

January 12, 2006

Note to DSaRM Advisory Committee Members:

This Office of Drug Safety (ODS) consult from April 2004 has been provided for general background information. It describes an analysis of post-marketing safety experience (AERS spontaneous reports) of sudden death and serious cardiovascular or cerebrovascular adverse events during stimulant therapy of ADHD.

Updated AERS information for amphetamine and methylphenidate products, as well as for atomoxetine (a more recently approved drug treatment of ADHD) will be presented by ODS at the DSaRM Advisory Committee meeting on February 9.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#: D030403

DATE: April 27, 2004

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THROUGH: Mark Avigan, M.D., C.M., Director
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TO: Russell Katz, M.D., Director
Division of Neuropharmacological Drug Products, HFD-120

SUBJECT: Review of AERS data for marketed safety experience during stimulant therapy: death, sudden death, cardiovascular SAEs (including stroke)

DRUGS: 1) **amphetamine / dextroamphetamine** (branded and generic, all formulations, including ADDERALL[®] and ADDERALL XR[®] [regular and extended release formulation of mixed salts of a single entity amphetamine product containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and dextroamphetamine sulfate], dextroamphetamine sulfate, Dexedrine[®], Dexedrine[®] Spansules, and DextroStat[®]);
2) **methylphenidate** (branded and generic, all formulations, including Concerta[®], Ritalin[®], Ritalin[®] SR, Ritalin[®] LA, Methylin[®], Methylin[®] ER, Metadate[®] ER, and Metadate[®] CD);
3) **methamphetamine** (Desoxyn[®]);
4) **dexmethylphenidate** (Focalin[®]).

THIS MEMORANDUM CONTAINS PROPRIETARY IMS HEALTH DATA
NOT FOR RELEASE OUTSIDE OF FDA WITHOUT CLEARANCE

EXECUTIVE SUMMARY

HFD-120 has requested assistance with analysis of AERS data for marketed safety experience with amphetamine and/or dextroamphetamine salts (including ADDERALL[®] products), as well as with other stimulants currently approved for the treatment of attention deficit hyperactivity disorder (ADHD), including

Pre-existing hypertension was described in three of the five adult sudden death cases during amphetamine therapy received during the five year period, which suggests that this may be an important risk factor for sudden death in the adult population. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure states that the risk of cardiovascular disease begins with a blood pressure of 115/75 mmHg and doubles with each increment of 20/10 mmHg. Since hypertension is the most common primary diagnosis in America, it is reasonable to deduce that the adult population at increased risk of suffering a cardiovascular event associated with stimulant-based ADHD treatment may be high.

Further evaluation of how these products affect long term cardiovascular outcomes is recommended.

I. INTRODUCTION

HFD-120 has requested assistance with analysis of AERS data for marketed safety experience with amphetamine and/or dextroamphetamine salts (including ADDERALL[®] products), as well as with other stimulants currently approved for the treatment of attention deficit hyperactivity disorder (ADHD), including methylphenidate, methamphetamine, and dexmethylphenidate. This analysis was requested due to safety questions raised during the review of two supplemental NDAs: 1) S-005, for the treatment of adults with ADHD and a 40 mg strength capsule of ADDERALL XR[®]; and, 2) S-006 for the addition of 50 mg and 60 mg capsule strengths of ADDERALL XR[®] for use in adults. This consult is a follow-up to a previous interim report.¹

A. **Definition of Terms**

In this consult, the term “**amphetamine**” is used to describe the following products in the AERS database: amphetamine and/or dextroamphetamine, branded and generic, all formulations, including ADDERALL[®] and ADDERALL XR[®] (regular and extended release formulation of mixed salts of a single entity amphetamine product containing amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, and

¹ ODS Consult, Division of Drug Risk Evaluation, HFD-430, “Safety evaluation of AERS data (interim report)”, August 14, 2003.

dextroamphetamine sulfate), Obetrol[®], dextroamphetamine sulfate, Dexedrine[®], Dexedrine[®] Spansules, and DextroStat[®]. The term “**methylphenidate**” is used to describe the following products, branded and generic, all formulations: methylphenidate HCl, Concerta[®], Ritalin[®], Ritalin[®] SR, Ritalin[®] LA, Methylin[®], Methylin[®] ER, Metadate[®] ER, and Metadate[®] CD. The term “**methamphetamine**” describes branded or generic Desoxyn[®] or methamphetamine HCl. The term “**dexmethylphenidate**” describes branded or generic Focalin[®] or dexmethylphenidate HCl.

B. Selection of Case Series / AERS Searches

For the purposes of this review, the following searches of the AERS safety database were performed. Results from these searches form the basis for the analyses included in this consult:

1. All serious² domestic reports (D, LT, H, Dis) in which **amphetamine** or **methylphenidate** were considered suspect (open dates).
2. All reports with a fatal outcome in which **amphetamine** or **methylphenidate** were considered suspect (open dates).
3. Serious reports (D, LT, H, Dis, RI) describing cardiovascular or cerebrovascular adverse events in which **amphetamine**, **methylphenidate**, **methamphetamine**, or **dexmethylphenidate** were considered suspect, coded with the following MedDRA terms: *accelerated and malignant hypertension (HLT)*, *blood pressure increased (PT)*, *cardiac disorders (SOC)*, *central nervous system haemorrhages and cerebrovascular accidents (HLT)*, *hypertension (PT)*, and with FDA receipt date between January 1, 1999 and December 31, 2003.
4. All reports with a fatal outcome in which **methamphetamine** or **dexmethylphenidate** were considered suspect, with FDA receipt date between January 1, 1999 and December 31, 2003.

² Serious criteria may include events that: result in death (D), are life-threatening (LT), require inpatient hospitalization or prolongation of existing hospitalization (H), result in persistent or significant disability (Dis), require intervention to

C. Case Evaluation Method

For searches #2, 3, and 4 (listed above) attempts were made to identify all duplicate reports, and the information was consolidated into a single case for the purposes of this review and analysis.

Reports were excluded from further review: 1) if death was caused by multi-drug intoxication; 2) if drug abuse was reported; 3) if the death was most likely due to another condition or drug; or, 4) if the specifics were otherwise not consistent with the usual therapeutic use of the drug (e.g., intravenous or intranasal administration of a drug intended for oral use). Complete information about the reason for exclusion of individual reports with a fatal outcome is presented in the appendices.

