatment with stimulants, alone and in combination with various behavioral treatments.

In 2001, the American Academy of Pediatrics (AAP) issued a clinical practice guideline for treatment of children between 6 and 12 years of age with ADHD.[5] The guideline was authored by a subcommittee composed of primary care and developmental-behavioral

[5] A more recent AAP report (Brown et al., 2005) reviews additional information on specific treatments for ADHD, summarizing the empirical literature which provided the basis for the practice guideline's recommendations for pharmacologic and/or behavioral intervention.

pediatricians, as well as experts in the fields of neurology, psychology, child psychiatry, education, family practice and epidemiology. The subcommittee's recommendations for treatment of children with ADHD were based on a systematic review of the published literature on this topic. A primary focus of this effort was an investigation of the efficacy and safety of stimulants[6] in treating the core symptoms of ADHD. Regarding the use of stimulants, the subcommittee reached the following conclusions:

- Three formal meta-analyses and one review of reviews support the short-term efficacy of stimulants in reducing the core symptoms of ADHD.
- Most studies of stimulants have been short-term, demonstrating efficacy over several days or weeks. One study involving 579 children[7] demonstrated efficacy for as long as 14 months.
- No significant differences were found in the efficacy of methylphenidate and amphetamine and the different forms of these drugs; both improved core symptoms equally. Further, the results of numerous crossover trials indicate the efficacy of different stimulants in the same child.
- Stimulant dosages usually are not weight dependent, and marked individual variability in the dose-response relationship exists. Therefore, clinicians should begin with a low dose and titrate upward.
- Stimulants are generally considered safe. Side effects occur early in treatment and tend to be mild and short-lived.
- The most common side effects of stimulants are decreased appetite, stomachache, headache, delayed sleep onset, jitteriness and social withdrawal. Rarely, with high doses, some children experience psychotic reactions, mood disturbances or hallucinations. Most of these side effects can be managed by adjusting the dose or the dosing schedule.
- In a review of seven studies that compared stimulants with placebo or other medications, there was no evidence of an increase in the frequency of motor tics in children treated with stimulants.
- Behavioral rebound, motor tics and growth delay have been reported clinically, but these effects have not been observed consistently in controlled studies.

In summary, all three reviews concluded pharmacological doses of methylphenidate and amphetamine provide an effective means of reducing the core symptoms of ADHD in children. However, as noted in the NIH review, the social, psychological and cognitive difficulties experienced by children with ADHD are not uniformly ameliorated by stimulant treatment; some behavior problems appear to be unaffected by these drugs. Moreover, there was clear consensus on the primary adverse effects of stimulants in children, with appetite suppression and insomnia being most commonly observed. Side

[6] "First-line" stimulants evaluated were Methylphenidate [short-acting (e.g., Ritalin®), intermediate-acting (e.g., Ritalin SR®) and extended release (e.g., Concerta®)] and d-Amphetamine [short-acting (e.g., Dexedrine®), intermediate-acting (e.g., Adderall®), and extended release (e.g., Adderall-XR®)]. Both Adderall formulations are composed to mixed amphetamine salts (75% *d*-amphetamine and 25% *l*-amphetamine). Methamphetamine was not included in this evaluation, presumably because there were no published studies that met the subcommittee's criteria for inclusion.

[7] This study is commonly referred to as the MTA, or multimodal treatment study of children with ADHD.

effects generally occur early in treatment, and tend to be mild and short-lived. In rare cases, however, children treated with higher doses may experience cognitive impairment, psychosis, mood disturbances and hallucinations, all of which would require reduction in the dose or cessation of treatment. Treatment durations as long as 14 weeks have been evaluated, but data on the effects of long-term treatment or potential adverse neurodevelopmental consequences are lacking.

Relevance of Studies on the Effects of Stimulants in Children with ADHD

While comprehensive and authoritative, the reviews cited above have limited relevance to the identification of the potential adverse health effects of low doses of methamphetamine in young children. In part, this is attributable to the fact that they primarily address the two most widely prescribed stimulants for treatment of ADHD, methylphenidate (e.g., Ritalin®) and amphetamine (e.g., Dexedrine®). While methamphetamine is occasionally prescribed to treat ADHD (Bhandary et al., 1997), controlled investigations of its use in children or adults with ADHD have not been published in peer-reviewed scientific journals. However, all three reviews concluded that, at prescribed pharmacological doses, different stimulants appear to equally efficacious and produce similar side effects. Nevertheless, in comparison with methylphenidate and amphetamine, methamphetamine is generally regarded to be a more potent central nervous system stimulant. Since the primary low-dose side effects of methylphenidate and amphetamine – appetite suppression and insomnia – are centrally mediated, it is likely that methamphetamine will elicit these effects at lower doses than the stimulants commonly prescribed for ADHD. Therefore, while qualitative conclusions regarding the potential adverse effects of methylphenidate and amphetamine are likely applicable to methamphetamine as well, it is reasonable to conclude that methamphetamine will produce these effects at lower doses.

It may be argued that the relevance of these studies is limited because they involve children with ADHD, not "normal" children. However, the prevalence of ADHD in school-age children is estimated to be in the general range of 4-12% (AAP, 2001), and estimates as high as 16% have been reported (Goldman et al., 1998). Therefore, children with ADHD represent a small but significant sub-population of children. Furthermore, as Goldman et al. (1998) have noted, several placebo-controlled studies have noted stimulants appear to produce similar behavioral changes in children with ADHD, children with various other psychological difficulties, and normal children. For this reason, the effects of stimulants in children with ADHD probably reflect the response of normal children to these drugs as well.

A third limitation of the studies cited in these reviews is their relatively short duration and narrow focus. For the most part, these studies examined the efficacy of short-term (approximately three months) stimulant treatment on improvement in symptoms of ADHD. As noted in the NIH consensus statement, little information exists concerning the longer-term effects of pharmacological doses of stimulants.

Additional Sources of Uncertainty

Uncertainty factors are used to derive an RfD from experimental data. As summarized by U.S. EPA, uncertainty factors are used to account for

- Variation in susceptibility among the members of the human population
- Uncertainty in extrapolating animal data to humans
- Uncertainty in extrapolating from the results of a short-term study to long-term exposure
- Uncertainty in extrapolating from a LOAEL to a NOAEL
- Uncertainty associated with extrapolation when the database is incomplete

The exposure assessment (presented in a separate report) presumes that methamphetamine residues will not persist in an indoor environment where people are living for longer than a few months. Over time, surface residue concentrations will be depleted by mechanisms such as transfer to uncontaminated surfaces and periodic cleaning. Since the RfD was derived from the results of a study in which subjects were exposed continuously to methamphetamine for a period of four months, an uncertainty factor that accounts for short-term to long-term exposure is not required. Similarly, since this study involved human subjects, an uncertainty factor that accounts for animal to human extrapolation is not needed. Standard 10-fold uncertainty factors were used to account for inter-individual variability in the human population and extrapolation from a LOAEL to a NOAEL. Uncertainties concerning the adequacy of the toxicity database include

- The possibility that early life exposure to methamphetamine will adversely affect neurological and psychosocial development later in life
- The possibility that early life exposure to methamphetamine will predispose children to substance abuse disorders later in life
- The possibility that very young children (1-2 years old) are more sensitive to the adverse effects of methamphetamine than older children (6-12 years old), who are typically evaluated in studies of the effects of stimulants in children with ADHD[8]

These concerns are discussed in more detail in the following section as justification for adoption of an additional 3-fold uncertainty factor.

Organization of the Report

This report was prepared to provide scientific justification for a reference dose for methamphetamine. The next section of the report provides a detailed analysis of the

[8] A limited number of studies have been conducted on the effects of stimulants in pre-school children. Of the 34 methylphenidate studies that were reviewed by the American Academy of Pediatrics, six were conducted in preschoolers (Brown et al., 2005). However, only the findings from studies in school-age children were included in AAP's technical report (2001).

Chapman (1961) study, the primary study that was used to derive theRfD. This is followed by summaries of approximately thirty-five studies that characterize the range of effects of methamphetamine in humans. The summaries are grouped according to the end-points that were investigated, such as appetite suppression and weight loss, endocrine effects, sympathomimetic effects, subjective effects and pharmacokinetics. Despite wide variations in experimental objectives, test doses, route of exposure and duration of exposure, these studies generally support the conclusion that the lowest experimentally-derived adverse effect level for methamphetamine in humans (adults and children) is 0.1 – 0.2 mg/kg-day. Using the results of the Chapman (1961) study and incorporating appropriate uncertainty factors, the sub-chronic RfD for methamphetamine is $2.7x10^{-4}$ mg/kg-day.

Summary of Principal Study for Identification of the Critical Effect and Determination of an RfD for Methamphetamine

Principal Study: Control of Weight Gain in Pregnancy, Utilizing Methamphetamine (Chapman, 1961)

Study Objective: evaluate the efficacy and safety of a sustained-release form of methamphetamine (Desoxyn® Gradumet®, Abbott Laboratories) for controlling weight gain in obstetric patients.

Study Design: placebo control, double blind
Patients were *not* randomly assigned to a treatment group; each patient's dose was adjusted according to her body weight (BW) at the beginning of the study.[9]

Table 1: Treatment Groups

	n[10]	Initial BW (kg)	Initial Dose (mg/kg BW)	Start of Dosing (gestation week)	Dosing Duration (weeks)
Placebo	23	67.2 ± 10.4	0	23.4 ± 3.9	16.4 ± 4.0
5 mg	10	61.2 ± 6.3	0.08	24.9 ± 4.6	14.7 ± 4.9
10 mg	35	67.5 ± 7.6	0.15	24.2 ± 3.3	15.3 ± 3.2
15 mg	16	87.7 ± 8.8	0.17	22.6 ± 3.8	16.5 ± 3.9

Values shown are mean ± standard deviation (SD).

Patients were selected for participation in the study because they were overweight or experienced excessive weight gain in the course of their pregnancy. Women in the first trimester were excluded from the study. All patients were given a standard vitamin and mineral supplement during the course of treatment. Diet was not controlled, although consumption of protein and fresh vegetables was stressed. A "six-meal-a-day" plan (not described) was "advised repeatedly."

Methamphetamine was administered orally in a sustained release formulation (Desoxyn® Gradumet®, Abbott Laboratories) that prolongs the duration of action and reduces the peak blood levels of the drug.

Patients were seen routinely every two weeks, at which time an evaluation of blood pressure, heart rate, body weight, urinanalysis, fetal size and uterine size was conducted. Blood counts were evaluated each trimester, and blood chemistry was tested at term.

[9] However, the data indicate that there was considerable overlap in the initial body weights of women in the placebo, 5 mg and 10 mg groups. Since women in the 15 mg group weighed more, their dose on a mg/kg body weight basis was only slightly higher than the women in the 10 mg group.
[10] Data from twelve women who withdrew from the study (designated "intolerant" by the study's author) and nine women who were administered a diuretic to treat edema are not included in summary statistics.

Randomly selected patients (approximately half the total) had electrocardiograms taken before and during the study, and were followed in labor with evaluation of total protein, albumin:globulin ratio, and electrolytes.

Nine patients, whose weight gain was judged to be excessive and edema was evident, were treated with a "suitable" (unspecified) diuretic. No patients in the placebo group were treated with a diuretic. Since diuretics usually cause weight loss, data from patients who were treated with a diuretic were not included in summary statistics presented in Tables 1 and 2.

Table 2: Summary of Results

	Weight Gain			Final Weight	Final Dose
	(kg)	(kg/week)	(kg/week/kg BW)	(kg)	(mg/kg)
Placebo	6.88 ± 3.27	0.43 ± 0.19	0.0064 ± 0.0027	74.1 ± 11.5	0
5 mg	1.27 ± 2.55	0.12 ± 0.20	0.0020 ± 0.0033	62.5 ± 6.4	0.08
10 mg	2.90 ± 3.44	0.18 ± 0.21	0.0027 ± 0.0032	70.4 ± 8.5	0.14
15 mg	-0.57 ± 3.03	-0.005 ± 0.021	-0.00005 ± 0.0022	87.1 ± 8.2	0.17

According to the study's author, "The normal weight curves of Thompson were utilized as standard for excessive weight gain, and in the last half of pregnancy a normal weight gain was considered to be 0.8 pound [0.36 kg] per week." Average weight gain in the placebo group was only slightly higher than this target rate.

Of the 61 women treated with methamphetamine, 23 lost weight over the course of treatment. According to the author, "The babies born to these mothers appeared normal and healthy." None of the women in the placebo group lost weight.

The original publication did not provide statistical analysis of the data. Therefore, the weight change data were analyzed using analysis of variance (ANOVA) based on general linear modeling (SAS 9.1, SAS Institute, Cary, NC). This analysis confirmed the significant group effect [$F(3,80) = 18.83$, $p < .0001$] and significant difference from control for the 5, 10 and 15 mg/kg groups (Bonferroni post hoc test, $p < .05$), as well as a difference between the 10 and 15 mg/kg groups ($p < .05$). An additional test for homogeneity of variance across groups (Levene test) did not support the null hypothesis of no difference in variance between groups [$F(3, 80) = 3.77$, $p = .01$]. Although ANOVA is robust to violation of the homogeneity assumption, a second analysis (Welch's ANOVA) which does not assume homogeneity of variance confirmed the group effect [$F(3, 27) = 49.98$, $p < .0001$].

All electrocardiogram and laboratory results for all patients evaluated were within normal ranges.

Reported side effects are shown in Table 3. No consistent dose-related effects are apparent.

Table 3: Summary of Side Effects

	Side Effects [# of patients (%)]							
	n	**Edema**	**Nervousness**	**Insomnia**	**↑ BP[11]**	**Depression**	**Intolerance**	**Σ**
Placebo	25	0	3 (15%)	1 (4%)	0	1 (4%)	2 (8%)	7 (28%)
5 mg	17	2 (12%)	0	0	0	0	5 (29%)	7 (41%)
10 mg	43	4 (9%)	5 (12%)	0	2 (5%)	0	4 (9%)	15 (35%)
15 mg	20	4 (20%)	2 (10%)	1 (5%)	0	0	1 (5%)	8 (40%)

Comments

1. Group sizes: Subjects in each group *at the beginning of the study* are shown.

2. Placebo group: One patient reportedly experienced increased hunger.

3. 5 mg group: Five patients "showed some degree of intolerance manifested as nervousness or insomnia" yet no patients were specifically indicated as having experienced these symptoms (in contrast to the other three treatment groups).

4. 15 mg group: Two patients who complained of nervousness, although one experienced this symptom only occasionally. The single patient who complained of insomnia also experienced this symptom only occasionally

5. Diuretics: All but one of the patients experiencing edema was treated with a "suitable diuretic." The patient with untreated edema was in the 15 mg group. In discussing the results for the 5 mg group, the report's author stated, "Two patients in the controlled weight group required diuretics to maintain the weight within acceptable limits," suggesting that, for some patients, a diuretic was used in combination with methamphetamine to control weight gain. However, of the nine patients who were treated with a diuretic, six gained no weight or actually lost weight. None of the patients in the placebo group was treated with a diuretic even though this group gained more weight than any of the three treated groups.

6. Summation of side effects: In the final column, patients experiencing any side effect were combined with patients described as "intolerant" to determine whether there was a dose-related increase in total adverse effects. No such increase is apparent.

7. Intolerance to drug treatment: Symptoms of "intolerance" were "nervousness, gastrointestinal complaints of a bizarre nature, tachycardia, and insomnia." The author noted that "….when intolerance was found…the dosage was diminished and the symptom pattern was found to be the same." However, four patients were switched to the placebo instead of receiving a lower dose, but they continued to experience symptoms of "intolerance."

[11] BP: blood pressure

Reference Dose Determination

The RfD determination is based on the LOAEL estimation of 0.08 mg/kg from the previous discussion and combining it with an aggregate uncertainty factors (UF). UFs are based on the uncertainties and variabilities in the estimation of the LOAEL in the Chapman (1961) study as well as the scientific literature on the effects of methamphetamine. The components of the aggregate uncertainty factor are discussed below.

Uncertainty Factors

- **LOAEL-to-NOEL extrapolation**
  - A no observed adverse effect level (NOAEL) was not observed in this study.
  - Of the ten women who received 5 mg methamphetamine, four lost weight and six (60%) experienced "normal" weight gain (identified by the author as no more than 0.36 kg/week). None of the 23 women receiving the placebo lost weight, and seven (30%) experienced "normal" weight gain.
  - Appetite suppression and consequent weight loss are widely recognized indicators of the effects of low doses of methamphetamine on the central nervous system.[12]
  - In a 1960 investigation conducted by Bayly, pregnant women who were given 10 mg/day of Desoxyn® Gradumet® for 15-16 weeks gained significantly less weight than placebo controls.[13] These results provide independent verification of the results obtained by Chapman (1961).
  - Given that methamphetamine produces CNS stimulation at relatively low doses, it is unclear whether any clinical study of methamphetamine can truly be regarded as "double blind." As Modell (1960) noted,

    … the ability to distinguish medication from placebo by any effect other than the one under examination (in this case weight loss) makes it exceedingly difficult to prevent bias and psychological factors from shaping the apparent effects of the drug. This tends to reduce the sensitivity of methods of clinical evaluation of these drugs as well as to make it especially difficult to design a study in which these factors do not bias results.

  Conclusion: apply a 10-fold uncertainty factor to estimate a NOAEL from a study where the lowest dose produced an adverse effect.