For each of the non-excluded cases, the cause and manner of death was determined (when possible) and a capsule summary was written (see appendices for summary listings of these cases, as well as capsule summaries).

Non-excluded deaths were further evaluated to identify domestic cases which meet the World Health Organization (WHO) definition of sudden death³ (i.e., death is instantaneous, or occurs within 24 hours of an acute collapse), and which were received by the FDA during the five year period between January 1, 1999 and December 31, 2003.

In addition, searches of the AERS database for serious cardiovascular or cerebrovascular adverse events were performed using the following MedDRA terms:

- Accelerated and malignant hypertension (HLT)
- Blood pressure increased (PT)
- Cardiac disorders (SOC)
- Central nervous system haemorrhages and cerebrovascular accidents (HLT)
- Hypertension (PT)

prevent permanent impairment or damage (RI), or are a congenital anomaly / birth defect (C). Particular serious criteria used in AERS searches for this consult are indicated.

³ Roberts, WC. Sudden cardiac death: definitions and causes. *Am J Cardiol* 1986; 57: 1410-13.

Reports of nonfatal serious cardiovascular and cerebrovascular adverse events were reviewed and tabulated. Cases were excluded from further review as described above, consolidating duplicates, and eliminating overdose cases, and drug abuse cases from further analysis.

D. Overview of amphetamine and methylphenidate marketed safety experience

A comprehensive search of the AERS safety database for serious (D, LT, H, Dis) domestic cases received since 1969 during marketed experience with **amphetamine** or **methylphenidate** indicated a total of 431 cases for **amphetamine** and 494 cases for **methylphenidate** (raw counts). The four most commonly reported MedDRA Preferred Terms (PTs) for **amphetamine** were psychotic disorder, overdose, cardiac arrest, and convulsion; for **methylphenidate**, the four most common PTs were non-accidental overdose, drug dependence, convulsion, and psychotic disorder.

Of note, roughly 73% of all serious, domestic **amphetamine** reports, and 50% of all serious, domestic **methylphenidate** reports, were received in the five year period between 1999 through 2003.

Cardiovascular and cerebrovascular serious adverse events were noted among the 50 most commonly reported PTs for **amphetamine**, and included (in decreasing order of frequency): cardiac arrest, arrhythmia, tachycardia, dyspnea, myocardial infarction, chest pain, hypertension, death, circulatory collapse, sudden death, cardiomegaly, cerebrovascular accident, cardio-respiratory arrest, cardiomyopathy, and hypotension. For **methylphenidate**, included among the 50 most common serious domestic PTs were: tachycardia, cardiac arrest, death, chest pain, syncope, hypertension, coronary artery disease, and myocardial infarction.

Since the MedDRA codes for cardiac arrest, death, and sudden death were noted among the most common terms, the decision was made to further explore these cases, and an analysis of all reports with a fatal outcome was undertaken to characterize the cause of

death. As might be expected, many such cases reflected intentional overdose or multiple-drug intoxication in a setting of drug abuse or suicidal behavior. These cases were excluded from further analysis, and only non-excluded cases were included in the case series used to calculate reporting rates. Some of these cases described unexpected collapse and death during usual doses of stimulant therapy. A case definition of sudden death based on World Health Organization (WHO) criteria ⁴ was used to identify these cases and calculate domestic reporting rates for this condition during the five year period from 1999 through 2003.

In addition, nonfatal cardiovascular and cerebrovascular serious adverse events were reviewed, and domestic reporting rates were also calculated for these cases for the same five year period.

⁴ Roberts, WC. *op cit*.

II. SUMMARY OF CASE SERIES

A. AMPHETAMINE

1) **Death and Sudden Death**

A total of 149 reports with a fatal outcome were identified in which **amphetamine** was considered suspect. Of the 149 reports with a fatal outcome identified in the search, 114 reports were excluded from further analysis. Most of the excluded cases described multi-drug intoxication or were duplicate reports.⁵

In the remaining 35 non-excluded cases⁶, the suspect drug was listed in the AERS database as ADDERALL (24), amphetamine (1), Biphphetamine (1), Dexedrine (8), and dextroamphetamine (1). All 35 cases were domestic in origin. The most common cause of death in these 35 cases was sudden death or cardiac arrest. Other causes of death included suicide (by hanging in three cases and with a gun in one case), cerebrovascular accident, pulmonary embolism, underlying disease progression, rhabdomyolysis, and heat stroke.

Twenty-eight (28) of these 35 cases, all domestic in origin, were received by the FDA between January 1, 1999 and December 31, 2003. These deaths represent all causes reported during usual therapeutic use of the drug, and include some cases in which the immediate cause of death was unrelated to the drug itself (e.g., suicide by hanging). A subset of these 28 cases was identified in which the details of the case were consistent with the WHO definition of sudden death (i.e., death is instantaneous or occurs within 24 hours of an acute collapse).⁷ A total of seventeen cases were identified which met these criteria, twelve pediatric cases (Table 1A) and five adults (Table 1B).

⁵ A summary listing of these reports, which includes available information regarding ISR number, case number, FDA receipt date, patient age and gender, country of origin, first suspect drug, and cause of death, is presented in Appendix A, Table A1.

⁶ A summary listing of these 35 cases, including ISR number, case number, FDA receipt date, patient age and gender, country of origin, first suspect drug, total daily dose of amphetamine, and cause of death, is presented in Appendix A, Table A2.