- **Inter-individual variation in population response**
  - Variation in human sensitivity to stimulants is well-characterized. Reports on the use of stimulants (amphetamine and methylphenidate) in children and adults with ADHD emphasize the need to individually titrate the dose of the drug.

[12] Several studies evaluating the dose-response relationships of these effects are summarized on pages 21-31in the section, *Supporting Studies for a Methamphetamine RfD*.
[13] A detailed summary of the Bayly (1960) report is provided on pages 21-22 in the section, *Supporting Studies for a Methamphetamine RfD*.

- Clinical studies of the use of stimulants for treatment of ADHD indicate that children are *not* more sensitive than adults to this class of medications and may in fact be less sensitive to them. According to Dulcan (1997), "Adults are more sensitive than children to both the therapeutic and side effects of stimulants. As a result, similar absolute doses are commonly used [for treatment of ADHD]." Furthermore, in a comprehensive review of the use of stimulants in children with ADHD, Greenhill et al. (1999) stated, "When dose is weight-adjusted, there do not appear to be age effects on dose." Therefore, even though the Chapman study examined the effects of methamphetamine on adult women, the doses used in the study (on a mg/kg body weight basis) are probably reasonably indicative of the sensitivity of children to the drug. The fact that LOAELs in the Chapman (1961) study and the Young and Turner (1965) study[14] are similar (see discussion on page 4) also indicates that children and adults have similar sensitivities to methamphetamine.
- The range of variation in children's sensitivity to low doses of methamphetamine is indicated by the results of the Young & Turner (1965) study, where children were dosed sub-chronically with methamphetamine. Most of the 110 treated children received a dose of 5 mg/day, but 8 required a dose of 2.5 mg/day because they experienced adverse effects (insomnia) at 5 mg/day. Conversely, one child was dosed with 10 mg/day and three were dosed with 7.5 mg/day without experiencing adverse effects. These results suggest at least four-fold range in children's sensitivity to the drug.
- The dose-response relationship for the CNS stimulating effects of methamphetamine appears to be relatively sharp (that is, a small increment in dose produces a pronounced increase in CNS stimulation). In a dose range-finding study conducted by Perez-Reyes et al. (1991b), doses of 20, 25, 30 and 40 mg were administered by inhalation to subjects familiar with the subjective effects of methamphetamine. Doses of 20 and 25 mg produced minimal subjective effects, while 30 mg produced more distinct and sustained effects. The highest dose, 40 mg, produced extreme subjective effects.[15]
- Some individuals are much *less* sensitive to methamphetamine than the general population. For example, a study examining the effectiveness of the drug in the treatment of narcolepsy utilized oral doses as high as 40-60 mg/day (Mitler et al. 1993).

Conclusion: apply a 10-fold uncertainty factor to account for variation in individual sensitivity to methamphetamine.

- **Completeness of the database**
  - Significant adverse effects on neurodevelopment have been reported in animal studies. For example, prenatal methamphetamine exposure in mice results in long-term hippocampus-dependent cognitive deficits (Acevedo et al., 2007). However, the doses used in laboratory animal studies are typically 10 to 100

[14] A detailed summary of the Young and Turner (1965) report is provided on pages 52-54 in the section, *Supporting Studies for a Methamphetamine RfD*.
[15] A detailed summary of the Perez-Reyes (1991b) report is provided on pages 43-44 in the section, *Supporting Studies for a Methamphetamine RfD*.

times greater than the doses employed in the Chapman study. [16] Furthermore, pronounced differences in the pharmacokinetics of methamphetamine in humans and rats have been reported [Cho et al. (2001)].[17] Also, Greenhill et al. (1999) have noted that the toxic effects of stimulants reported in animal studies have not been observed in humans receiving therapeutic doses. Consequently, quantitative methamphetamine toxicity data generated using rats as an animal model must be carefully evaluated because its relevance to human health may be limited.

- Research reports examining the safety and efficacy of stimulants in children with ADHD were evaluated by Greenhill et al. (1999), who noted

> *Stimulant-related adverse events occur early in treatment for children with ADHD and appear to be mild, short-lived and responsive to dose or timing adjustments…Delay of sleep onset, reduced appetite, stomachache, headache and jitteriness are the most frequently cited…Twenty-three controlled studies found no differences for these adverse events among the stimulants, with only abdominal discomfort, sleep delay, and headache being reported more often in those treated with stimulants than those receiving placebo in 2 or more of the 23 controlled trials.*

The same report also noted,

> *Rarely, children [receiving stimulants] have been reported to display cognitive impairments or perseverative behaviors, but these usually respond to a decrease in dose. Very rarely children receiving high doses of stimulants have shown psychotic reactions, hallucinosis, or mood disturbances.*

- The risk-based cleanup standard for methamphetamine is based on an exposure scenario involving 1-2 year olds as the most exposed population. Children in the 1-2 year age bracket are also widely regarded as being more sensitive to the adverse effects of neurotoxins. However, there is no research on the effects of methamphetamine in 1-2 year olds. Three studies of the use of methamphetamine to treat enuresis in children are reviewed elsewhere in this document,[18] but none of these studies involved children younger than 5 years of age. For example, in an investigation conducted by Young & Turner (1965), children whose average age was 7 years were administered methamphetamine for an average duration of 2 months.
- Concerns that exposure to stimulants during childhood may enhance the likelihood of stimulant abuse later in life are not supported by currently available data. In a 16-year follow-up study of children who were given methylphenidate (Ritalin®) for 12-18 weeks[19], Mannuzza et al. (2003)

[16] The methamphetamine dose used in the mouse studies conducted by Acevedo et al. was 5 mg/kg, which is 62.5-fold greater than the lowest dose (0.08 mg/kg) in the Chapman study.

[17] For example, the elimination half-life for methamphetamine is 11-12 hours in humans and 70 minutes in rats.

[18] See pages 52-55 under the heading, *Supporting Studies for a Methamphetamine RfD.*

[19] Children with ADHD have been found to be at increased risk of substance abuse disorder (SUD) in adolescence and adulthood. Children evaluated in the Mannuzza et al. study had developmental reading disorders but no other psychiatric diagnoses.

reported no significant difference between children treated with Ritalin® (n=43) and a matching placebo group (n=66) in the prevalence of substance abuse disorder (abuse or dependence) for any of the seven drug categories evaluated. In addition, a meta analysis of six studies – two with follow-up in adolescence and four in young adulthood[20] – indicated a 1.9-fold *reduction* in risk for substance use disorder in youths who were administered stimulants compared with children who did not receive pharmacotherapy for treatment of ADHD (Wilens et al., 2003). On the other hand, stimulants differ in their capacity to induce euphoria, which in turn appears to be related to their abuse potential. Since methamphetamine's euphoria-inducing effect is a significant aspect of its pharmacodynamic action, and stimulants used for the treatment of ADHD are less potent in this regard,[21] these studies may not reflect the potential for substance abuse problems to develop in individuals exposed to methamphetamine early in life.

- Hundreds of studies examining adverse effects of methamphetamine in humans have been published. Unfortunately, many of these studies are marginally useful or largely irrelevant because
  - They characterized adverse effects in meth-dependent addicts.
  - They characterized adverse effects in persons who recently used or concurrently use methamphetamine or another psychoactive drug for recreational purposes.
  - The drug was administered by intravenous injection or inhalation, causing extremely rapid absorption and higher peak blood levels than would be achieved by dermal absorption and ingestion, exposure routes that are most relevant for a 1-2 year old child in a residence previously used as a clandestine methamphetamine manufacturing lab.
  - The effects of just a single dose of the drug were characterized. Multiple dose studies of methamphetamine's effects in humans are unusual.
- Human studies have a very significant advantage over animal studies insofar as the subjects can report any subjective effects they experience. These effects may or may not result in measurable biochemical response and are even less likely to result in discernable pathology.

Conclusion: add a 3-fold uncertainty factor for incompleteness of the database.

- **Duration of treatment vs. anticipated exposure scenario duration**
  - In this study, the average duration of treatment was four months.
  - The risk-based cleanup standard for methamphetamine is based in part on a post-cleanup exposure scenario, with all surfaces remediated to a target cleanup level. Re-contamination of surfaces will not occur because a primary contaminant source ("reservoir") does not exist. Repeated contact and other activities as well as periodic cleaning will cause contaminant levels to decline over time. Therefore, the post-cleanup scenario will produce sub-chronic exposure to meth lab contaminants.

[20] Pooled data comprised 674 stimulant-treated subjects and 360 untreated subjects who were followed at least four years.

[21] For example, data published by Volkow et al. (1998) suggest that methylphenidate's uptake into the brain is too slow to produce rapid blockade of dopamine transporters, which is thought to be the biochemical mechanism responsible for induction of euphoria.

Conclusion: no additional uncertainty factor to account for longer-term exposure is required.

RfD Calculation

The sub-chronic RfD is calculated as

$$\frac{LOAEL}{UF} = RfD = \frac{0.08\ mg/kg-day}{(10 \times 10 \times 3)} = 2.7 \times 10^{-4}\ mg/kg-day = 0.3\ \mu g/kg-day$$

Where

0.08 mg/kg-day	=	the experimentally observed LOAEL
10	=	uncertainty factor used to estimate a NOAEL from a LOAEL
10	=	uncertainty factor used to account for inter-individual variation in sensitivity
3	=	uncertainty factor used to account for deficiencies in the toxicity database

List of Supporting Studies for a Methamphetamine RfD

1. Other Studies Evaluating Methamphetamine for Treatment of Obesity:
    Bayly (1960)
    Shutter and Garell (1966)
    Simkin and Wallace (1960)
    Matthews (1970) (note description of side effects)
    Hughes (1960)
    Kolecki (1998)

2. Effects of Methamphetamine on Appetite and Caloric Intake:
    Johnson et al. (1999a)
    Martin et al. (1971)
    Comer et al. (2001)
    Ong et al. (1983)

3. Effects of Methamphetamine on Fatty Acid Metabolism:
    Pinter and Pattee (1968)
    Pinter and Pattee (1970)

4. Endocrine Effects of Methamphetamine: p. 37
    Besser et al. (1969)
    Rees et al. (1970)

5. Cardiovascular and Sympathomimetic Effects of Methamphetamine:
    Johnson et a. (2000)
    Martin et al. (1971)
    Mitler et al. (1993)

6. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Amphetamine-Naïve Subjects:
    Schepers et al. (2003)
    Shappell et al. (1996)

7. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Recreational Amphetamine Users:
    Perez-Reyes et al. (1991a)
        Cook et al. (1992)
        Cook et al. (1993)
    Perez-Reyes et al. (1991b)
        Cook et al. (1993)

8. Assessment of Euphoric and Dysphoric Subjective Effects of Methamphetamine:
    Johnson et al. (1999b)
    Wachtel et al. (2002)
    Soderpalm et al. (2003)

9. Effects of Methamphetamine on Psychomotor Performance, Resistance to Fatigue, Decision Making and Memory:

Shappell et al. (1992)
Stanny et al. (1993)
Wiegmann et al. (1996)
Mewaldt and Ghonheim (1979)

10. Utilization of MRI to Identify Brain Regions Affected by Methamphetamine: Correlation with Subjective Effects:

Vollm et al. (2004)

11. Studies Evaluating the Use of Methamphetamine to Treat Children for Enuresis:

Young and Turner (1965)
Kapoor & Saksena (1969)
Kennedy & Sloop (1965)

12. Case Studies of Children treated with Methamphetamine:

Zike (1972)
Bussing and Levin (1993)

13. Potential Developmental Toxicity of Methamphetamine:

Sussmann (1963)

Supporting Studies for a Methamphetamine RfD

1. Other Studies Evaluating Methamphetamine for Treatment of Obesity

A number of studies have evaluated the effectiveness of methamphetamine for the treatment of obesity. A study conducted by Bayly (1960) provides the strongest support for the results obtained by Chapman (1961). In this study, pregnant women were administered daily doses of 10 mg Desoxyn® Gradumet®, the same sustained-release methamphetamine formulation used in the Chapman investigation, for a similar period of time (15-16 weeks). Women administered methamphetamine gained approximately 60% as much weight as women in the placebo group. No significant side effects were reported. Although this study was conducted under double blind conditions, the 1961 Chapman study is more robust scientifically for the following reasons:

1) The Chapman study evaluated three doses of methamphetamine (5, 10 and 15 mg) while the Bayly study examined just one dose (10 mg).

2) In both studies, a number of women were administered diuretics to control weight gain as an adjunct to methamphetamine therapy. Since the Chapman report provided data on individual women, those who received a diuretic could easily be identified and eliminated from the data set and the effects of methamphetamine treatment alone could be evaluated. The Bayly report simply provided the number of women in each group who received a diuretic, so the effects of methamphetamine treatment alone could not be examined.

There are several other published investigations of methamphetamine's anorectic effect, but the design of these studies renders them less suitable for development of an RfD. For example, studies conducted by Shutter and Garell (1966) and Simkin and Wallace (1960) evaluated the effectiveness of 16-20 weeks' treatment with Ambar Extentabs #1, (A.H. Robbins), a combination drug that contained 10 mg d-methamphetamine hydrochloride and 65 mg phenobarbital. Similarly, Hughes (1960) evaluated the effectiveness of Du-Oria (B.F. Ascher), a combination of 25 mg d-methamphetamine hydrochloride and 0.25 mg reserpine. The weight loss effects reported in each of these studies were probably due to methamphetamine administration, but it is also likely that phenobarbital and reserpine acted to suppress symptoms of CNS stimulation (e.g., agitation and sleep disturbance), thereby masking some of the primary side effects of methamphetamine. Each of these investigations is summarized in greater detail below.

Bayly (1960) published a one-page report on the use of methamphetamine as an aid in controlling weight gain in pregnant patients. The drug or a placebo was administered under double blind conditions. Patients in the drug treatment group received a single 10 mg oral dose of methamphetamine in a sustained-release formulation (Desoxyn® Gradumet®, Abbott Laboratories) each morning. Thirty patients received methamphetamine and thirty received placebo. Criteria for selection of patients to be included in the study were not specified; it appears that they were simply chosen as they enrolled at the prenatal clinics of the Chicago Maternity Center. The initial weight of the methamphetamine-treated group averaged 174 pounds, "…though height and habitus

would suggest an optimal average of 127 pounds." Similarly, the initial weight of the placebo group averaged 156 pounds, although the ideal weight for these women would have been 128 pounds. A reference for the ideal weights that were cited was not provided.

The results of the study are summarized in the table below.

	Treatment Duration (weeks)	Weight Gain (pounds/week)	Number Gaining No Weight	Number Given a Diuretic	Cases of Nausea	Cases of Nerv
Meth (n=30)	15	0.302	8	9	0	1
Placebo (n=30)	16	0.534	2	13	1	2

Data from Bayly (1960). "Cases of Nerv" refers to the number of cases of nervousness in each group.

Upon questioning, nine patients in the methamphetamine treatment group admitted that they did not take their tablets regularly, while 13 were "occasionally delinquent" in the placebo group.

The results suggest that women taking methamphetamine gained less weight than women administered the placebo. Also, methamphetamine treatment was associated with a four-fold increase in the number of women who gained no weight during the course of treatment. A low incidence of side effects (nausea, nervousness) was noted in both groups, but side effects were actually lower in the methamphetamine treatment group than in the placebo group. Diuretics may be of use in reducing weight gain during pregnancy, but in this study a greater proportion of women in the placebo group received a diuretic (13 out of 30) than in the methamphetamine group (9 out of 30). Therefore, it does not appear that the use of diuretics in this study could account for the reduced rate of weight gain in women treated with methamphetamine.

These results are consistent with those of the Chapman (1961) study. For comparison, in the Chapman study, the average weight gain of women administered the placebo was 0.948 pounds per week, while those administered 10 mg Desoxyn® Gradumet® gained 0.397 pounds per week. Treatment durations in the two studies were virtually identical (15-16 weeks).

Shutter and Garell (1966) evaluated the effectiveness of methamphetamine as a treatment for obesity in 78 children and adolescents, 5 through 18 years of age. The 12-week study was conducted under double blind, placebo controlled conditions with a crossover at six weeks. The drug was administered orally as an enteric-coated, controlled release extended action tablet (Ambar Extentabs #1, A.H. Robbins), containing 10 mg methamphetamine hydrochloride and 65 mg phenobarbital.[22] Weight loss was greatest in the first six weeks of the study regardless of treatment (Ambar or placebo), suggesting a significant initial placebo effect. However, during the second six weeks, children who received Amber lost more weight than those receiving placebo. Over the course of the

[22] The composition of Ambar Extentabs #1 was not indicated in the report by Shutter and Garell. Composition data was taken from an earlier report by Stuart (1962), although the isomeric composition of methamphetamine (d-isomer or racemic) was not specified.

study, the mean weight loss for children receiving Ambar was 6.6 pounds while those receiving placebo lost 3.4 pounds. According to the authors of the study, "No side effects were observed during this study," although this statement is difficult to evaluate given the lack of any description of assessment methods for side effects.

Simkin and Wallace (1960) also evaluated the effectiveness of Ambar Extentabs for treatment of obesity. All study participants were registered in a special outpatient obesity clinic of a large hospital. Two studies were conducted, the first under double blind conditions and the second under subject-blind conditions. In the double blind study, 30 patients were placed on the active drug and 23 on the placebo. Patients in this study ranged in age from 50 to 53 years. In the single blind study, 27 were placed on the active drug and 21 on placebo. These patients ranged in age from 43 to 48 years. Most of the patients were women, but the precise number of female and male patients in the two studies was not specified.