⁷ Roberts WC. *op cit*.

a) *Pediatric age group (1-18 years) – sudden death*

TABLE 1A – Amphetamine

*Characteristics of domestic pediatric sudden death cases reported during past five years (N=12)**

Age:	7-16 years (mean 12.5 years)
Gender:	12 male, 0 female
Suspect drug:	Adderall or Adderall XR(12)
Total daily dose:	10mg (1), 20mg (5), 30mg (1), 40mg (1), 50mg (1), NR (3)
Duration of therapy:	1 day – 8 years (range)
Autopsy:	yes (11), not mentioned or not done (1)
Cardiac risk factors:	aberrant origin of coronary artery (1), idiopathic hypertrophic subaortic stenosis (1), bicuspid aortic valve (1), unexplained increase or toxic amphetamine level (3), cardiac hypertrophy (3), positive maternal history of ventricular arrhythmia (1), history of heart murmur (3), none mentioned (4)
Concomitant meds:	none mentioned (9), 1 med (3)
Year reported:	1999 (0), 2000 (2), 2001 (6), 2002 (2), 2003 (2)

* numbers in parentheses represent count of cases

Narrative Summaries for Pediatric Cases (N=12)

3811155-1/US (3723113): A pediatrician reported that a 7 year old male with a history of heart murmur died suddenly during therapy with Adderall (dose, duration of therapy, and indication not reported). The child was found dead in his bed on [REDACTED]. Autopsy showed bicuspid aortic valve and no other abnormalities. The “tox screen was negative for amphetamines”. The coroner considered that the child died of an arrhythmia.

3818607-9/US (3727777): A pharmacist reported via a sales representative that a 10 year old male died suddenly during therapy with Adderall (dose, duration of therapy, and indication not reported). The pharmacist stated that three or four years ago she heard that a 10 year old boy collapsed and died on a soccer field, possibly in [REDACTED]. The child had reportedly been taking Adderall since he was two years old. The pharmacist didn't remember the source of the information, and was unable to provide additional information.

3789506-6/US (3706321): A physician reported that an 11 year old male with a history of insulin dependent diabetes “went to bed and never woke up” after four years of therapy with Adderall 10 mg twice daily for the treatment of ADHD. The last dose had been taken two days prior to the child's death. Concomitant medications included insulin only. The coroner reportedly told the child's physician that the amphetamine level was “out of sight (900-1000)”. The child had no known renal or hepatic abnormalities.

3978812-8/US (3844047) (dup 3982225): A physician reported that an 11 year old male died suddenly during therapy with Adderall 20 mg daily (duration of therapy, and indication not reported). The reporting physician also provided information from an article in the [REDACTED]. According to the article, the patient collapsed during activities at a camp. He had been taking Adderall 20 mg daily “for some time”. An autopsy and toxicology testing showed that he “died as a result of an elevated level of the prescription drug Adderall.” Blood level of the drug at the time of death was 210 ng/mL, with toxic levels considered to be ≥ 150 ng/mL. The number of tablets of the drug remaining in the child's prescription bottle was correct according to the number purchased and his medication schedule. The remaining tablets were sent for independent analysis, which confirmed that the concentration of the drug in each of the tablets

tested was consistent with product labeling. The coroner stated that the elevated level of Adderall found in the blood was the result of "his body's apparent inability to properly metabolize and dispose of the medicine normally, resulting in a buildup of the drug that ultimately reached a toxic level sufficient to cause arrhythmia and death."

4163447-7/US (3985139) (dup 3972359-0): A pediatrician reported via a sales representative that a 12 year old male died suddenly on _____ after taking a single dose of Adderall XR 10 mg for the treatment of ADHD. Previous treatment for ADHD included Ritalin (methylphenidate) for about four years (dose not reported). Medication was changed to Adderall XR 10 mg, and the child took his first dose on _____. At about 4 pm that day, he collapsed while running cross country. He had run about one to two miles. He could not be revived. Autopsy results were not reported. Family history was positive for maternal arrhythmia (ventricular tachycardia treated with implanted defibrillation and ablation) which the child's mother had developed about three years prior. The death certificate indicated the cause of death was sudden cardiac death.

3782505-X/US (3701541) (dup 3859036-1): A pediatrician reported that a 13 year old male collapsed while working at his computer and died suddenly after taking a single dose of Adderall 20 mg for the treatment of ADHD. He had been seen by a physician for a physical exam the previous day, with complaints of school problems and was diagnosed with ADHD. Blood pressure and heart rate were normal. Weight was 118 pounds. He was active in sports. The patient took a single dose of Adderall 20 mg at 10:30 am, complained of tiredness about midday, and collapsed at his computer in late afternoon. A pulse was present when emergency personnel arrived, but he was pulseless at the hospital. An autopsy showed idiopathic hypertrophic subaortic stenosis (IHSS), "apparently a genetic disorder", and an enlarged heart "filling complete chest". The number of Adderall tablets was correct in the remaining drug supply. No concomitant medications were reported. Final pathology report and drug screening results were not provided. The reporting physician considered that the cause of death was cardiomegaly (unrelated to Adderall), and arrhythmia possibly caused by Adderall.

3789498-X/US (3706375) (dup 3788756-2): A medical examiner reported that a 14 year old male died of complications from heat exhaustion, dehydration, and near-drowning after several weeks of therapy with Adderall 30 mg daily for the treatment of ADHD. Concomitant medications included divalproex sodium 775 mg daily for the treatment of post traumatic stress disorder. Medical history included depression, possibly psychotic symptoms, but no other significant medical or surgical history. Weight was 205 pounds. The patient was living at a tent based facility for troubled youth near _____. On the day of his death, the temperature at the boot camp was between 109 to 111 degrees Fahrenheit. The patient was reportedly given 50 mg of Adderall instead of his usual 30 mg dose. According to the reporter, "the patient was being punished and was told to sit in the dirt for two to three hours." Access to water was reportedly restricted. The patient became delirious and began eating dirt. He was taken to a hotel and was put in a bathtub. He was found face down in the bathtub. He was still breathing when taken out of the bathtub. He was lethargic and his pulse was 160 to 180. No body temperature was taken. Emergency services were called. He was found to be in asystole and was air-transported to a hospital. The patient was dead on arrival at the hospital. Adderall was considered a suspect medication. Autopsy results identified the cause of death as complications from near-drowning and dehydration due to heat exposure. The patient died approximately four to five hours after first becoming delirious.