In both studies, a single Ambar Extentab #1 (10 mg methamphetamine hydrochloride plus 65 mg phenobarbital) was taken immediately before breakfast, and a lower dose tablet ("Ambar," containing 3.33 mg methamphetamine hydrochloride and 20 mg phenobarbital) was taken at 5 PM. All study participants were placed on a 1000-calorie high protein diet. During the initial four weeks of treatment, the patients were seen by a physician on a weekly basis. Thereafter, they were seen every two weeks for a maximum of 20 weeks. Treatment durations varied, and ranged up to 20 weeks.

As shown in the table below, there was a significant decline in the number of patients participating in the two studies with duration of treatment. However, there was no difference in patient persistence between the active drug and placebo groups.

		Patients in Each 4-Week Period				
Type of Study	**Medication**	**1st**	**2nd**	**3rd**	**4th**	**5th**
Double Blind	Ambar	27	21	17	14	10
	Placebo	22	20	15	9	7
Single Blind	Ambar	26	23	15	10	4
	Placebo	19	18	11	7	3

Data from Simkin and Wallace (1960). Number of patients in each treatment group persisting in treatment from the fourth week of the investigation through the twentieth week.

Greater weight loss was observed in patients receiving the combination drug treatment than placebo. (Data reproduced below.) A placebo effect is apparent during the first four-week interval, as patients in both studies lost more weight during this period than any other. However, in subsequent weeks, patients receiving placebo lost significantly less weight than those treated with the methamphetamine-phenobarbital combination. On average, patients administered Anbar lost approximately one pound per week over the entire course of the study, while those receiving placebo lost just 0.2 pounds per week.

TABLE 2.—WEIGHT LOSS PER PATIENT PER WEEK BY 4-WEEK PERIOD

Type of Study	Medication	Average Pounds Lost per Patient per Week				
		Period 1	Period 2	Period 3	Period 4	Period 5
Double-blind	Ambar	1.8 ± 0.2*	1.2 ± 0.2	0.9 ± 0.1	1.0 ± 0.2	0.7 ± 0.1
	Placebo	1.3 ± 0.2	0.2 ± 0.2	0.1 ± 0.1	0.3 ± 0.2	0.2 ± 0.2
Single-blind	Ambar	1.9 ± 0.1	1.4 ± 0.1	1.1 ± 0.2	0.5 ± 0.2	0.6
	Placebo	0.9 ± 0.2	0.3 ± 0.2	0.3 ± 0.2	−0.1 ± 0.5	0

*Mean and Standard Error of the Mean.

Data from Simkin and Wallace (1960).

Matthews (1970) conducted a study to evaluate the effectiveness of a special program of dietary training and caloric control on the rate of weight gain relapse in subjects who had previously lost weight using a combination of methamphetamine and pentobarbital in a sustained release formulation (Desbutal® Gradumet®, Abbott Laboratories).

A total of fifty overweight female patients were evaluated in this study. Age and body weight statistics for the control and the trained groups are shown below.

	Body Weight (pounds) mean (range)	**Age (years)**
Instructed Group (n=26)	156.3 (132 – 218.3)	36.5
Control Group (n=24)	155.9 (126 – 223.5)	38.9

Initially, study participants were given a single tablet containing 10 mg methamphetamine hydrochloride and 60 mg pentobarbital sodium once each day for two weeks. Thereafter, the daily dose was increased to 15 mg methamphetamine hydrochloride and 90 mg pentobarbital sodium. Patients in the instructed group were treated for an average of 11 weeks and were given caloric intake diaries to afford a well-balanced diet of 1,000 calories per day. Patients in the control group were treated with the drug combination alone for an average of 16 weeks. According to the author, "Cases with slow rates of weight reduction requiring more weeks of treatment than usual were given medication intermittently to avoid possible tachyphylaxis." Within 48 hours of cessation of medication, all patients were administered a self-rating test for depression. Weekly follow-up continued for an average of seven weeks in the instructed group and 12.6 weeks in the control group.

Side effects of drug treatment were described by the author as "minor" and included the following:

- anxiety and motor restlessness (usually in the first week) in 20 percent of the patients
- insomnia in 10 percent
- changes in blood pressure (defined as variation in diastolic blood pressure of 10 mm Hg or more on one or more occasions) in 10 percent
- changes in pulse rate (defined as variation in pulse rate of 10 on one or more occasions, primarily consisting of sinus rate increase of 10 to 20 above baseline values) in 46 percent

Dependence on medication and significant post-withdrawal depression were not observed. The absence of these effects was attributed to "low dosage, slow release dosage form, the "buffering" of undesired cortical effects by pentobarbital, plus the limited, intermittent access to medication within therapeutic guidelines."

For the purpose of identifying a potential threshold dose for methamphetamine in humans, this study is limited because methamphetamine was administered in combination with pentobarbital. In addition, a control group that was not administered the drug combination was not included in the study, and data for individual patients were not provided.

Hughes (1960) evaluated the effectiveness of a methamphetamine-reserpine combination drug as an adjunct to a low-calorie diet for treatment of obesity. The drug, Du-Oria (B.F. Ascher and Company), contained of 25 mg d-methamphetamine hydrochloride and 0.25 mg reserpine in tablet form. The drug was administered orally at about 10 AM each day. Average treatment duration was 57.6 days (range: 8-147 days).

The subjects were 32 obese patients ranging in age from 14 to 68 years, although only four patients were under 30 years of age. Twenty six subjects were female and six were male. Initial body weights of the subjects averaged 179 pounds (range: 135-296 pounds). Two subjects were diagnosed with essential hypertension. Another subject, initially diagnosed with hypothyroidism, withdrew from the study after 33 days because the drug was judged to be ineffective. Twenty-eight subjects were placed on a 1,000 calorie per day diet; the remaining four were placed on diets of 1200-1500 calories. In this regard, five patients were uncooperative and did not consistently adhere to the prescribed diet. On average, these five lost just 2.3 pounds over the course of treatment.

All but two subjects lost weight during the course of treatment. With the exception of these two subjects, average weight loss was 12 pounds after the first six-week period and 20 pounds at the end of 12 weeks.

The only side effect observed was drowsiness in four patients. One patient withdrew from the study after eight days of treatment due to severe drowsiness. The author stated, "There was a remarkable absence of any side effects such as irritability, jitters, nervous tension or overstimulation."

While somewhat informative, this study was complicated by the variation in (1) the health of the study population, (2) the age (14-68 years) and initial body weight (135-296 pounds) of the study population, (3) the diets that the patients were placed on (1000, 1200 or 1500 calories), (4) the patients' success (or lack thereof) in adhering to the diets, and (5) the duration of treatment (8-147 days). In addition, it appears that any adverse side effects potentially attributable to methamphetamine (such as anxiety or sleep disturbance) were masked by co-administration of reserpine since the primary side effect observed in the study was drowsiness. The study also failed to include a concurrent control group (calorie restricted diet only).

High doses of methamphetamine, as might occur in cases of accidental overdose, are also associated with rhabdomyolysis (destruction of skeletal muscle cells). In a nine-year

retrospective chart review, *Kolecki (1998*) identified eighteen cases of pediatric poisoning with methamphetamine and noted that rhabdomyolysis was the most common complication observed. Rhabdomyolysis could also lead to weight loss and, in extreme cases, the wasting syndrome typically associated with long-term exposure to high doses of methamphetamine in adults. However, to our knowledge, rhabdomyolysis has not been observed in persons exposed to low doses of methamphetamine typically utilized in controlled studies of the effects of methamphetamine in humans.[23]

2. Effects of Methamphetamine on Appetite and Calorie Intake

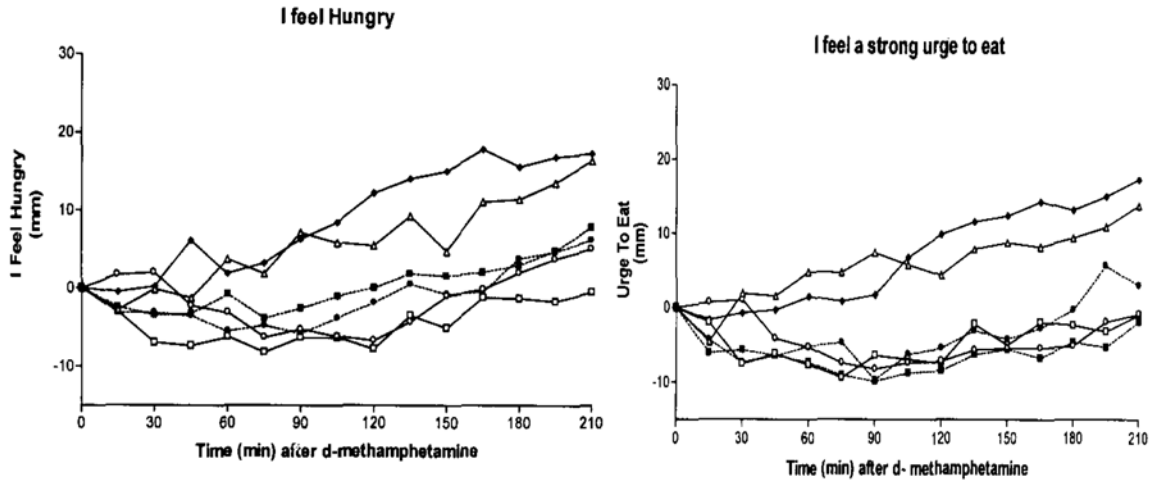
Suppression of appetite and consequent reduction of caloric intake are consistently observed in individuals taking methamphetamine and amphetamine. These effects appear to be largely responsible for the reduction in weigh gain and the weight loss reported in the studies described in the previous section. Several studies, summarized below, have examined the dose-response relationship of appetite suppression in humans.

Johnson et al. (1999a) evaluated the effects of d-methamphetamine (Desoxyn®) and isradipine, a calcium channel antagonist, on somatic and psychological perceptions of hunger using a placebo-controlled, double blind, Latin Square, cross-over design in healthy male (n=11) and female (n=7) volunteers. The volunteers ranged in age from 18 to 45 years; average age was 31 years. None of the volunteers had a history of substance abuse or dependence. Two single doses of methamphetamine (0.21 and 0.42 mg/kg body weight) were tested. To provide the appropriate mg/kg doses, Desoxyn® tablets were crushed, mixed with cornstarch and administered orally in royal blue size 0 gelatin capsules. Placebo capsules contained cornstarch only.

Subjective hunger effects were evaluated using Visual Analog Scales (VAS), and all participants were trained on the use of VAS prior to commencement of the studies. VAS ratings ranged from "not at all" on the left to "extremely" on the right, and were used to rate the subjects' perception of "I feel hungry" (to rate the somatic perception of hunger) and "I feel the urge to eat" (to rate the psychological perception of hunger).

Data are shown in the two graphs below. d-Methamphetamine administration was associated with significant reductions in both somatic and psychological perceptions of hunger. Both doses produced similar responses, with the peak reduction in hunger occurring approximately two hours after dosing. Crushing the Desoxyn® tablets prior to administration may have enhanced the rate of methamphetamine absorption, leading to more rapid onset of maximal effect than might otherwise have occurred.

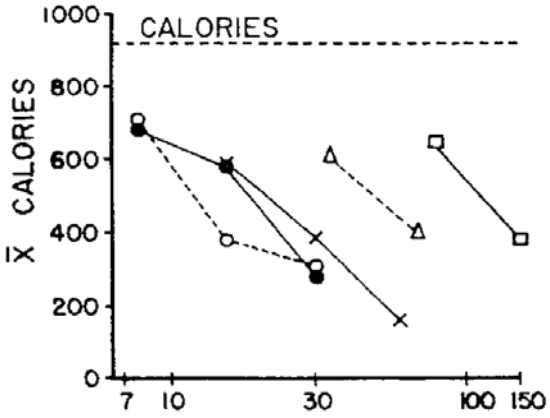
[23] Clinically, rhabdomyolysis is indicated by an increase in total creatine phosphokinase in urine. Evidence of rhabdomyolysis warrants aggressive measures to maintain urine output in order to prevent myoglobinuric renal failure (Kolecki, 1998).



Data from Johnson et al. (1999a). Methamphetamine-induced changes in the somatic and psychological perceptions of hunger in 18 human subjects. Placebo responses are shown by open triangles (Δ), low dose methamphetamine (0.21 mg/kg) responses are shown by open circles (○), and high dose methamphetamine (0.42 mg/kg) responses are shown by open squares (□).

Martin et al. (1971) evaluated the physiologic, subjective and behavioral effects of methamphetamine and four other centrally acting sympathomimetic amines in 12 adult male prisoners. Baseline data were collected 30-60 minutes prior to drug administration. The drugs were administered subcutaneously in a 2 ml volume under double blind conditions. The doses of methamphetamine were 7.5, 15 and 30 mg per 70 kg body weight (equivalent to 0.11, 0.21 and 0.43 mg/kg, respectively). Physiologic and subjective effects were assessed at 30 minutes and 1, 2, 3, 4 and 8 hours thereafter.

Changes in appetite were assessed 3.5 hours after methamphetamine injection by calculating the caloric content of food selected and consumed by the subjects. Data are shown in the graph below. Data obtained when the subjects were administered methamphetamine are indicated by open circles; data obtained following administration of the placebo are indicated by a horizontal dashed line. Methamphetamine produced a clear dose-related decrease in calorie intake, with the lowest dose reducing calorie intake by approximately 22% compared to placebo controls.



Data from Martin et al. (1971). Drug treatments represented are placebo (-----), amphetamine (●—●), methamphetamine (○---○), ephedrine (□—□), phenmetrazine (Δ---Δ) and methylphenidate (x—x). The x-axis represents the log dose in units of mg/70 kg.

Martin et al. also observed that methamphetamine caused a significant dose-related increase in urinary excretion of epinephrine. Twenty years later, Perez-Reyes et al. (1991b) suggested that this finding may reflect methamphetamine-induced release of epinephrine from the adrenal medulla.

In their discussion of these results, the authors stated, "On the basis of physiologic response as well as subjective changes [data not shown], amphetamine and methamphetamine were equipotent with respect to most parameters, and no evidence was obtained that supported the view that the central stimulatory actions of methamphetamine relative to its peripheral effects are greater than those of amphetamine in man when then two drugs are administered subcutaneously."

Comer et al. (2001) evaluated the effects of repeated oral doses of methamphetamine in seven volunteers in a 15-day residential study.[24] Oral methamphetamine[25] (5 and 10 mg, twice each day) was administered on days 4 through 6 and 10 through 12; placebo was administered on all other study days. The first three days of the study were referred to as "placebo baseline days." During the first dosing period (days 4 though 6), four of the participants received the low dose and the other three received the high dose. During the second dosing period (days 10 through 12), subjects who had earlier been given the low dose were given the high dose, and *vice-versa*. Throughout each day, subjects completed a battery of psychomotor tasks and responded to questionnaires rating their subjective perceptions.

All participants in this study reported previous experience with stimulants. Several participants reported current use of cocaine (n=1), caffeine (n=5), alcohol (n=4), marijuana (n=1) and cigarettes (n=4).

Relative to placebo baseline results, only two positive subjective ratings ("I feel a good drug effect" and "I feel high") were elevated, but these results were statistically significant only on the first day that the high dose was administered. (Data reproduced below.) The authors believed that the return to baseline was an indication of the rapid development of tolerance (i.e., tachyphylaxis) to these effects.

[24] An eighth participant who began the study left because of difficulty sleeping following methamphetamine administration. The report does not state explicitly whether this individual received the high dose or the low dose, although it appears that he/she was in the group that was given the high dose (10 mg, BID) during the first dosing period.

[25] Desoxyn® (Abbott Laboratories), 5 mg tablets in white #00 opaque capsules with lactose filler

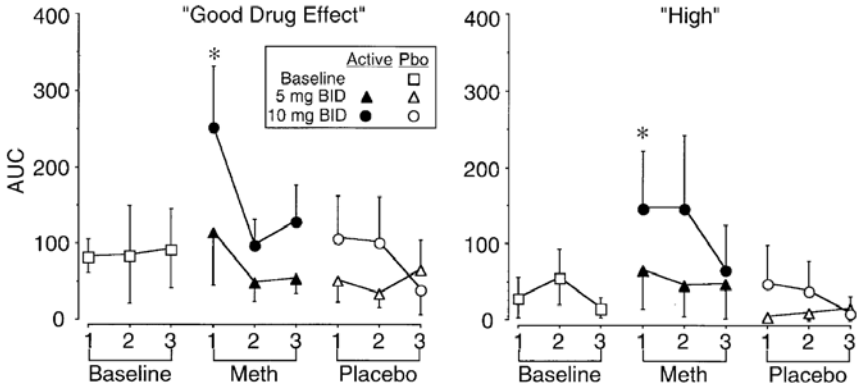


Fig. 1 Area-under-the-curve (*AUC*) values for visual analog scale ratings of "good drug effect" (*left panel*) and "high" (*right panel*) during the 3 placebo baseline days, the 3 days of active methamphetamine administration, and the 3 days of placebo administration immediately following administration of each of the active methamphetamine doses. *Error bars* represent ±1 SEM. An *asterisk* indicates a significant difference between that day and placebo baseline ($P<0.01$)

Data from Comer et al. (2001). Pbo: placebo; BID: twice each day; SEM: standard error of the mean

A number of negative ratings (e.g., "I feel dizzy" and "I feel flu-like symptoms") were also elevated. In contrast to the positive ratings, negative ratings generally became more apparent on the third day of the 3-day dosing periods. Negative ratings were clearly dose related, with the variety and frequency of negative subjective effects being much more apparent at the high dose.