3887728-7/US (3776530): A newspaper reporter and a medical examiner reported that a 14 year old male developed shortness of breath while running, followed by collapse and full cardiac arrest after approximately four years of therapy with Adderall (dose not specified) for the treatment of ADHD. The patient collapsed during exercises for his high school ROTC class. Prior therapy included Ritalin (dose and duration of therapy not reported). Autopsy showed the heart weighed 315 grams. The coroner stated that the expected cardiac weight for this child's body weight is 206-299 grams, and the expected cardiac weight for the child's age is 213-237 grams. Heart blood amphetamine level was 0.22 mg/L. Mild ventricular hypertrophy was noted, and was concentric, with no definite septal asymmetry noted. Microscopic examination showed "equivocal evidence of myocardial cell hypertrophy." Postmortem diagnosis was "Sudden collapse and death of 14 year old male during exercise class at school; past history of cardiac murmur diagnosed as a functional murmur; short history of dyspnea prior to terminal collapse; cardiac

hypertrophy; pulmonary congestion and edema; no evidence of trauma; history of treatment with Adderall (amphetamine) for attention deficit disorder, treatment lasted several years; toxicological examination (heart blood) positive for amphetamine.” The coroner concluded that the cause of death was “cardiac hypertrophy, years, due to chronic amphetamine toxicity, years, due to Adderall therapy, years.” The coroner commented that “the subject died as a result of a cardiac arrhythmia due to amphetamine-related cardiac hypertrophy. The level of amphetamine in the blood at the time of death was higher than would be generally expected with a therapeutic dose.”

3555682-3/US (3521975): A newspaper article and the father of the patient reported that a 15 year old male collapsed while playing basketball on _____, and was subsequently pronounced dead at the hospital after approximately three years of therapy with Adderall 20 mg for the treatment of ADD. The child’s father stated that the cause of death was explained to him as “an arrhythmia caused by an increased density of the muscle around the heart”, and that “neither the family physician nor the medical examiner considered Adderall a suspect in his son’s death.” Since his son had been asymptomatic, “the condition remained undiagnosed”. The child had “appeared healthy during a recent sports physical.” His son was an honor student with no history of drug abuse. Medical history included an unspecified “heart murmur” which had been diagnosed at age nine months, which was followed by the physicians until it was felt to have “resolved” at age two years. There is no family history of cardiac disease.

3613516-2/US (3569797): A physician reported that a 15 year old male died suddenly after 18 months of therapy with Adderall 20 mg daily for the treatment of ADHD. There were no concomitant medications. Autopsy showed “no gross major organ abnormalities, including his heart. A toxicology screen was negative. The only significant post-mortem finding, based on tissue assay, was neutropenia. The patient had no prior history of neutropenia.” No additional information was provided.

3753892-3/US (3678776) (dup 3731168-8): A pediatrician reported that a 16 year old male died suddenly after two years of therapy with Adderall 40 mg daily for the treatment of ADD and one to two years of therapy with Zyprexa (olanzapine) 5 mg daily for the treatment of ADHD and personality disorder. On _____ he was found dead on the floor beside his bed. The autopsy showed hepatic steatosis. The reporting physician considered that there may have been an interaction between the two medications, but there was no evidence of an interaction.

4223562-6/US (4029308) (dup 4258509-X): A reviewing psychiatrist in a legal case reported that a 12 year old male with a history of bipolar disorder, oppositional defiant disorder, and other unspecified conditions, experienced a fatal myocardial infarction during therapy with ADDERALL immediate release formulation 15 mg twice daily. Total duration of therapy was not specified, but the reporter stated that the dose had been increased to 15 mg twice daily “several months prior to his death”. The child collapsed after playing basketball at about 5 pm. His “cardiac enzymes were increased at the 1 am blood draw”. At 5:30 am on _____ the “wall of his heart blew out and CPR was performed”. The child died. An autopsy showed “aberrant origin of right main coronary around aorta and embedded in fibrous tissue”. The reporter stated that the child had experienced “palpitations and dizziness at the lower dose”, and there had been “at least one episode of tachycardia during treatment (not followed well)”. Reportedly, his “general practitioner had wanted cardiac studies but did not share this information with the prescribing psychiatrist”. The child had a pre-existing cardiac malformation which was not known. No information was provided pertaining to concomitant medications.

b) *Adult age group (19+ years) - sudden death*

TABLE 1B - Amphetamine

Characteristics of domestic adult sudden death cases during past five years (N=5)*

Age:	22-76 years (mean 46 years)
Gender:	2 male, 2 female, 1 not reported
Suspect drug:	Adderall or Adderall XR (4), Dexedrine (1)
Total daily dose:	10mg(1), 15mg (2), 20mg (1), NR (1)
Duration of therapy:	13 days – 9 months (range)
Autopsy:	yes (1), not mentioned or not done (4)
Cardiac risk factors:	hypertension (3), coronary artery disease (1), dysrhythmia (1), not reported (2)
Concomitant meds:	none (1), 1 med (2), 2 meds (1), 15 meds (1)
Year reported:	1999 (1), 2000 (1), 2001 (1), 2002 (0), 2003 (2)

* numbers in parentheses represent count of cases

Narrative Summaries for Adult Cases (N=5)

3534227-8/US (3505904) (dup 3562120): A psychiatrist reported via a sales representative that a 22 year old female was “found dead in the community home in which she lived” in _____ after four months of therapy with Adderall 20 mg daily for the treatment of ADD and one year of therapy with Wellbutrin (bupropion) 225 mg daily (indication not reported). The cause of death was unknown but it did not appear that any physical harm was done to her. Medical history and other concomitant medications were not reported. Results of an autopsy were not reported.

3686984-8/US (3625300) (dup 3671472-5 and 3677969-6): A physician reported via a sales representative that a 28 year old patient developed flu-like symptoms and chest pain, and died suddenly, during therapy with Adderall and Celexa (citalopram). No additional information was provided.

4151000-0/US (3974885) (dup 4111983): A physician reported via a sales representative that a 42 year old male with a history of hypertension, obstructive sleep apnea, and dysrhythmia (unspecified), developed chest pain, ventricular fibrillation (witnessed in the hospital emergency room), asystole, and subsequently expired despite resuscitation efforts, after approximately nine months of therapy with Adderall XR 15 mg daily intermittently for the treatment of ADD. The patient weighed 239 pounds. Concomitant medications included hydrochlorothiazide and quinapril. An autopsy was not done. The reporter considered that the events were probably related to Adderall therapy.

3195487-9/US (3206763): A physician reported that a 62 year old male experienced a fatal myocardial infarction while shoveling snow after thirteen days of therapy with Adderall 15 mg daily (10 mg in the morning and 5 mg in the evening) for the treatment of ADD. The patient was dead at the time EMT personnel arrived. The patient had not taken any Adderall on the day of his death, _____. His last dose was taken on the previous day at approximately 3:30 pm. The dose of Adderall had been titrated from a starting dose of 5 mg daily for three days to a total daily dose of 15 mg on _____. The patient was seen by his physician on _____, and “denied any comorbid health conditions”. Blood pressure at that time was 155/95 and weight was 210 pounds. No cardiovascular function tests were performed. The patient did not take any other prescription, herbal, or over the counter drugs. Past medical history included alcoholism (no alcohol use over the past nine years), and “poor dietary habits”.

4041466-9/US (3889978): An attorney reported that a 76 year old female with a history of irritable bowel syndrome, urinary incontinence, osteoarthritis, hypertension, headaches, hiatal hernia, depression, anxiety, memory deficits, chronic fatigue syndrome, deep vein thrombosis, pulmonary embolism, peptic ulcer disease, and obesity, developed dizziness, and was later found dead lying face down in the hall, after four months of therapy with Lotronex 1 mg twice daily for the treatment of diarrhea-predominant irritable bowel

syndrome, and Dexedrine 5 mg twice daily for the treatment of fatigue (duration of therapy not specified). The patient's physician had recently advised her to decrease her dose of Dexedrine because of hypertension. Concomitant medications included citalopram, venlafaxine, ranitidine, lansoprazole, donepezil, methylcellulose, oxybutynin, verapamil, warfarin, allopurinol, thyroxine, losartan, Celecoxib and Excedrin. The death certificate indicated the cause of death as cardiac dysrhythmia and arrest due to pre-existing coronary artery disease.

2) Nonfatal Cardiovascular and Cerebrovascular Serious Adverse Events

A total of 35 non-excluded reports of nonfatal domestic cardiovascular or cerebrovascular serious adverse events received in the past five years were identified. These cases are summarized in Tables 2A (pediatric cases) and 2B (adult cases).⁸

a) Pediatric age group (1-18 years) – nonfatal cardiovascular SAEs and stroke

TABLE 2A - Amphetamine

*Characteristics of nonfatal pediatric serious cardiovascular cases during past five years (N=18)**

Age:	7-17 years (mean 11.4 years)
Gender:	15 male, 3 female
Suspect drug:	Adderall or Adderall XR (18)
Serious adverse events:	syncope (2), increased blood pressure / hypertension (6), dyspnea (4), myocardial infarction (1), arrhythmia (5), left ventricular hypertrophy (1), thromboembolic stroke (1), sub-arachnoid hemorrhage (1)
Concomitant meds:	none mentioned (6), 1 med (7), 2 meds (1), 3 meds (2), 4 meds (2)
Year reported:	1999 (1), 2000 (4), 2001 (4), 2002 (4), 2003 (5)

* numbers in parentheses represent count of cases

b) Adult age group (19+ years) – nonfatal cardiovascular SAEs and stroke

TABLE 2B - Amphetamine

*Characteristics of nonfatal adult serious cardiovascular cases during past five years (N=17)**

Age:	19-58 years (mean 42 years)
Gender:	11 male, 6 female
Suspect drug:	Adderall or Adderall XR (12), Dexedrine (5)
Serious adverse events:	syncope (2), increased blood pressure / hypertension (3), chest pain (4), dyspnea (3), myocardial infarction (5), arrhythmia (6), cardiomyopathy (3), stroke (3), cardiac arrest (2)
Concomitant meds:	none mentioned (8), 1 med (7), 3 meds (1), 4 meds (1)
Year reported:	1999 (2), 2000 (2), 2001 (6), 2002 (0), 2003 (7)

* numbers in parentheses represent count of cases

⁸ A summary listing of these 35 reports which includes information about ISR number, patient age and gender, suspect and concomitant drugs, cardiovascular and cerebrovascular serious adverse events, and serious criteria, is included in Appendix A, Table A3.

B. METHYLPHENIDATE

1) Death and Sudden Death

A total of 160 reports were identified in a search of the AERS database for reports with a fatal outcome in which **methylphenidate** was considered suspect. In addition, three potential cases were identified in published literature. Of the total 163 reports, 117 were excluded from further analysis. Most of the excluded cases described intoxication with multiple drugs or were duplicate reports.⁹ Sixteen (16) of the remaining 46 cases¹⁰ were received by the FDA between January 1, 1999 and December 31, 2003, and were domestic in origin. A subset of the 16 domestic cases received during the five year period between 1999 and 2003 was identified in which the details of the case were consistent with the WHO definition of sudden death (i.e., death is instantaneous or occurs within 24 hours of an acute collapse). A total of eight sudden death cases were identified, seven pediatric cases (Table 3A) and one adult (Table 3B).

a) Pediatric age group (1-18 years) – sudden death

TABLE 3A - Methylphenidate

Characteristics of domestic pediatric sudden death cases during past five years (N=7)*

Age:	9-14 years (mean 11.7 years)
Gender:	3 male, 4 female
Suspect drug:	Ritalin (3), Concerta (4)
Total daily dose:	18mg (1), 20mg (1), 36mg (2), 40mg (1), 60mg (1), NR (1)
Duration of therapy:	2 months – 10 years (range)
Autopsy:	yes (4), not mentioned or not done (3)
Potential risk factors:	congenital cardiac malformation and concomitant clonidine therapy (1), cardiac small vessel damage, cardiac hypertrophy, and obesity (1), unexplained toxic methylphenidate level at usual dosages and surgery nine days prior (1), history of syncope (1), none mentioned (3)
Concomitant meds:	none mentioned (4), 1 med (2), 5 meds (1)
Year reported:	1999 (1), 2000 (1), 2001 (1), 2002 (1), 2003 (3)

* numbers in parentheses represent count of cases

⁹ A summary listing of these 163 reports, which includes available information regarding ISR number, patient age and gender, duration of methylphenidate therapy, suspect drugs, dose of methylphenidate, medical history, and cause of death, is presented in Appendix B.

¹⁰ A summary listing of these 46 non-excluded cases with a fatal outcome, as well as narrative summaries for each case, are included in Appendix B.