Both doses of methamphetamine reduced total caloric intake on all three days of dosing. Caloric intake on the first placebo day after the 3-day methamphetamine dosing period was also reduced relative to intake during the baseline placebo period. In part, the reduction in caloric intake was attributable to a decrease in the number of eating occasions throughout the day. (Data reproduced below.)

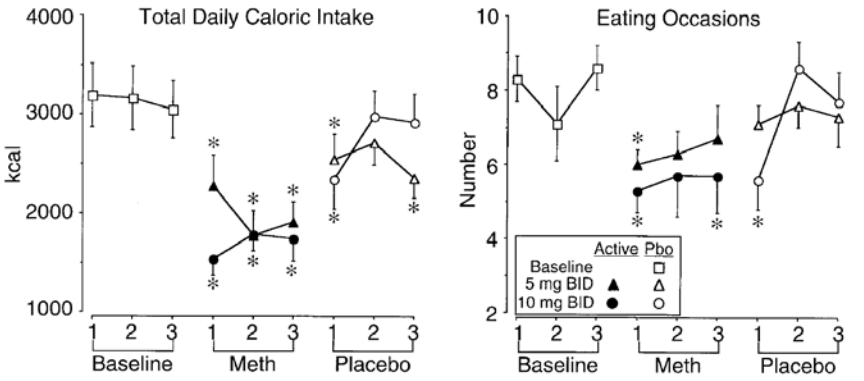
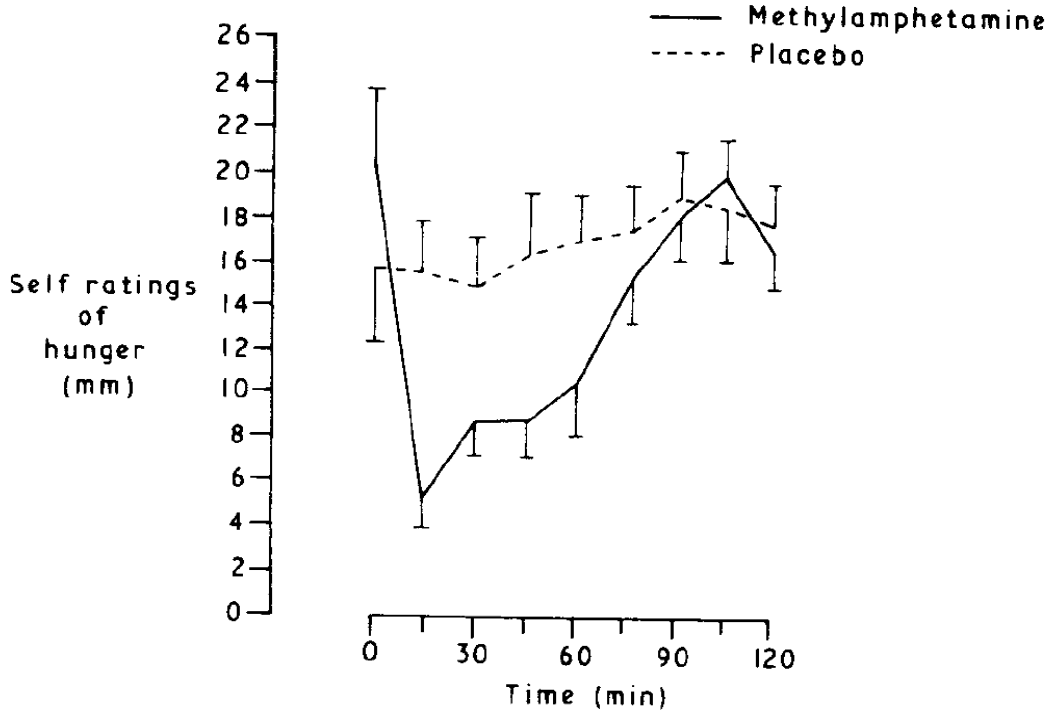


Fig. 3 Total daily caloric intake (*left panel*) and number of eating occasions (*right panel*). For details, see Fig. 1

Data from Comer et al. (2001).

On the first night of treatment with 5 mg methamphetamine, subjective ratings of "fell asleep easily" decreased significantly and ratings of "woke up often" increased significantly. On the second and third nights, no changes in sleep patterns were observed. A number of changes in sleep patterns were observed on the first night of treatment with 10 mg methamphetamine, including decreased total sleep time, sleep efficiency and total non-REM (rapid eye movement) sleep, and increased ratings of "woke up often." Alterations in the objective and subjective measures of sleep occurred primarily on the first day, but not on the second or third day, of 10 mg methamphetamine administration. These results suggest that rapid tolerance to the sleep disrupting effects of methamphetamine occurred in this study.

Ong et al. (1983) investigated the effects of methamphetamine on eating behavior in eight patients (seven female, one male) with bulimia nervosa. The drug (15 mg/75 kg body weight) was administered intravenously under double blind conditions. The study focused changes in mood, hunger and food intake under laboratory conditions. Subjective ratings of hunger, anxiety, urgency to eat, well-being, helplessness, tension, and distress were made by the patients before drug injection and at 15 minute intervals for 2 hours after drug injection. Two hours after drug injection, each patient was allowed to eat and the caloric content of food consumed in 30 minutes was determined. After injection of the placebo, patients consumed 943 ± 222 (mean ± standard error) calories. After methamphetamine injection, intake was just 224 ± 111calories. Self ratings of hunger (data reproduced below) dropped rapidly within 15 minutes of injection of methamphetamine and remained low for approximately one hour. Although this study evaluated effects of methamphetamine in bulimic patients, the primary effects that were observed (reduced subjective sensation of hunger and reduced caloric intake) are typical of those observed at the same dose (0.2 mg/kg) in normal individuals.



Data from Ong et al. (1993). Self ratings of hunger in bulimic patients administered 0.2 mg/kg methamphetamine by intravenous injection. Relative hunger ratings were quantified using a 100 mm visual analog scale. Appetite suppression was also indicated by substantially reduced caloric intake when the patients were allowed to eat, two hours after drug injection.

3. Effects of Methamphetamine on Fatty Acid Mobilization

Pinter and Pattee (1968) examined the effects of several adipokinetic substances [chemicals capable of causing release of free fatty acids (FFA) from adipose tissue], including methamphetamine, in lean and obese volunteers of both sexes. In a typical investigation, three venous blood samples were withdrawn at 20 minute intervals to establish baseline conditions. Methamphetamine or another test compound, dissolved in 50 ml of normal saline, was then infused into the antecubital vein over a period of 15 minutes. The dose of methamphetamine was 0.2 mg/kg. Blood samples were collected at the tenth minute of the infusion and at 0, 10, 20, 30, 45, 60 and 90 minutes after the infusion. Fat mobilizing effects of methamphetamine were evaluated in six subjects.

Methamphetamine infusion caused a significant increase in the plasma FFA, but no changes were found in blood glucose, total serum fat or triglyceride concentrations. In comparison with the immediate effect of exogenously administered epinephrine, the peak effect of methamphetamine on plasma FFA was consistently delayed by about 20 minutes (data reproduced below). Kinetic studies, utilizing successive injections of ^{14}C-labeled, albumin-bound palmitic acid, indicated that methamphetamine augmented the plasma FFA pool by increasing the rate of FFA production.

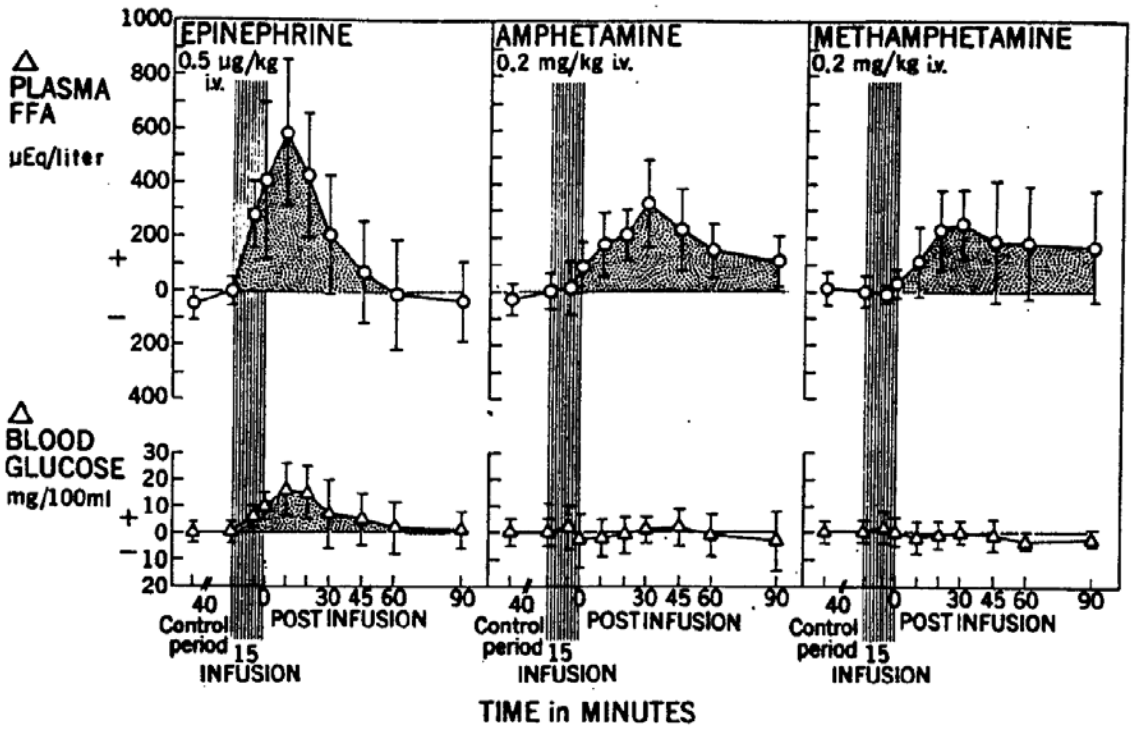


FIGURE 1 The effect of intravenous epinephrine, amphetamine, and methamphetamine infusions on plasma FFA and blood glucose levels (in 14, 15, and 6 subjects respectively). The individual curves show the mean changes ($\bar{\Delta}$) ± SD in relation to the base line levels obtained in the control periods. The shaded areas represent the + ΔFFA and + Δ blood glucose areas; bounded by the temporal plot of ΔFFA and Δ blood glucose from the beginning of the infusions up to 90 min and by a horizontal line drawn at the level of base line concentrations.

Data from Pinter and Pattee (1968).

Additional studies were conducted to clarify the role of endogenous catecholamine release in the FFA response. Catecholamine depletion, achieved by six intramuscular injections of 5 mg reserpine at eight hour intervals, nearly completely abolished the adipokinetic effect of amphetamine (Benzedrine sulfate, 0.2 mg/kg, administered by intravenous infusion). In contrast, epinephrine given after reserpine pretreatment produced an enhanced response in comparison to the response when the same individuals were not pretreated with reserpine. These data were interpreted as evidence for the dependence of amphetamine-induced fat mobilization on endogenous catecholamine release, although a direct action of amphetamine in fat mobilization could not be ruled out entirely.

Taken together, the results of this study were interpreted as evidence that amphetamines cause increased fat mobilization from adipose tissue.

A subsequent investigation by the same authors (Pinter and Pattee, 1970) demonstrated that intravenous infusion of 0.2 mg/kg methamphetamine in four subjects increased in plasma corticoids. The authors speculated that changes in pituitary-adrenal hormone secretions may contribute to the indirect adipokinetic action of amphetamines. Furthermore, they suggested that

…needless hypermobilization of fat caused by the abuse of [amphetamines]… theoretically, may lead to adverse consequences, such as acceleration of thrombogenesis, increased endogenous triglyceride formation and hyperlipidemia with fatty infiltration of the liver, and decreased carbohydrate tolerance. On the other hand, the possibility exists of decreasing the mass of adipose tissue by a metabolic action (fat mobilization) independent of appetite regulation.

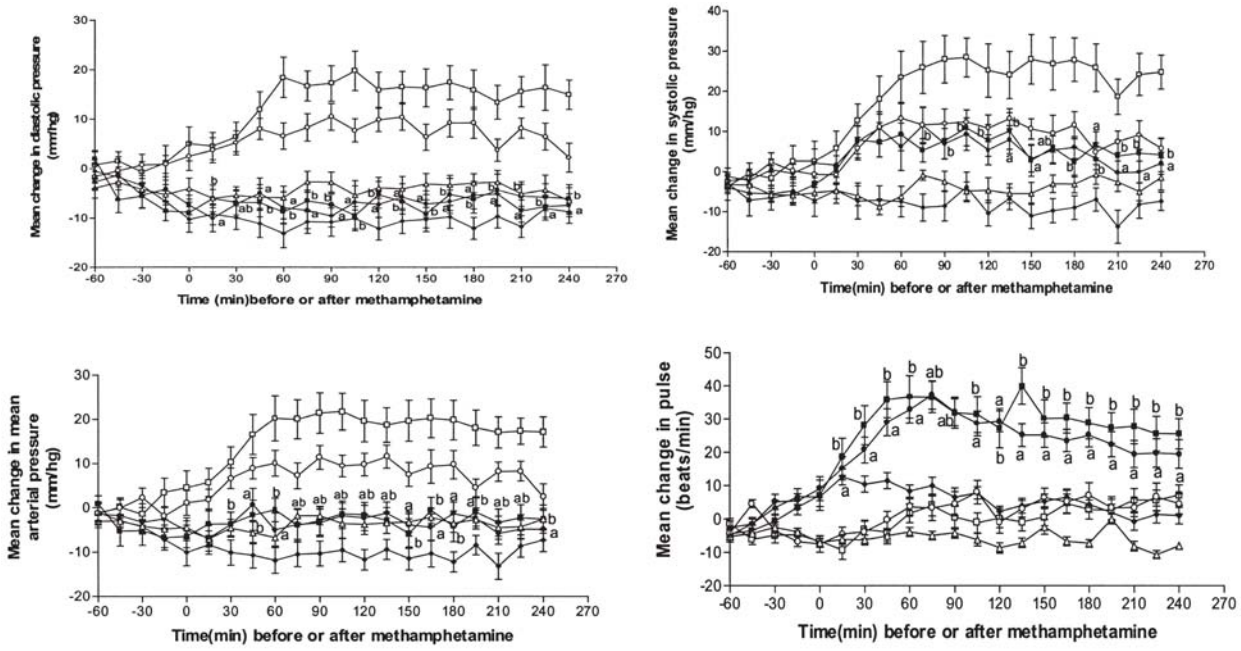
4. Endocrine Effects of Methamphetamine

Besser et al. (1969) examined the behavioral and psychomotor effects of methamphetamine and their relationships to plasma corticosteroid, adrenocorticotrophic hormone and growth hormone levels. Subjects were six healthy male volunteers, 20 to 29 years of age. The drug was administered intravenously via an indwelling catheter at two doses, 7.5 and 15 mg, at various times during the day. Results following methamphetamine administration were compared with those obtained after administration of a placebo. Treatments were allocated on a double-blind, crossover, randomized basis using a Latin square design. There was a seven-day interval between treatments for each subject. Dose-related increases in plasma corticosteroid levels were observed 30, 45 and 60 minutes after methamphetamine administration. The rise was most pronounced after evening administration of the drug. Growth hormone levels also rose in a dose-related fashion but the increase was statistically significant only at the higher dose.

Rees et al. (1970) examined the effects of methamphetamine on plasma corticosteroids and growth hormone in six normal adult male subjects ranging in age from 19 to 34 years. Subjects were pre-treated with an intravenous injection of thymoxamine (a relatively specific α adrenergic blocking agent), propranolol (a β adrenergic blocker) or placebo. Five minutes later, 15 mg (approximately 0.1 mg/kg) intravenous methamphetamine was administered. Blood samples were collected before and 15, 30, 45 and 60 minutes after methamphetamine administration for determination of plasma levels of growth hormone and corticosteroids. Treatments were administered at seven-day intervals using a double blind crossover method and a Latin square design. Methamphetamine alone produced a modest rise in plasma corticosteroids and growth hormone over the one-hour observation period. The rise in corticosteroids was prevented by prior administration of thymoxamine and enhanced by prior administration of propranolol. In contrast, the rise in growth hormone levels was enhanced by both thymoxamine and propranolol.

5. Cardiovascular and Sympathomimetic Effects of Methamphetamine

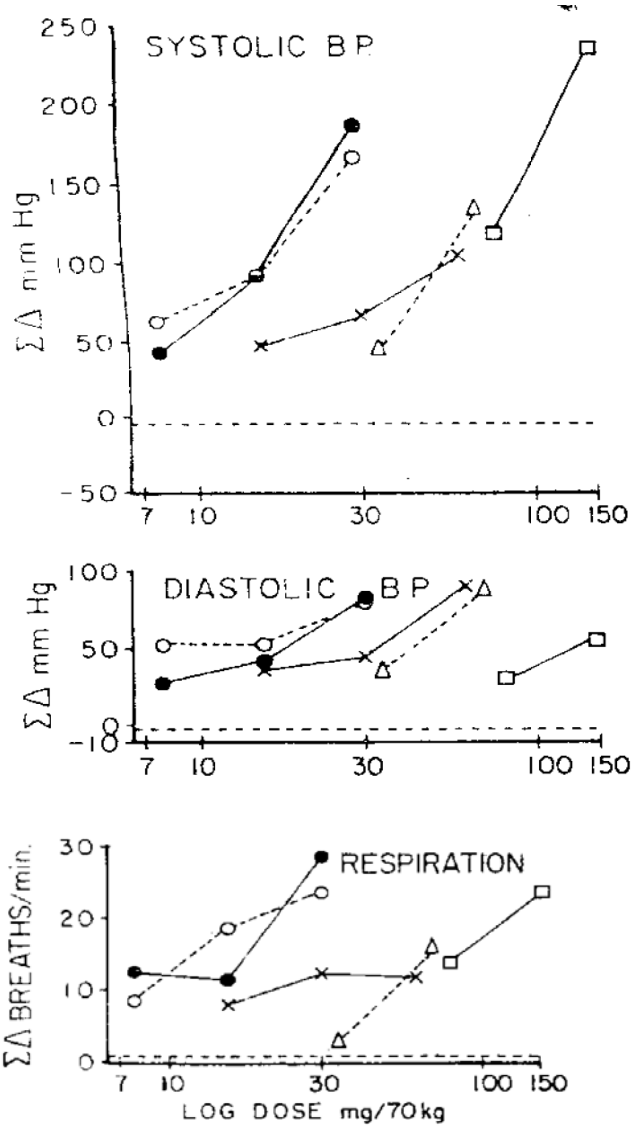
Johnson et al. (2000) examined the utility of isradipine in treating d-methamphetamine induced hypertension and changes in cognitive function. As described above, two doses of d-methamphetamine (0.21 and 0.42 mg/kg, oral) were evaluated in a placebo-controlled, double blind, Latin Square, cross-over design. d-Methamphetamine increased systolic and diastolic blood pressure, mean arterial pressure and pulse rate in a dose-dependent fashion. The drug also improved attention, accuracy of reasoning ability and performance on computerized cognitive functioning tasks. Cardiovascular changes are shown in the graphs below.



Data from Johnson et al. (2000). Methamphetamine-induced cardiovascular changes in 18 human subjects. Data points are mean ± SE. Placebo responses are shown by open triangles, low dose methamphetamine (0.21 mg/kg) responses are shown by open circles, and high dose methamphetamine (0.42 mg/kg) responses are shown by open squares.

Martin et al. (1971) evaluated the physiologic of methamphetamine and four other centrally acting sympathomimetic amines in 12 adult male prisoners. The drugs were administered subcutaneously in a 2 ml volume under double blind conditions. Baseline data were collected 30-60 minutes prior to drug administration. The drugs were administered subcutaneously in a 2 ml volume under double blind conditions. Physiologic and subjective effects were assessed at 30 minutes and 1, 2, 3, 4 and 8 hours thereafter.

Changes in respiration and systolic and diastolic blood pressure are shown in the graphs below. Note that changes in blood pressure and respiration are indicated as the summation of changes across all subjects. Methamphetamine produced a dose-related increase in systolic blood pressure, a slight increase in diastolic blood pressure, and a dose-related increase in the rate of respiration.



Data from Martin et al. (1971). Drug treatments represented are placebo (-----), amphetamine (●—●), methamphetamine (○---○), ephedrine (⊡—⊡), phenmetrazine (Δ---Δ) and methylphenidate (x—x).

In a study undertaken to test the suitability of methamphetamine as a drug for the treatment of narcolepsy, Mitler et al. (1993) evaluated the effectiveness of the drug in eight pairs of subjects, consisting of a narcoleptic and a control matched on the basis of age, sex, educational background and job. Treatment conditions (baseline, placebo, low and high doses of methamphetamine) were randomized and administered under double blind conditions. Each treatment condition was evaluated on four successive days followed by three days of washout. The total duration of the study was 28 days. The drug was administered once in the morning. Doses were 20 or 40-60 mg for narcoleptic patients and 5 or 10 mg for controls. Tests were conducted to assess daytime sleep tendency, nighttime sleep parameters, performance on a computer-based driving task, cardiovascular effects (blood pressure, pulse rate and respiration rate), and possible treatment-associated side effects.

In control and narcoleptic subjects, there were no treatment-related effects on systolic and diastolic blood pressure, pulse rate, or respiration rate. (Data reproduced below).

TABLE 6. *Measures of blood pressure, pulse rate and respiratory rate listed according to group and measure (vertically) and experimental condition (horizontally). ns: not significant*

	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 20 mg	High dose 40–60 mg	
Narcoleptics					
Systolic BP	122.8 ± 21.8	117.3 ± 19.3	115.8 ± 20.1	118.4 ± 19.4	ns
Diastolic BP	68.9 ± 15.7	66.1 ± 10.5	66.4 ± 10.4	70.9 ± 10.7	ns
Pulse rate	67.9 ± 3.6	70.8 ± 5.7	67.5 ± 7.0	71.8 ± 6.5	ns
Respiration rate	18.5 ± 3.3	18.3 ± 3.7	17.1 ± 3.5	17.8 ± 3.9	ns
	Experimental conditions				p-level of *F*-ratio for conditions
	Baseline	Placebo	Low dose 5 mg	High dose 10 mg	
Controls					
Systolic BP	124.6 ± 30.1	115.0 ± 6.7	115.4 ± 12.2	116.8 ± 8.5	ns
Diastolic BP	66.9 ± 6.3	64.6 ± 6.1	66.8 ± 10.5	67.1 ± 7.0	ns
Pulse rate	63.0 ± 7.9	63.0 ± 8.8	60.3 ± 75.8	63.3 ± 9.6	ns
Respiration rate	16.0 ± 3.6	17.0 ± 4.5	16.4 ± 2.6	17.9 ± 3.2	ns

Data from Mitler et al. (1993).

In general, possible treatment-related side effects were dose-dependent. These consisted primarily of central nervous system effects (nervousness, insomnia and headaches) and gastrointestinal effects (nausea, abdominal pain and loss of appetite) and dry mouth. According to the authors of the study, "No complaints were judged severe enough to necessitate medical intervention, termination of drug treatment or exclusion from the study. Likert scale intensity data revealed that the side effects were generally mild to moderate (Likert rating <7) and did not interfere with normal daily activity." Behavioral changes noted in both narcoleptic and control subjects were increased talkativeness and increased willingness to take on new projects at home and work. Side effects data from this study are reproduced below.

TABLE 7. *Number of narcoleptic and control subjects who reported possible treatment-associated side effects. Data are presented according to organ system (vertically) and experimental condition (horizontally)*

	Narcoleptics (n = 8)				Controls (n = 8)			
			LD	HD			LD	HD
Symptoms by system	BL	PL	20 mg	40–60 mg	BL	PL	5 mg	10 mg
Nervous								
Nervousness	0	0	2	2	0	0	1	2
Insomnia	0	0	2	5	0	0	0	3
Dizziness	0	0	1	0	0	0	0	1
Headache	1	0	3	4	0	0	1	2
Akathisia	0	0	2	3	0	0	0	1
Dyskinesia	0	0	0	0	0	0	0	1
Chest discomfort	0	0	1	1	0	0	0	1
Gastrointestinal								
Nausea	0	1	0	0	0	0	0	1
Abdominal pain	0	0	1	1	0	0	0	1
Loss of appetite	0	0	4	3	0	0	1	2
Weight loss	0	0	1	1	0	0	0	0
Eyes, ears, nose and throat								
Dry eyes	0	0	1	1	0	0	0	0
Dry mouth	0	0	0	3	0	0	1	4
Blurred vision	0	0	0	0	0	0	0	1
Difficulty in accommodation	0	0	0	0	0	0	0	0
Skin								
Pain	0	0	0	0	0	0	0	0
Itching	0	0	1	0	0	0	0	1
Peeling	0	0	0	0	0	0	0	0
Discoloration	0	0	0	0	0	0	0	0
Other								
Impotence (n = 3 males)	0	0	0	0	0	0	0	0
Libido change	0	0	0	0	0	0	0	0
Irritability	0	0	0	0	0	0	0	0

Data from Mitler et al. (1993).

6. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Amphetamine-Naïve Subjects

Schepers et al. (2003) evaluated the pharmacokinetics and pharmacodynamics of short-term administration of Desoxyn® Gradumet® (a sustained-release form of *d*-methamphetamine) in eight normal (amphetamine-naïve) individuals. Four males and four females participated in the study. Their average age was 35 ± 4 years (range 26-40 years) and their mean weight was 72 ± 18 kg (range 55-103 kg). All eight participants received the low dose regimen of methamphetamine (four daily oral doses of 10 mg, administered over a seven day period). Three weeks later, five individuals from the original group of eight received the high dose regimen of methamphetamine (four daily oral doses of 20 mg methamphetamine). Drugs were administered in gelatin capsules with lactose. Placebo capsules contained lactose only. All drug treatments were administered under subject-blind conditions. After administration of the drug, blood samples were collected for up to 24 hours and oral fluid samples were collected for up to 72 hours. Pharmacodynamic effects (systolic and diastolic blood pressure, heart rate, pupil diameter, core and skin temperature, respiratory rate and blood oxygen saturation) were evaluated for 12 hours following drug administration.

According to the report, dissolution tests of the Gradumet® formulation demonstrated that 20-40% of methamphetamine is released after 30 minutes, 35-55% after one hour, and 60-80% after four hours. It was not clear whether these data were generated by the authors or provided by Abbott Laboratories, the manufacturer of Desoxyn® Gradumet®.

Following administration of the first 10 mg dose, maximum plasma concentrations averaged 20.2 ± 6.4 µg/L, in very good agreement with results obtained by Perez-Reyes et al (1991a), discussed below. After the 20 mg dose, the average maximum plasma concentrations averaged 32.4 ± 7.7 µg/L. Plasma methamphetamine half-lives were 9.3 ± 3.7 and 11.1 ± 7.2 hours for the low and high dose, respectively, providing an overall mean half-life of 10.0 ± 5.2 hours. Oral fluid concentrations of methamphetamine were on average two-fold higher than those detected in plasma but were highly variable. In one subject, the concentration of methamphetamine in oral fluid exceeded 300 µg/L after the 10 mg dose.

Diastolic blood pressure and heart rate both showed significant dose-related increases following methamphetamine administration. Systolic blood pressure, core and skin temperature, blood oxygen saturation, and pupil diameter were not significantly altered by drug treatment.

Shappell et al. (1996) investigated the pharmacokinetics and pharmacodynamics of a single dose of methamphetamine administered in the morning or evening. Subjects were ten male Marine Corps officers ranging in age from 23 to 29 years. All were nonsmokers with a history of little or no alcohol use and were not taking any prescription medications at the time of the study. The subjects were divided into two groups of five each. They were administered 30 mg/70 kg oral d-methamphetamine hydrochloride in two sessions, the first starting at 6:30 AM and ending at 9:00 PM (day session; methamphetamine administered at 8:40 AM) and the second starting at 6:30 PM and ending at 9:00 AM (night session; methamphetamine administered at 8:40 PM). A crossover design was adopted with each subject serving as his own control. Cognitive ability, subjective fatigue and blood pressure were evaluated beginning 1.5 hours before drug administration and continued every half hour until 12.5 hours after administration. Over the same time period, blood and urine samples were collected for analysis of methamphetamine and one of its primary metabolites, amphetamine.

No differences in the day *vs.* night pharmacokinetics of orally administered methamphetamine were found. Apparent peak serum drug concentrations (mean ± standard deviation) were 94.1 ± 70.9 and 60.4 ± 16.9 ng/ml for the daytime and nighttime sessions, respectively. (Data reproduced below.) In comparison to results obtained by Schepers et al. (2003), higher peak blood concentrations were achieved in this study because (1) a higher dose was administered (30 mg *vs.* 10 and 20 mg) and (2) Schepers et al. evaluated the pharmacokinetics of a slow release formulation, which would be expected to reduce the rate of drug absorption and reduce peak blood levels. Apparent terminal elimination half-lives were 9.1 ± 4.0 and 10.8 ± 8.0 hours for the daytime and nighttime sessions, respectively, which is virtually identical to the half-lives reported by Schepers et al. (2003).

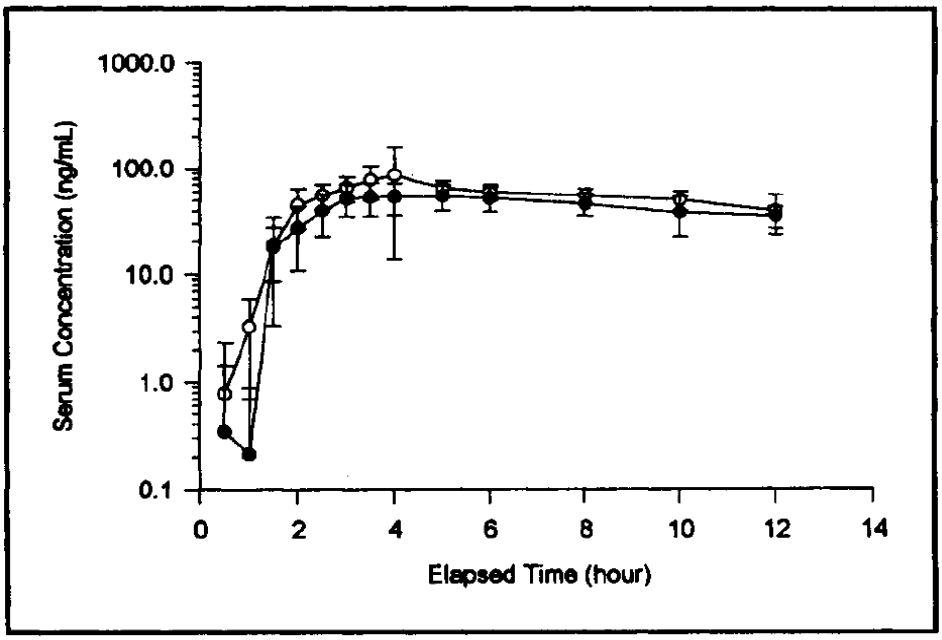
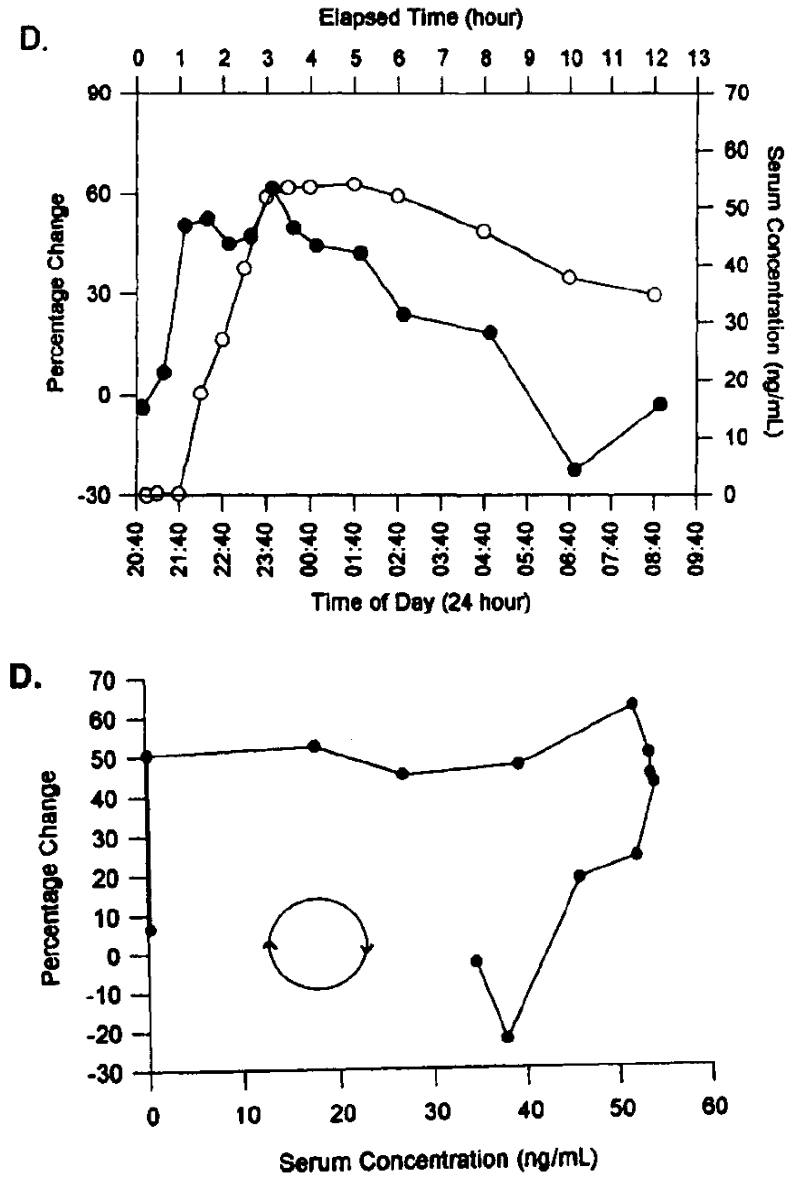


Figure 1. Logarithmic mean serum concentration of methamphetamine as a function of time after drug administration during the day (open circles) and night (filled circles).
Data from Shappell et al. (1996).