Narrative Summaries for Pediatric Cases (N=7)

3240721, (dup 1680461, 1784758, 1842644, 3240724) / U.S.: A case report in published literature described the death of a 10 year old male taking Ritalin 10 mg BID concurrently with clonidine patch (.2 mg Q 5 days). The patient had a history of treated ADHD since kindergarten and had been started on clonidine within 6 months of his death to treat tics that had developed with higher doses of methylphenidate. The patient had a history of exercise induced syncopal events with subsequent normal ECG, normal EEG, and a normal head CT scan. While swimming, the patient complained of feeling faint. After resting, the child swam again, passed out, and appeared to experience a tonic-clonic seizure. Cardiopulmonary resuscitation was unsuccessful. The autopsy revealed a congenital cardiac malformation that was thought to be capable of causing transient ischemia and arrhythmia. His left coronary artery originated in the right sinus of Valsalva and was subject to compression by the aortic root. The left coronary artery orifice was stenotic. Clonidine blood levels were within normal limits and there was no evidence of ischemic changes. (Case 4 of Cantwell et al., Case Study: Adverse Response to Clonidine, Cantwell et al., J. Am. Acad. Child Adoles. Psychiatry, 36:4, April 1997)

3775962 (dup 3446728) / U.S.: A mother and an attorney reported the death of an 11 year old female who was taking Ritalin for ADHD for 4 years and 3 months. One day prior to her death, her doctor changed her dose from 20 mg QAM and 15 mg Q lunch to 25mg QAM and 15 mg Q lunch. According to her mother, the child seemed "out of it" on the first morning of the dose increase but seemed fine after school. The following morning, the child was found dead in bed. The mother states that the autopsy did not reveal cardiac abnormalities and that the coroner described death due to cardiac arrhythmia.

4106370 / U.S.: A newspaper journalist reported the death of a 12 year old girl who was being treated with Concerta for ADHD for an unknown period of time. The patient had a history of migraine headaches and had a skating accident with head trauma 11 months prior to her death. The patient was found in the bathtub approximately 20 minutes after entering with her face partially submerged in water. Cardiopulmonary resuscitation was initiated and she was transported to a hospital. She was pronounced dead one hour after she was found. A police detective speculated that the patient may have experienced seizures after the skating accident but neurological tests at the time of the accident were inconclusive.

4115324, (dup 4226201) / U.S.: A physician reported that a 13 year old male with a history of ADHD experienced sudden cardiac death while at camp. The patient was started on Concerta 18 mg QD for 1 month and was then titrated up to 36 mg QD. Six months after initiating treatment the patient had a syncopal event. ECG performed on that day was normal. Ten months after starting Concerta the boy suffered polymorphic ventricular tachycardia and could not be resuscitated. Autopsy was not mentioned.

4143391 / U.S.: An unknown reporter states that a 13 year old female with a history of ADHD and seasonal allergies died in her sleep due to a cardiac arrhythmia. The patient had been taking Concerta 36 mg QD for 9 months and had been on Zyrtec for an unknown period of time. She had no prior cardiac history and autopsy was not mentioned.

3489120, (dup 3616770, 3894289, 4034273, 4035868) / U.S.: A physician's office, coroner, and lawyer report that a 14 year old obese male weighing 198 lbs died while taking Ritalin 20 mg TID for 10 years. The report mentions a literature report but the source was not provided. The physician providing the report did not care for the patient but received information about the case from the patient's father (also a physician). Per the father, the autopsy revealed small vessel damage of the heart and the heart weighed approximately 402 grams. The patient did not have preexisting heart disease but did complain of chest pain for an unknown period of time prior to death. The patient's methylphenidate level was 6.5 ng/ml (therapeutic range is 3.6-6.8 ng/ml).

3986870 / US: A pharmacist and a physician reported that a 9 year old female with a history of ADHD, asthma, chronic otitis media, and surgical placement of tubes in her ears nine days prior, was admitted to the hospital for sinusitis, vomiting, and increasing respiratory symptoms. The child was reportedly given IV fluids and three hours later experienced cardio-respiratory arrest and expired. Medications included

Concerta, cefuroxime axetil, ceftriaxone, albuterol, loratadine, and fluticasone propionate. Concerta 18 mg daily had been initiated two months prior for the treatment of ADHD. At the time of hospital admission, the methylphenidate level was 156 ng/mL (therapeutic range is 3.6 – 6.8 ng/mL), and blood glucose was 402 mg/dL, SGOT 132 U/L, and SGPT 42 U/L. The child's grandmother stated that there were no additional tablets missing from the bottle of Concerta. The pharmacist reported that no Concerta shells were found in the bowel at autopsy. The official autopsy report was unavailable.

b) Adult age group (19+ Years) – sudden death

TABLE 3B - Methylphenidate

Characteristics of domestic adult sudden death cases during past five years (N=1)

Age:	42 years
Gender:	female
Suspect drug:	Concerta
Total daily dose:	not reported
Duration of therapy:	not reported
Autopsy:	not mentioned
Cardiac risk factors:	not reported
Concomitant meds:	4
Year reported:	2002

Narrative Summary for Adult Case (N=1)

3997822/ U.S.: A toxicologist reported the death of a 42 year old female with an unknown medical history. The patient was found unresponsive and was transferred to a local emergency room. She was actively seizing upon arrival, was intubated, and was given IV alprazolam and phenytoin which failed to control the seizures. Activated charcoal was administered. The patient was taking bupropion SR, methylphenidate, chlorthalidone/ clidinium, Singulair, and levothyroxine. The patient died in the ER 3 hours after arriving. The primary suspect drug is listed in the AERS database as Concerta. This report was published in the American Journal of Emergency Medicine, Sept 2002, Case No. 612, 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System.