Methamphetamine significantly increased systolic blood pressure (25-30 mm Hg increase, baseline to peak) and diastolic blood pressure (7-13 mm Hg increase). Maximal changes in both parameters were observed before the maximum serum concentrations of methamphetamine were attained. Daytime dosing produced improvements in cognitive performance and reduced subjective fatigue, but these effects were suppressed during a circadian trough, which occurred at approximately 4:30 AM (eight hours into the night session). However, improved cognitive performance and reduced subjective fatigue were *not* correlated with serum concentrations of methamphetamine. For example, nighttime fatigue declined markedly as serum methamphetamine concentrations rose, but it set in once again later on in the study even though serum concentrations of the drug remained above 30 ng/ml. (Data reproduced below.) The authors used the term "clockwise hysteresis loop" to describe this phenomenon, where less effect was observed at the same serum concentration at later time points.



Data from Shappell et al. (1996). Upper graph: Subjective fatigue, mean percentage change from baseline (●) and serum methamphetamine concentration (○) as a function of time after nighttime drug administration. Lower graph: subjective fatigue, mean percentage change from baseline (●) as a function of serum methamphetamine concentration, demonstrating discordance ("clockwise hysteresis loop") between subjective effects and serum methamphetamine level.

7. Pharmacokinetics of Methamphetamine and the Time Course of Physiological and Subjective Effects in Recreational Amphetamine Users

Perez-Reyes et al. (1991a) evaluated the pharmacokinetics of methamphetamine in six male volunteers who had previously used amphetamines for recreational purposes. Average lifetime use of amphetamines (amphetamine, dextroamphetamine and methamphetamine) was 8 ± 3.9 times. However, subjects were asked to abstain from using amphetamines or any other illegal drug two weeks prior to commencement of the study and throughout its duration. Compliance with this request was verified by analysis

of daily urine samples. The age of the subjects was 24 ± 2 years, and they weighed 72.6 ± 1.1 kg.

Subjects were administered daily oral doses of 10 mg d-methamphetamine hydrochloride in a sustained-release formulation (Desoxyn® Gradumet®, Abbott Laboratories) for 13 consecutive days (days 2-14 of the study). On days 1 and 15, the subjects were challenged with 0.125 mg/kg mg of deuterated methamphetamine hydrochloride to investigate both the pharmacological effects and the disposition of methamphetamine. Deuterated methamphetamine was administered orally in gelatin capsules and was *not* prepared as a slow release formulation. The drug was deuterated in order to differentiate plasma levels of the challenge doses from the residual levels undeuterated methamphetamine remaining after the daily doses. Subjective drug effects were evaluated by having the subjects rate the effects of the drug using a visual analog scale (VAS). The scale ranged from 0 to 100, with 0 representing no drug effects and 100 representing the "highest" they had ever experienced after using amphetamines. Cardiovascular parameters were examined prior to methamphetamine administration (i.e., baseline conditions) and at 2.5 and 3.5 hours after administration of the drug.

The time course of plasma concentrations of deuterated methamphetamine was virtually identical on test days 1 and 15. The peak plasma concentration of methamphetamine was approximately 22 ng/ml and was achieved approximately three hours after dosing. After 10 hours, the plasma concentration was approximately 15 ng/ml.

Over the same time period, the plasma concentration of non-deuterated methamphetamine, administered once/day on the previous 13 days as a sustained release formulation, remained relatively stable. The initial plasma concentration (measured before administration of the challenge dose of deuterated methamphetamine) was approximately 5 ng/ml, and declined slowly to approximately 3 ng/ml over the ensuing 10 hours. After 48 hours, the drug was no longer detected in plasma.

Consistent with the plasma concentrations of deuterated methamphetamine obtained on challenge days 1 and 15, there were no differences in the subjects' ratings of a drug related "high" at the beginning and end of the study. However, in comparison to results obtained on day 1, there was a significant decrease in the acceleration of heart rate produced in response to the methamphetamine challenge on day 15.

According to the authors, "These findings indicate that the disposition of methamphetamine and its subjective effects were not altered by this [13 day] period of daily exposure to a low dose of the drug. In contrast, tolerance to the heart-rate accelerating effect was observed."

A similar study was conducted on a different group of subjects by several members of the same research team (Cook et al., 1992). The study design was virtually identical to that adopted by Perez-Reyes et al. (1991): on day 1, a single oral dose of deuterated methamphetamine was administered; on days 2-14, a single 10 mg tablet of Desoxyn® Gradumet® was administered orally each morning; and on day 15, a second challenge dose of deuterated methamphetamine was administered orally. In this study, however, two dose levels of deuterated methamphetamine were used: 0.125 and 0.250 mg/kg. Subjects were eight paid, informed volunteers who had previously used amphetamines

for recreational purposes. All were required to abstain from using amphetamines or any other drug for two weeks prior the beginning of the experiment. Samples of blood, saliva and urine were collected and analyzed for methamphetamine and amphetamine.

The average elimination half-life of methamphetamine was 10.1 hours (range: 6.4 – 15.1 hours). Evaluation of methamphetamine pharmacokinetics following the lower challenge dose (0.125 mg/kg) of the deuterated drug revealed no statistically significant differences. However, at the higher challenge dose (0.250 mg/kg), the peak plasma concentration was slightly but significantly greater at the end of the 13-day oral dosing period than it was at the beginning of the study. (Data reproduced below.) There was no evidence that sub-chronic treatment with low doses of methamphetamine resulted in induction of metabolism.

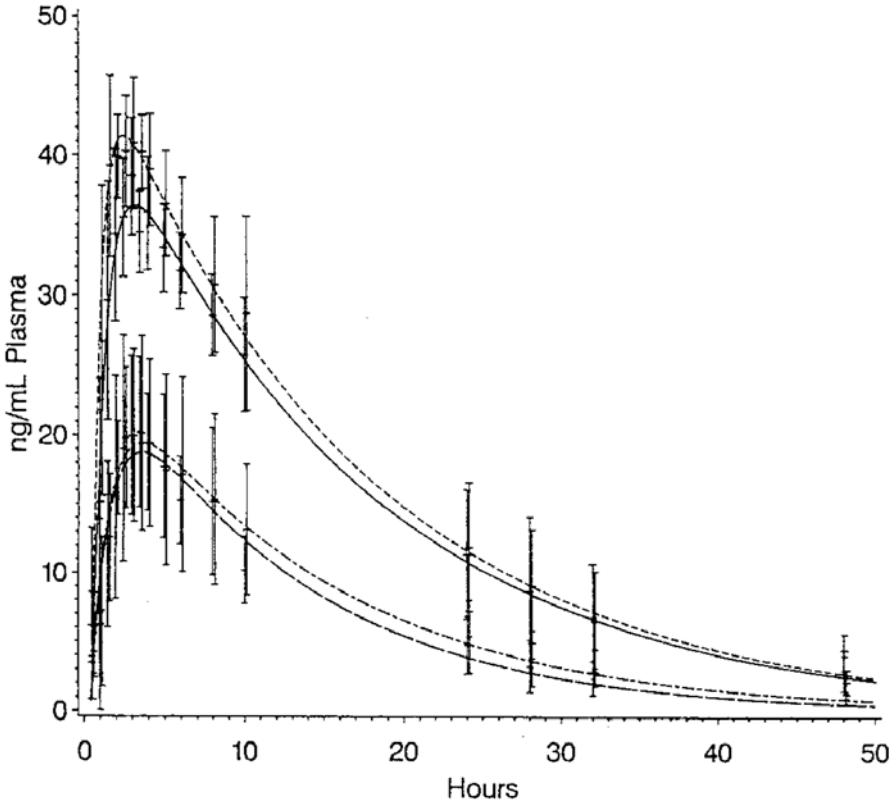


FIG. 1. *Concentration of S-methamphetamine-d_3 in plasma.*

Vertical bars show mean ± SD. *Curves* are computer fit of average pharmacokinetic data. *Curves* are day 1, 0.125 mg/kg dose (– –); day 15, 0.125 mg/kg (– - – -); and day 1, 0.250 mg/kg (——); day 15, 0.250 mg/kg(– – – –).

Data from Cook et al. (1992).

In a subsequent report (Cook et al., 1993), the authors used the data from this study to estimate an average oral bioavailability of 67.2 ± 3.1%. This value applies to methamphetamine hydrochloride, not the sustained release form of the drug (Desoxyn® Gradumet®) that the subjects received on days 2-13 of the study.

Saliva concentrations of deuterated methamphetamine were on average 7.8 times higher than those detected in plasma. The correlation between plasma and saliva concentrations was modest ($r^2 = 0.62$), and large inter-individual variation was observed. These results suggest that saliva concentrations, which are frequently used for drug testing purposes, cannot reliably be used to predict plasma concentrations.

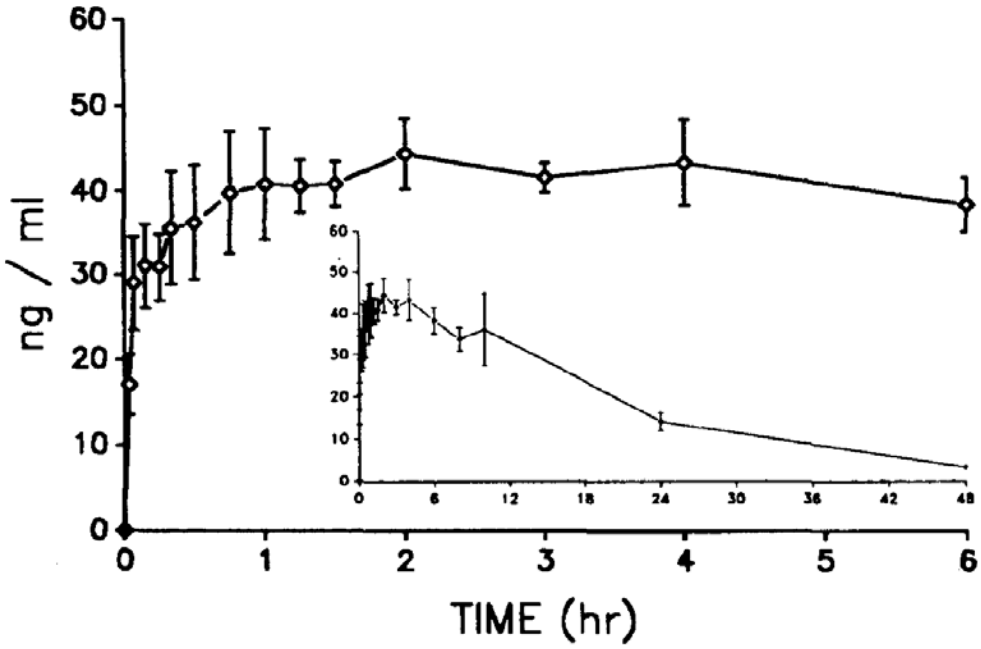
The same researcher team also examined the clinical effects of inhaled methamphetamine vapor in recreational amphetamine users (Perez-Reyes et al., 1991b). Six healthy male volunteers (age 26.7 ± 1.7 years, weight 84.1 ± 5.2 kg) participated in the study. All had significant experience using amphetamines [17.7 ± 4.3 times (range 6-35)]. Methamphetamine vapor was produced using a glass pipe that was placed in an aluminum block pre-heated to 305 ºC. Preliminary studies with this setup demonstrated that pyrolytic degradation of the drug was negligible. The pipe was capped to prevent escape of methamphetamine vapors to the atmosphere. Subjects were asked to rate their subjective impression of a methamphetamine "high" using a visual analog scale (described above), and cardiovascular effects (heart rate, blood pressure, systemic vascular resistance and indices of myocardial contractility) were determined at various intervals up to three hours after vapor inhalation. Blood samples were collected up to 48 hours after inhalation and analyzed for methamphetamine.

Dose range-finding studies were conducted to investigate the subjective and cardiovascular effects produced by progressively increasing doses of methamphetamine (20, 25, 30 and 40 mg). According to the authors,

> *…20 and 25 mg doses produced minimal subjective and cardiovascular effects, while the 30 mg dose produced more distinct and sustained effects. However, on one occasion in which a 40 mg dose was administered, it produced extreme subjective effects characterized by feelings of omnipotence and omniscience that were highly seductive and frightening…[this subject] experienced hypomanic symptoms for approximately two hours, intense craving for further dosing, decreased appetite, difficulty in concentration, memory lapses, and insomnia.*

Consequently, 30 mg was selected as the dose to use for the investigation to produce moderate subjective effects. Subsequent analysis of the amount of drug remaining in the pipe after inhalation indicated that the actual inhaled dose was 22.0 ± 0.3 mg (range: 20.7 – 22.6 mg), or 73% of the amount placed in the pipe. Using the assumption that the other three doses were similarly reduced by adherence to the pipe, it may be concluded that inhalation of 14.6 – 18.3 mg methamphetamine produced minimal subjective effects in this particular cohort of subjects, and 29.2 mg produced extremely euphoric (and thereby potentially reinforcing) subjective effects. Based on an average body weight of 84.1 kg, the delivered doses used in this study were equivalent to 0.17, 0.22, 0.26 and 0.35 mg/kg.

Methamphetamine levels in plasma rose rapidly, reaching approximately 30 ng/ml within the first five minutes after inhalation and continuing to rise during the subsequent two hours. Peak plasma concentrations reached 45 ng/ml and remained above 30 ng/ml for 10 hours after drug administration (data reproduced below).



Data from Perez-Reyes et al. (1991b). Time course of plasma methamphetamine concentrations in six subjects following vapor inhalation (smoking) of the drug. Data points are means ± SEM.

Subjective ratings of methamphetamine "high" reached a peak at 18 ± 2 minutes after the beginning of inhalation of the drug. Subjective effects completely subsided within eight hours even though plasma levels of the methamphetamine were still in excess of 30 ng/ml. The authors believed this finding was suggestive of the development of acute tolerance (tachyphylaxis).

Peak changes in cardiovascular parameters generally appeared within 10-20 minutes of inhalation. Heart rate, systolic and diastolic blood pressure, stroke volume, cardiac output, and myocardial contractility were all increased, while systemic vascular resistance was decreased. The authors of the study suggested that the pattern of cardiovascular effects observed in this study resembled those produced by circulating norepinephrine, and was probably a result of methamphetamine-induced release of norepinephrine from the adrenal medulla. In support of this hypothesis, they cited the 1971 study by Martin et al., who observed that subcutaneous injection of methamphetamine caused a significant dose-related increase in urinary excretion of epinephrine.

In a subsequent report (Cook et al., 1993), the authors used the data from this study to estimate an average inhalation bioavailability of 90.3% for smoked methamphetamine hydrochloride.

8. Assessment of Euphoric and Dysphoric Effects of Methamphetamine

(Johnson et al., 1999b) evaluated the effects of isradipine on the positive subjective effects associated with the abuse liability of methamphetamine in the same cohort of 18

subjects discussed above.[26] Doses (0.21 and 0.42 mg/kg, oral) and experimental design were the same as described above. Prior to commencement of the experiments, subjects were trained to use the Addiction Research Center Inventory (ARCI) and Visual Analog Scales of Mood (VAS-M) to assess their subjective psychological status. The ARCI incorporates five sub-scales that reflect the subjective effects of different classes of abused substances: Amphetamine and Benzedrine group (A and BG scales; stimulation), Morphine-Benzedrine group (MBG scale; euphoria), Pentobarbital, Chlorpromazine and Alcohol group ((PCAG scale; sedation), and Lysergic Acid Diethylamide (LSD scale; dysphoria). VAS-M provided a means of scoring subjective ratings ranging from "not at all" to "extremely" for positive mood items (e.g., "cheerful," "feel good," "alert"), negative mood items ("lethargy" and "not liking drug effects") and craving ratings ("urge to use" and "if offered I could refuse").

d-Methamphetamine generally produced dose-dependent measures of both stimulation and mood. At both doses maximal euphoric effects were reported two hours after administration of the drug. As noted above, crushing the methamphetamine (Desoxyn®) tablets prior to administration to the subjects may have enhanced the rate of drug absorption, thereby affecting the time course of subjective effects.

Wachtel et al. (2002) evaluated the haloperidol, a drug that primarily blocks D_2 dopamine receptors, and risperidone, a drug that blocks both dopamine and serotonin receptors, on the physiological effects and subjective responses to a single 20 mg oral dose of methamphetamine. Subjects were male (n=22) and female (n=14) volunteers ranging in age from 18 to 35 years.[27] The study was a double-blind, placebo-controlled, within-subject, 2 x 2 repeated measures design. The subjects were divided into two groups of 18 subjects each: haloperidol (3 mg) was administered to one group and risperidone (0.75 mg) was administered to the other. Thus, each subject participated in four test sessions, receiving all combinations of antagonist or placebo followed by methamphetamine or placebo. Sessions were separated by at least one week. Methamphetamine was administered in size 00 gelatin capsules with dextrose filler. However, the manufacturer of the drug and its physical form (tablet or powder) were not specified in the report. Identical placebo capsules contained dextrose only.

According to the authors, a 20 mg oral dose of methamphetamine was selected "…to match previous studies with *d*-amphetamine on prototypical subjective, behavioral and physiological measures." Furthermore, "Methamphetamine is roughly equipotent with *d*-amphetamine on most measures in humans, and it substitutes readily for *d*-amphetamine in drug procedures in this dose range."

Methamphetamine alone produced stimulant effects similar to those that have been observed in human subjects who were administered *d*-amphetamine. Effects peaked 1-2 hours after administration of the drug and declined over the subsequent 3-4 hours. Responses on the 49-item Addiction Research Center Inventory (ARCI) Amphetamine (ARCI-A) and Benzedrine Group (ARCI-BG) scales (both of which are indices of stimulant effects) as well as the Morphine-Benzedrine (ARCI-MBG) scale (an index of

[26] See Johnson et al. (1999a), summarized on pages 26-27, and Johnson et al (2000), summarized on pages 33-34.

[27] Details regarding the weight, sex, race/ethnicity, education, current drug use (including alcohol and cigarettes) and lifetime drug use of all subjects were provided in the report.

euphoria) were highly statistically significant. (ARCI-A data reproduced below.) Systolic blood pressure and heart rate were significantly elevated in both groups. Neither haloperidol nor risperidone consistently reduced the acute euphoric and reinforcing effects of methamphetamine, suggesting that the reinforcing subjective effects of methamphetamine in humans are not mediated solely via dopamine and serotonin receptors.

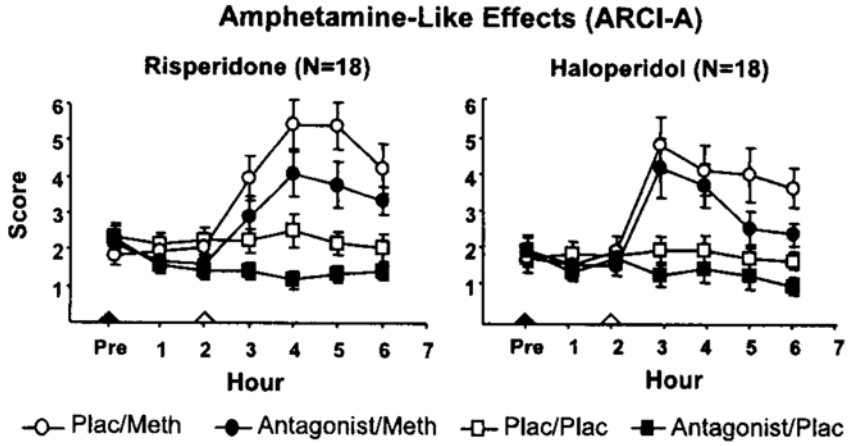


Fig. 1. Mean (±SEM) scores on the ARCI A scale, a measure of amphetamine-like effects. Circles represent methamphetamine conditions and filled symbols represent antagonist pretreatment (risperidone or haloperidol). Filled triangles on the x-axis indicate when the pretreatment capsule was administered; open triangles indicate when the methamphetamine or placebo was administered. In the Risperidone experiment on this measure there were main effects of both risperidone and methamphetamine, but no interaction between the two. In the Haloperidol experiment on this measure there was a main effect of methamphetamine but no effect of haloperidol.

Data from Wachtel et al. (2002). ARCI-A: Addiction Research Center Inventory scale that reflects the effects of Amphetamine drugs (stimulation).

In a similar comprehensive investigation of the subjective effects of methamphetamine, Söderpalm et al. (2003) conducted a study to determine whether acute stress alters the subjective responses to a single low (10 mg) oral dose of methamphetamine (Desoxyn®, Abbott Laboratories) in adult males. The drug was dissolved in 20 ml water and 20 ml orange juice to enhance absorption and ensure rapid onset of effects. Twenty-eight healthy men, 18-24 years of age with an average body weight of 73 kg, were recruited to participate the study. They were randomly divided into two groups that received methamphetamine (n=16) or placebo (n=12) on two successive sessions, separated by a minimum of 48 hours. Each participant was subjected to stress during one session and no stress during the other, in random order. Methamphetamine or placebo was administered immediately after the stress or no stress session. Acute stress was induced using a modified version of the Trier Social Stress Test[28], a psychosocial stressor that has been

[28] In this procedure, subjects were required to face two observers and count backwards from 1754 in intervals of 13 for 10 minutes. They were informed that the test was being recorded and their performance would be analyzed for accuracy. If they hesitated or stopped, they were instructed to continue. Four subjects were tested together, and they were called upon in random order to perform the arithmetic task.

demonstrated to reliably induce cardiovascular and endocrine responses, increase subjective ratings of stress, and increase plasma levels of the adrenal steroid corticosterone. Thus there were four experimental conditions: stress + methamphetamine, no stress + methamphetamine, stress + placebo, and no stress + placebo. Subjective mood effects, salivary cortisol levels and cardiovascular effects (blood pressure and heart rate) were assessed periodically for 90 minutes after drug administration.

Methamphetamine increased feelings of stimulation and decreased feelings of fatigue and sedation. (Data reproduced below.) These effects became apparent as early as 20 minutes after drug administration and generally peaked at 60-90 minutes, although this is difficult to conclude definitively because no data were collected beyond 90 minutes. Stress appeared to have little effect on the subjective responses to methamphetamine, particularly at the later time points. For example, methamphetamine increased scores on the ARCI MBG scale (euphoric effects) and the A scales (stimulant effects), and reduced scores on the PCAG scale (sedative effects) at multiple post-drug time points in both the stress and no stress sessions. Similarly, 30 to 90 minutes after drug administration, methamphetamine produced several of its prototypical subjective effects (e.g., increased ratings of "outgoing," "stimulated," "lively," and "want more drug") and increased heart rate irrespective of whether or not the subjects had been subjected psychosocial stress. Nevertheless, it is clear that a number of methamphetamine's characteristic subjective effects were only observed during the no stress session (e.g., increased ratings of "jittery," "alert," "on edge," and "focused," as well as increased scores on the ARCI BG scale (stimulant effects).

Table 3 Times (in min after stress) at which significant differences (*t*-tests) were obtained between stress and no stress within the groups (*columns 3* and *4*), or between the groups on either the stress or no stress sessions (*columns 1* and *2*). Letters denote the direction of the differences. *M* METH, *P* PLAC, *S* Stress, *NS* No stress

Dependent measures	Stress METH vs PLAC	No stress METH vs PLAC	METH Stress vs No stress	PLAC Stress vs No stress
Salivary cortisol	–	–	S>NS, 20*	S>NS, 0**,20***, 40*
Systolic BP	–	M>P, 40**, 60*, 90*	S>NS, 0*	S>NS, 0*
Diastolic BP	–	–	S>NS, 0*	S>NS, 0*
Heart rate	M>P, 90*	M>P, 60*, 90**	S>NS, 0*	S>NS, 0*, 20*, 60*
Like drug	M>P, 60*, 90*	–	–	–
Want more drug	M>P, 20*, 40*, 90*	M>P, 60*	S>NS, 20*	–
Energetic	P>M, 20*, 40*	M>P, 60*	NS>S, 20*, 40*	–
Sedative	M>P, 20*, 40*	–	S>NS, 60*	–
Anxious	–	–	S>NS, 0**	S>NS, 0*, 20*
Cheerful	M>P, 60*, 90*	–	–	–
Restless	–	P>M, 20**	–	–
Slow	M>P, 40*	–	–	–
Dreamy	M>P, 20*, 40*	–	S>NS, 20*	–
Outgoing	M>P, 40*, 60***, 90***	M>P, 40*, 60*, 90**	–	–
Drowsy	–	P>M, 60*, 90*	–	–
Focused	–	M>P, 40**, 60**, 90*	–	–
Heavy	M>P, 40*	–	–	NS>S, 40*
Stimulated	M>P, 60*, 90***	M>P, 60*, 90*	–	–
Peace	M>P, 20*, 60*, 90*	–	–	–
Tired	P>M, 60*	P>M, 60*, 90*	S>NS, 20*	–
Sluggish	–	P>M, 60*	–	NS>S, 60*
Lively	M>P, 60*, 90*	M>P, 90*	–	–
Jittery	–	M>P, 20*, 90**	–	–
Alert	–	M>P, 60*, 90*	–	–
On edge	–	M>P, 20*	–	–
Worn out	–	P>M, 60*	–	NS>S, 40*
Calm	–	P>M, 40*	NS>S, 0*	NS>S, 0**, 20*, 60*, 90*
Nervous	–	–	S>NS, 0*	S>NS, 0**
Content	M>P, 60*	P>M, 20**	–	NS>S, 20*, 40*, 60**, 90*
Relaxed	–	P>M, 20**	–	NS>S, 20**, 40*, 90*
Happy	M>P, 60**	–	–	–
Uneasy	–	–	–	NS>S, 0**
Mellow	–	–	–	NS>S, 40*, 90*
ARCI A	M>P, 60*, 90**	M>P, 60*	–	NS>S, 90*
ARCI BG	–	M>P, 60*, 90*	NS>S, 20**, 40*	–
ARCI MBG	M>P, 40*, 60**, 90**	M>P, 60*, 90*	–	–
ARCI PCAG	P>M, 90**	P>M, 20*, 60**, 90*	–	–

*$P<0.05$, **$P<0.01$, ***$P<0.001$

Data from Söderpalm et al. (2003). ARCI: Addiction Research Center Inventory scales, consisting of 49 true or false questions, that reflect effects of Amphetamine (A) and Benzedrine Group (BG) drugs (stimulation), Morphine-Benzedrine Group (MBG) drugs (euphoria), and Pentobarbital-Chlorpromazine-Alcohol Group (PCAG) drugs (sedation). Subjective mood effects were evaluated using visual analog scales [ranging from "not at all" (0) to "extremely" (100)] to score each participant's feelings in relation to each of 30 adjectives.

9. Effects of Methamphetamine on Psychomotor Performance, Resistance to Fatigue, Decision Making and Memory

Shappell et al. (1992) examined the capacity of a single low dose of d-methamphetamine (10 mg/70kg, or 0.14 mg/kg) to ameliorate the detrimental effects of simulated sustained flights operations (SUSOPs) in 13 male U.S. Marine Corps commissioned officers, 22-28 years of age. Twelve control subjects received a placebo. The study was conducted under double blind conditions, and diet was strictly controlled. The SUSOP scenario consisted of a 9-hour planning session followed by 4 hours of rest and a 14-hour mission. After 6 hours of rest, the same 9 hour work /4 hour rest /14 hour work pattern was repeated. Methamphetamine was administered 4 hours and 20 minutes into the second "mission." As the simulated SUSOP scenario progressed, control subjects appeared to shift from a conservative to a more risky decision strategy. Administration of methamphetamine reduced subjective fatigue, improved scores on a generic performance assessment battery, and reduced apparent risky behavior on two spatial memory tasks.

A similar study was conducted by Stanny et al. (1993) to evaluate the effects of a single dose of d-methamphetamine hydrochloride on fatigue-induced deficits in long-and short-term memory. Thirteen subjects, all male Navy and Marine aviation candidates, participated in this study. All subjects were extensively trained to perform tasks that required long-and short-term memory. Performance on these tasks was assessed at 90-minute intervals over a 13.5-hour sustained performance session, beginning at 7:30 PM and ending the following day at 9:00 AM. At 1:16 AM, seven received a single capsule containing 10 mg/70 kg methamphetamine in cornstarch filler. Six received a placebo, identical capsules containing cornstarch alone. The study was conducted under double blind conditions.

Performance (accuracy) on both tasks declined during the night. Methamphetamine reversed the decline in performance and improved decision speed within two hours of administration of the drug. However, improved performance was not a result of risky, impulsive responding, since there was an absence of any effect on impulsive responses ("fast guesses"). The positive drug effects were maintained through the remainder of testing, about seven hours after drug administration.

Wiegmann et al. (1996) examined the effects of methamphetamine on vigilance and tracking in a 13.5-hour sustained-performance session. Subjects were male naval aviation candidates 24 ± 1.4 years of age weighing 79.7 ± 9.3 kg (mean ± SD). Three groups of ten subjects each were evaluated after administration of a placebo, 5 mg/70 kg methamphetamine or 10 mg/70 kg methamphetamine. Treatments were administered under double blind conditions.

Subjects were trained on two computer-administered objective performance tasks, a high event rate vigilance (running memory) task and a two-dimensional compensatory tracking task, for four days prior to the sustained performance session. The sustained performance session began at 7:30 PM on day of the last practice session and ended at 7:00 AM the following morning. The session consisted of nine testing blocks spaced 90 minutes apart, and the drug or placebo was administered approximately halfway between the fourth and fifth block.

In the placebo group, performance on both tests degraded markedly during the sustained performance session: response accuracy declined and the rate of non-responses (lapses) and tracking errors increased. However, within approximately three hours of drug administration, methamphetamine reversed these deteriorations. Furthermore, at this point in the session, the two doses of the drug appeared to be equally effective. Nevertheless, by the end of session, the effects of the 5-mg dose had disappeared while the 10-mg dose continued to be effective. (Example data from the tracking task are reproduced below.)

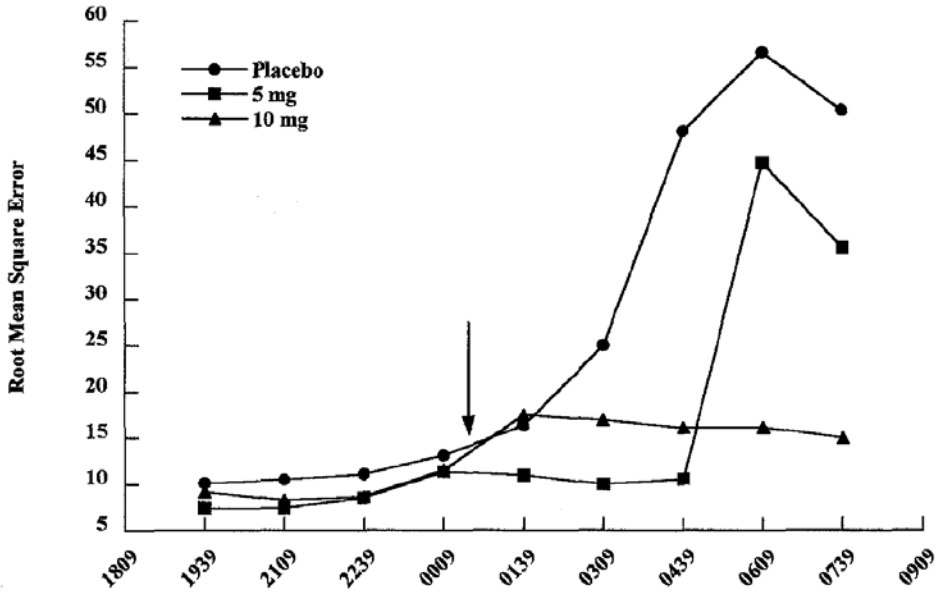


FIGURE 4 Tracking error versus time for the placebo and amphetamine groups. The arrow indicates drug administration.

Data from Wiegmann et al. (1996). In the two-dimensional tracking task, subjects were required to use a joystick to compensate for random directional changes in a continuously moving cursor displayed on a computer screen. The objective was to keep the cursor's *X-Y* position centered on a set of crosshairs in the middle of the screen. This task lasted about 9 minutes.

Mewaldt and Ghonheim (1979) evaluated the effects of physostigmine, scopolamine and methamphetamine on memory in human subjects. Subjects ranged in age from 18 to 32 years; average age was 22.6. Two doses of methamphetamine (0.2 and 0.3 mg/kg) were each administered intramuscularly to five subjects. Treatments were determined by randomized block procedure, and drugs were administered under double blind conditions. Following administration of the drug, subjects were administered a subjective rating questionnaire and several tests requiring immediate recall, delayed recall, and delayed recognition. Both doses of methamphetamine produced feelings of mental and physical arousal and generally increased feelings of happiness and friendliness or extroversion. The drug had no effect on retrieval of information learned prior to injection, and performance on two immediate recall tasks was similarly unaffected. In contrast, methamphetamine produced significant improvement in delayed recall of information that was acquired while the subjects were under the influence of the drug. However, the drug also produced a large increase in incorrect recall of words learned after injection. According to the authors of the study, the latter effects may reflect a change in the subjects' response strategy, i.e., improvement in both correct and incorrect recall may have been an artifact of improved confidence and reduced inhibition of recall.

10. Utilization of MRI to Identify Brain Regions Affected by Methamphetamine: Correlation with Subjective Effects

Völlm et al. (2004) utilized functional magnetic resonance imaging (fMRI) to identify areas of the brain that become activated as a result of methamphetamine administration in drug-naïve subjects. Subjects were healthy volunteers (four female, three male, average

age 29 years) with no history of psychostimulant use. The study was a single-blind within-subjects design. Baseline imaging and behavioral ratings were established during a 10-15 minute period of i.v. saline infusion. Thereafter, methamphetamine (0.15 mg/kg) was administered intravenously (i.v.) over a 1-minute period. According to the authors, "The choice of this specific dose was based on pilot data obtained from drug-naïve volunteers where it was established as the smallest i.v. dose that reliably separated the effects of methamphetamine from placebo on subjective ratings." The entire session lasted 41 minutes (i.e., 26-31 minutes after infusion of the drug). During this period, fMRI images were obtained and subjects rated themselves for the subjective experience of "mind racing" at one-minute intervals. Subjective ratings ranged from 0 (no mind racing) to 4 (high), and a clear description of the term "mind racing" was provided to the subjects.[29]

All subjects experienced an increase in "mind racing" within 2-3 minutes of i.v. methamphetamine infusion. Peak response occurred 10-15 minutes after the infusion. By the end of the session, subjective ratings had dropped significantly. (Data reproduced below.) Post-session interviews indicated that the subjects experienced the subjective effects of the drug as positive and rewarding.