2) Nonfatal Cardiovascular and Cerebrovascular Serious Adverse Events

A total of 19 non-excluded reports of nonfatal domestic cardiovascular or cerebrovascular serious adverse events received in the past five years were identified. These cases are summarized in Tables 4A (pediatric cases) and 4B (adult cases).¹¹

¹¹ A summary listing of these 19 reports which includes information about ISR number, patient age and gender, suspect and concomitant drugs, cardiovascular and cerebrovascular serious adverse events, and serious criteria, is included in Appendix B.

a) *Pediatric age group (1-18 years) – nonfatal cardiovascular SAEs and stroke*

TABLE 4A - Methylphenidate

*Characteristics of nonfatal pediatric serious cardiovascular cases during past five years (N=8)**

Age:	7-18 years (mean 11.5 years)
Gender:	5 male, 3 female
Suspect drug:	Ritalin (1), Concerta (7)
Serious adverse events:	syncope (1), loss of consciousness (1), dyspnea (1), palpitations / arrhythmia (6), abnormal heart biopsy (1), cardiac arrest (1), stroke (1), QT prolongation (1)
Concomitant meds:	none mentioned (2), 1 med (3), 2 meds (3)
Year reported:	1999 (0), 2000 (0), 2001 (3), 2002 (1), 2003 (4)

* numbers in parentheses represent count of cases

b) *Adult age group (19+ years) – nonfatal cardiovascular SAEs and stroke*

TABLE 4B – Methylphenidate

*Characteristics of nonfatal adult serious cardiovascular cases during past five years (N=11)**

Age:	33-75 years (mean 50.6 years)
Gender:	6 male, 4 female, 1 not reported
Suspect drug:	Ritalin (6), methylphenidate (3), Metadate (1), Concerta (1)
Serious adverse events:	syncope (2), increased blood pressure / hypertension (3), chest pain (3), heart failure (1), myocardial infarction (3), arrhythmia (2), mitral valve prolapse (1), stroke (1)
Concomitant meds:	none mentioned (6), 1 med (2), 2 meds (2), 3 meds (1)
Year reported:	1999 (3), 2000 (1), 2001 (2), 2002 (3), 2003 (2)

* numbers in parentheses represent count of cases

C. METHAMPHETAMINE

1) Death and Sudden Death

A total of 68 reports were identified in a search of the AERS database for reports with a fatal outcome in which **methamphetamine** was considered suspect. The search was limited to domestic reports received by the FDA between January 1, 1999 and December 31, 2003. None of the 68 reports identified in this search qualified for additional analysis as cases of death during usual therapeutic use of **methamphetamine**. Most of the

excluded cases either described drug abuse with “crank” or “crystal meth”, were characterized by intoxication with multiple drugs, or were duplicate reports.¹²

2) **Nonfatal Cardiovascular and Cerebrovascular Serious Adverse Events**

None of the 35 reports identified in this search qualified for additional analysis as cases of nonfatal cardiovascular or cerebrovascular serious adverse events during usual therapeutic use of **methamphetamine**. Almost all of these 35 cases described either drug abuse or intoxication with multiple drugs in a setting of drug abuse or suicide. Nine of these 35 cases were taken from a single published case series¹³ describing patients with acute coronary syndrome associated with methamphetamine use who were seen in a single large hospital emergency department over a two year period.

D. **DEXMETHYLPHENIDATE**

1) **Death and Sudden Death**

A comprehensive search of the AERS safety database was performed to identify all reports with a fatal outcome which had been received by the FDA as of December 31, 2003, in which **dexmethylphenidate** was considered suspect. A total of two fatal reports were identified, neither of which met the criteria for sudden death during therapy with this drug.

2) **Nonfatal Cardiovascular and Cerebrovascular Serious Adverse Events**

No reports were identified in a search of the AERS database for nonfatal domestic cardiovascular or cerebrovascular serious adverse events.

¹² A summary listing of each of these 68 reports, which includes available information regarding ISR number, case number, FDA receipt date, patient age and gender, first coded adverse event, and cause of death, is presented in Appendix C.

¹³ Turnipseed SD, Richards JR, Kirk JD, Diercks DB, and Amsterdam EA. Frequency of acute coronary syndrome in patients presenting to the emergency department with chest pain after methamphetamine use. *J Emerg Med* 2003; 24(4): 369-373.

III. EPIDEMIOLOGY

Objective: To calculate reporting rates, based on cases per million prescriptions dispensed, for domestic cases of death (non-excluded cases), sudden death, and serious nonfatal cardiovascular or cerebrovascular adverse events associated with stimulant therapy which were received by the FDA during the five year period from January 1, 1999 through December 31, 2003,

- in children (1-18 years)
- in adults (19+ years).

A. METHODS

1) Numerator / Case Collection

An analysis of all reports with a fatal outcome was undertaken to characterize the cause of death, and exclude cases from further review which were not representative of usual therapeutic use of stimulants (as described previously). Non-excluded death cases were further reviewed to identify cases of sudden death, based on World Health Organization (WHO) criteria. In addition, cases of nonfatal domestic cardiovascular and cerebrovascular serious adverse events were reviewed and analyzed. Cases were identified which were received by the FDA during the five year period between January 1, 1999 and December 31, 2003. Separate analyses were conducted for the pediatric (age 1-18 years) and adult (age ≥ 19 years) age groups.

2) Denominator / Drug Utilization Data

IMS data were obtained to estimate the number of prescriptions for these drugs dispensed in the United States during the comparable five year period. Data sources used for this consult included an IMS Health audit, National Prescription Audit Plus™ (NPA Plus™), and prescription claims for a 25-month period of time from AdvancePCS Pharmacy Benefit Management Company (Dimension Rx™). The projected number of total prescriptions dispensed (TRx) for the relevant time period using a moving annual total

(MAT) from the last quarter of 1998 through the third quarter of 2003 was obtained from NPA Plus™. A four month time lag between the FDA receipt date period (January 1, 1999 through December 31, 2003) and the drug utilization data period (September 1998 through August 2003) was considered to be acceptable based on the reasonable assumption that the actual date of occurrence of the adverse event (in this case, death) will usually fall within a few months prior to the FDA receipt date.

Since NPA Plus™ does not include demographic information, the proportions of pediatric and adult prescriptions in Advance PCS were applied to NPA Plus™ totals in order to estimate the number of stimulant prescriptions dispensed nationwide by age group.