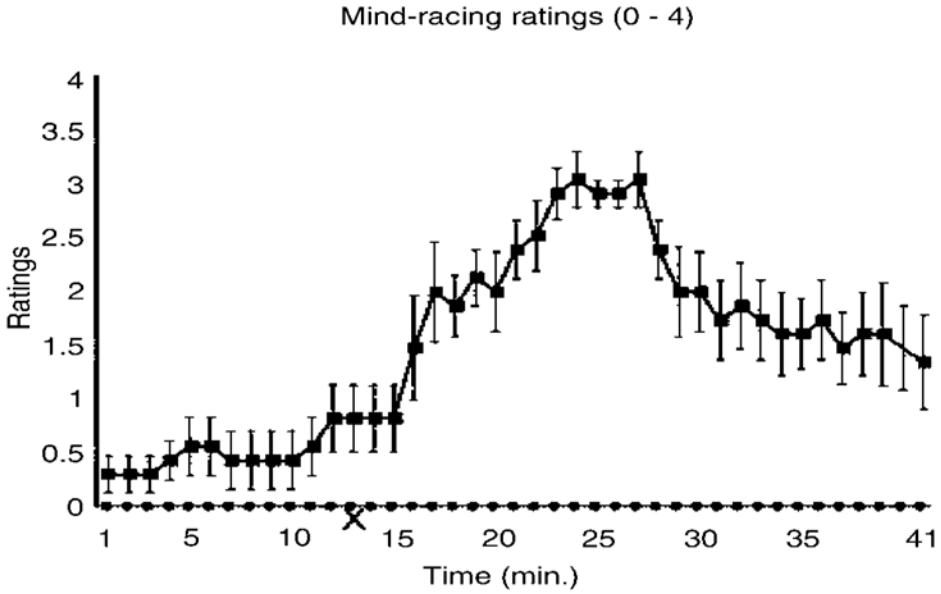


Figure 1 Averaged (mean ± SEM) behavioral ('mind racing') ratings given by subjects across the experiment. The 'X' in the time axis shows the average time of the amphetamine infusion.

Data from Völlm et al. (2004). (In the figure legend, "amphetamine" actually refers to methamphetamine.)

fMRI imaging demonstrated activation of the medial orbitofrontal cortex, the rostral portion of the anterior cingulated cortex and the ventral striatum. (fMRI images reproduced below.) Activations of the latter two regions correlated with ratings of "mind

[29] Specifically, "Mind racing is a condition you would not normally experience in day to day life. It is a state where your thoughts run far too quickly as if they were racing. One thought is replaced by another very quickly and it is difficult to hold on to your thoughts. You might have experienced a similar condition when you were very anxious or excited."

racing." Activations of the medial orbitofrontal cortex were observed during the entire post-infusion period and were independent of any motor-related activity (i.e., responses required to make subjective ratings). The authors suggested that these results provide evidence of activation of classical reward circuitry in the brain, and that activation of the orbitofrontal cortex may play a central role in drug reinforcement and the development of drug addiction.

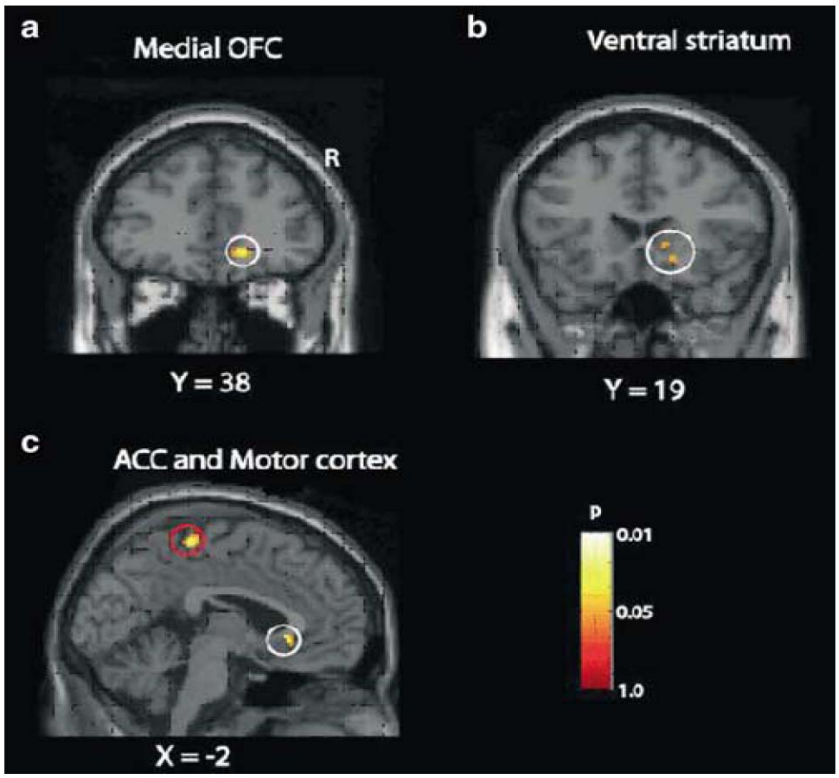


Figure 2 Results of the comparison Amphetamine–Saline. Activations (shown within the white circles) were found in (a) the medial orbitofrontal cortex, (b) ventral striatum, and (c) anterior cingulate cortex, and motor cortex (red circle). The *p*-values shown are with the small volume correction procedure (SVC, see 'Materials and methods').

Data from Völlm et al. (2004). (In the figure legend, "amphetamine" actually refers to methamphetamine.)

11. Studies Evaluating the Use of Methamphetamine to Treat Children for Enuresis

Young and Turner (1965) conducted a study to test the hypothesis that stimulant drugs would facilitate conditioning (negative reinforcement) in the treatment of nocturnal enuresis (bed wetting) in children. As summarized in the table below, 299 children 4-15 years of age were placed in one of three treatment groups.

Treatment Groups:	n	Mean Age (years)	Duration (months)
Conditioning alone	105	8.1	2.2
Conditioning + Dexedrine (d-amphetamine)	84	8.0	2.0
Conditioning + Methedrine (d-methamphetamine)	110	7.1	1.9

In conditioning treatment, a buzzer alarm is triggered by the discharge of urine onto an electronic detector placed under the sleeping child. The alarm wakens the child very soon after enuresis begins and therefore serves as negative reinforcement for bed wetting. Successful treatment was defined as 14 consecutive "dry" nights. The average treatment duration for all three groups was approximately two months, although some children were treated for as long as four months. If a child had not achieved the criterion for success after four months, the case was considered a failure.

The groups were not matched according to sex. In the control group (conditioning alone) 57.4% of the children were boys. In the conditioning + Methedrine group, 72.2% of the children were boys. Using mean number of wet nights as a measure of success, girls slightly outperformed boys, although the differences between girls and boys were not statistically significant.

For children under five years of age, the initial dose of methamphetamine was 2.5 mg, but was increased to 5 mg and maintained at this level or reduced if side effects became apparent. Children of five years of age and older received an initial dose of 5 mg and were maintained at this level or reduced, again depending on the appearance of side effects. For three children the dose was increased to 7.5 mg, with 2.5 mg given between 4-5 PM and 5 mg at bedtime. One child received 10 mg in divided doses. These higher doses were tolerated without any side effects. With the exception of these four cases, parents were required to administer the drugs at bedtime.

The parents of children who participated in this study were closely involved in treatment. Parents and children were seen at the clinic together at 14-day intervals; regular attendance at these interviews was made a condition of treatment. Parents were specifically questioned about any disturbance of sleep pattern. In the 189 cases where drugs were administered, side effects were experienced by four children taking Dexedrine and by eight children taking Methedrine. These side effects disappeared when dosages were reduced.

Sleep disturbance and insomnia are widely recognized, characteristic side effects of amphetamines and other stimulants (e.g., methylphenidate). In this study, the children were administered the drugs at bedtime, greatly increasing the likelihood that CNS stimulation and consequent sleep disruption would be observed. While the published report does not state this explicitly, it appears that the eight children in the conditioning + Methedrine group who experienced sleep disturbance were receiving 5 mg/day. When the dose was reduced to 2.5 mg/day, these effects disappeared. Thus, 8 of 110 children dosed with methamphetamine experienced adverse effects at 5 mg but not at 2.5 mg. Based on this study, the critical effect of methamphetamine would be defined as sleep disturbance (insomnia). The LOAEL was 5 mg per day, and the NOAEL was 2.5 mg/day. Since the average body weight of a 7 year-old child is 25.1 kg (Exposure

Factors Handbook; U.S. EPA, 1997), the LOAEL and NOAEL are equivalent to 0.2 and 0.1 mg/kg-day, respectively.

Methamphetamine treatment improved the success rate and reduced the duration needed to achieve the criterion for treatment success. In the control group (conditioning alone), 68% of the children were treated successfully. In contrast, 90% of children receiving conditioning + methedrine) were treated successfully. Mean number of wet nights (14.2 for conditioning alone vs. 10.1 for conditioning + Methedrine) also indicated that methamphetamine improved treatment outcome.

A 1969 report by Kapoor and Saksena also evaluated the effects of d-methamphetamine (Methedrine, Burroughs Wellcome) for treatment of enuresis in children. Thirty children were placed on a single oral dose of 5-10 mg methamphetamine each day, and fifteen children received a placebo. The ages of these children ranged from 5-14 years. Additional study details are lacking, although it appears that the parents of the children administered the drug. Parents were asked to report any adverse reactions, including insomnia and loss of appetite, immediately. The duration of treatment was not specified. The investigators assessed each child's progress with weekly follow-ups. If no improvement was noted after one week of treatment, the daily dose was increased (presumably, from 5 mg/day to 10 mg/day, although this was not stated explicitly). Results are shown in the table below.

	Methamphetamine (n=30)	**Placebo (n=15)**
Complete cessation of enuresis	15	1
Great improvement (2-3 wet nights/week)	4	3
Moderate improvement (4-5 wet nights/week)	8	2
Unchanged (6-7 wet nights/week)	2	9

Three of the children receiving methamphetamine experienced drug-related side effects (insomnia, constipation, dry mouth and anorexia) and the dose of the drug was reduced (presumably, from 10 mg/day to 5 mg/day, although this was not stated explicitly). Drug treatment of one child had to be stopped, presumably due to the occurrence of significant side effects. The authors concluded that methamphetamine produced earlier and more complete cessation of enuresis than placebo.

In a study designed to replicate the findings of Young and Turner (1965), Kennedy and Sloop (1968) evaluated the use of d-methamphetamine as an adjunct to conditioning treatment of nocturnal enuresis in normal and institutionalized retarded children.

Among the non-retarded children, three boys and one girl received 5 mg/day Methedrine (d-methamphetamine hydrochloride) just before bedtime. The control group, which consisted of five boys and one girl, was treated with conditioning alone using a commercially available alarm system similar to the device used by Young and Turner. The non-retarded children ranged in age from 6 to 12 years. Eight institutionalized retarded children were 9 to 12 years of age and had measured IQs ranging from 26 to 65. Five retarded children were treated with conditioning alone, and three received conditioning plus Methedrine. The criterion for successful treatment was 14 consecutive dry nights.

The authors concluded that methamphetamine failed to enhance either the rate of achieving success or completeness of success compared to conditioning alone. However, among the retarded children, the data do not necessarily support this conclusion (see graph below). Furthermore, the small size of the study probably precludes drawing definitive conclusions about the relative success of the two treatments.

12. Case Studies of Children Treated with Methamphetamine

Zike (1972) described a case study of treatment of an 8-year old child with "developmental dyslexic learning disability" with methamphetamine. Initially, the child was observed for a period of five days. On days 6 to 18, one placebo tablet was given at 7:00 AM each day. This was followed by daily doses of 5 mg methamphetamine[30] on days 19 to 29, also at 7:00 AM. On days 30 and 31, the dose of methamphetamine was increased to 10 mg/day. On each day of the study, the child was rated for thirty minutes on the following:

- attention-to-task ("not looking away from the boundaries of his desk, ignoring surrounding stimuli unless physically involving, and carrying out the task assigned")
- talks-outs ("speaks without raising his hand for the teacher's attention or speech is inappropriate to the task assigned or he vocalizes in any other way which is not acceptable")
- jump-ups ("leaves his seat without permission or direction from teacher")

Observations were made at the same time each day by the same observer, who was blind to treatment.

Details regarding the outcome of treatment were not provided, and side effects were not discussed. However, a single chart showing baseline behavior, behavior during treatment with the placebo and behavior during treatment with methamphetamine (reproduced below) indicates that the drug was successful in improving attention to task and reducing talk-outs and jump-ups.

[30] The drug administered was "desoxyephedrine [methamphetamine] in a time-release form" but details regarding the manufacturer or the form of the drug were not provided.

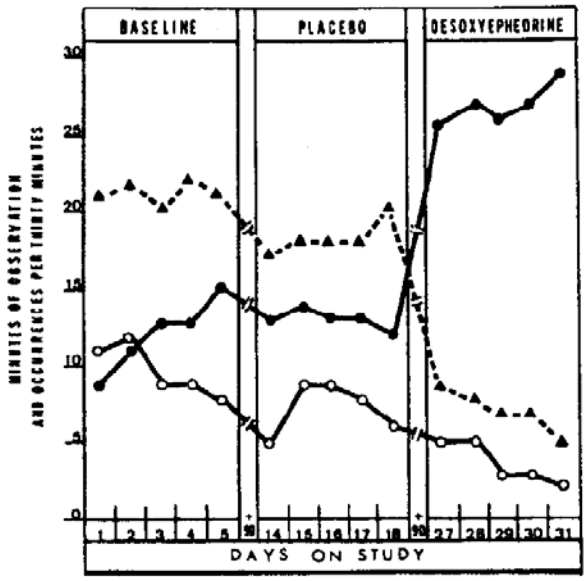


Fig. 2. Eight-year-old DYSLX-LD hyperkinetic boy of normal intelligence. Drug: desoxyephedrine, time-release form, 5 mg orally 7.00 a.m. daily (days 19 to 29); 10 mg orally 7.00 a.m. (days 30 to 31).
●——● attention-to-task; ○——○ talk-outs; ▲- - -▲ jump-ups.

Data from Zike (1972).

Bussing and Levin (1993) described a case study of an 11-year-old boy with obsessive-compulsive disorder (OCD), major depression and ADHD who was successfully treated with a combination of fluoxetine and methamphetamine. Fluoxetine (Prozac®) was started initially to treat OCD and depression. The initial dose was 20mg every other day, and after one week was increased to 20 mg/day. After three weeks, OCD and symptoms of depression showed significant improvement, but ADHD symptoms increased. Consequently, a stimulant was added to the fluoxetine regimen. Initial twice daily oral doses of 5 mg dextroamphetamine produced an increase in symptoms of hyperactivity. The authors suspected this may have been caused by the presence of FD&C Yellow No. 5 (tartrazine) in the medication. Consequently, they switched stimulant medication to methamphetamine (which does not contain tartrazine), 5 mg orally twice each day. Other reasons for selecting methamphetamine were its reliable and rapid onset of action and its lack of potential for altering the metabolism of fluoxetine. Eventually, the dose was changed to 10 mg of a sustained-release form of methamphetamine every morning. Given that the body weight of the child was 37 kg, the daily dose of methamphetamine was 0.27 mg/kg-day.

Treatment with methamphetamine produced marked reduction of symptoms associated with ADHD. The authors noted that the child "….has tolerated this regimen of fluoxetine and methamphetamine without untoward effects." Unfortunately, no long-term follow-up information on this case was available (Regina Bussing, personal communication).

13. Potential Developmental Toxicity of Methamphetamine

Sussman (1963) reported on four case studies of women who used methamphetamine during pregnancy and the effects on their delivery and infants. Salient features of these cases are summarized in the table below. Two of the infants were born prematurely, and one case was complicated by breech delivery. On admission to the hospital, all four mothers were asymptomatic. In two cases, the time period since the last methamphetamine dose was at least ten days, and neither infant experienced withdrawal symptoms. In the other two cases, the time since the last methamphetamine dose was unknown, and both of the infants born to these mothers experienced withdrawal symptoms. Physical examination of one infant (case #4) at four months of age was normal, although both the weight and head size of this infant were small. An associated finding in this case was "suspect hepatitis" but the report did not elaborate on this.

The cases presented in this report exemplify several of the problems associated with attempts to assess methamphetamine's potential to adversely affect prenatal development. The author noted, "The exact drug dose taken by a pregnant addict is rarely known. The drug purchased illegally is often diluted, and the history referable to this point is usually inaccurate." Other factors such as multiple drug use and poor nutrition during pregnancy have significant potential to adversely affect prenatal development, but obtaining accurate information on them is equally difficult.

Last "Fix," Pre-delivery	Weight (kg)	Withdrawal Symptoms	Onset of Withdrawal	Associated Findings	Follow-Up Age (mo)	Follow-Up Findings
unknown	2.7	shrill cry, irritable, jerky, moro	5 hours	respiratory distress at & after birth	none	
unknown	2.9	irritable, sneezing	1st day	none	none	
10 days	2.4	none	–	none	none	
6 months	2.2	none	–	suspect hepatitis	4	normal; weight 3 %ile head 10 %ile

Data from Sussman (1963). Summary of case studies of infants born to mothers who were users of methamphetamine. Details of each case were limited and not discussed in detail. In the first case, "moro" refers to a small abscess or tumor resembling a mulberry. Two of the births were premature, but the author did not identify the two premature births among the four cases.

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