A summary table of total prescriptions dispensed (TRx) over a five year period (moving annual total for September 1998 to August 2003) for the stimulant drugs of interest is presented in Appendix D. Complete information about the drug use data used in this analysis is presented in a separate consult.¹⁴

B. REPORTING RATE ESTIMATES

1) Pediatric age group (1-18 years)

a) Amphetamine

A reporting rate per million prescriptions dispensed was calculated using an IMS Health projection for the five year period between September 1998 and August 2003 (moving annual total). For the pediatric age group (1-18 years), there were 0.56 non-excluded deaths reported per million **amphetamine** prescriptions dispensed. These deaths represent cases reported during usual therapeutic use of the drug, and include some cases in which the immediate cause of death was unrelated to the drug itself (e.g., suicide by hanging). With regard to sudden death in the pediatric age group (1-18 years), there were

¹⁴ ODS Consult, Division of Surveillance, Research and Communication Support, HFD-410, "CNS Stimulant Drug Use and Duration of Therapy Review", March 1, 2004.

twelve reports identified which met the case definition, which corresponds to 0.36 sudden deaths reported per million **amphetamine** prescriptions dispensed.

The reporting rate for nonfatal pediatric cardiovascular and cerebrovascular serious adverse events was 0.53 cases per million **amphetamine** prescriptions dispensed.

b) Methylphenidate

For the pediatric age group (1-18 years), there were 0.22 deaths reported per million **methylphenidate** prescriptions dispensed. Age was not reported in one case, leaving the adult or pediatric population one less case. These deaths represent all causes reported during usual therapeutic use of the drug, and include some cases in which the immediate cause of death was unrelated to the drug itself. With regard to sudden death in the pediatric age group (1-18 years), there were seven reports identified which met the case definition, which corresponds to 0.16 sudden deaths per million **methylphenidate** prescriptions dispensed.

The reporting rate for nonfatal pediatric cardiovascular and cerebrovascular serious adverse events was 0.18 cases per million **methylphenidate** prescriptions dispensed.

A tabular summary of calculated reporting rates for all pediatric non-excluded deaths, sudden death, and nonfatal cardiovascular or cerebrovascular serious adverse events (non-excluded) during the five year period are presented in Table 5.

Table 5
Pediatric Reporting Rates for non-excluded deaths, sudden deaths, and nonfatal cardiovascular SAEs

Methylphenidate and Amphetamine Pediatric (1-18 years) Cases (includes only domestic cases from 1999-2003 ^a)						
	Methylphenidate			Amphetamine		
	Number of cases	Number of RXs (%)	Cases per 1,000,000 RXs	Number of cases	Number of RXs (%)	Cases per 1,000,000 RXs
Non-excluded deaths ^b	10 ^c	44,692,761 (75.1%)	0.22	19	33,701,460 (78.0%)	0.56
Sudden deaths	7	44,692,761 (75.1%)	0.16	12	33,701,460 (78.0%)	0.36
Nonfatal serious cardiovascular events ^d	8	44,692,761 (75.1%)	0.18	18	33,701,460 (78.0%)	0.53

^a RX data only included up until August 2003 (moving annual total for five-year period).

^b Non-excluded deaths include all cases with a fatal outcome during usual therapeutic use of the drug (i.e., not overdose or drug abuse), and in which other more likely causes of death were not identified.

^c One case in the methylphenidate category had missing age data leaving the pediatric or adult population one less case.

^d This category also includes nonfatal cerebrovascular accidents.

2) Adult age group (19+ years)

a) Amphetamine

A reporting rate per million prescriptions dispensed was calculated using an IMS Health projection for the five year period between September 1998 and August 2003 (moving annual total). For the adult age group (19+ years), there were 0.95 non-excluded deaths reported per million **amphetamine** prescriptions dispensed. These deaths represent cases reported during usual therapeutic use of the drug. With regard to sudden death in the adult age group (19+ years), there were 0.53 sudden deaths reported per million **amphetamine** prescriptions dispensed.

The reporting rate for nonfatal adult cardiovascular and cerebrovascular serious adverse events was 1.79 cases per million **amphetamine** prescriptions dispensed.

b) Methylphenidate

For the adult age group (19+ years), there were 0.34 non-excluded deaths reported per million **methylphenidate** prescriptions dispensed. Age was not reported in one case, leaving the adult or pediatric population one less case. These deaths represent all causes reported during usual therapeutic use of the drug. With regard to sudden death in the adult age group (19+ years), there were 0.07 sudden deaths reported per million **methylphenidate** prescriptions dispensed.

The reporting rate for nonfatal adult cardiovascular and cerebrovascular serious adverse events was 0.74 cases per million **methylphenidate** prescriptions dispensed.

A tabular summary of calculated reporting rates for all adult age group non-excluded deaths, sudden death, and nonfatal cardiovascular or cerebrovascular serious adverse events (non-excluded) during the five year period are presented below in Table 6.

Table 6
Adult Reporting Rates for non-excluded deaths, sudden deaths, and nonfatal cardiovascular SAEs

Methylphenidate and Amphetamine Adult (19+ years) Cases (includes only domestic cases from 1999-2003 ^a)						
	Methylphenidate			Amphetamine		
	Number of cases	Number of RXs (%)	Cases per 1,000,000 RXs	Number of cases	Number of RXs (%)	Cases per 1,000,000 RXs
Non-excluded deaths ^b	5 ^c	14,818,239 (24.9%)	0.34	9	9,505,540 (22.0%)	0.95
Sudden deaths	1	14,818,239 (24.9%)	0.07	5	9,505,540 (22.0%)	0.53
Nonfatal serious cardiovascular events ^d	11 ^e	14,818,239 (24.9%)	0.74	17 ^f	9,505,540 (22.0%)	1.79

^a RX data only included up until August 2003 (moving annual total for five-year period)

^b Non-excluded deaths include all cases with a fatal outcome during usual therapeutic use of the drug (i.e., not overdose or drug abuse), and in which other more likely causes of death were not identified.

^c One case in the methylphenidate category had missing age data leaving the pediatric or adult population one less case.

^d This category also includes nonfatal cerebrovascular accidents.

^e Includes three cases in which exact age was not reported, but appear to be adult age group.

^f Includes one case in which exact age was not reported, but appears to be adult age group.

3) Reporting Rate Ratios

In each of the categories studied, none of the reporting rates exceeded one case per million stimulant prescriptions dispensed, with one exception: for nonfatal cardiovascular and cerebrovascular serious adverse events associated with **amphetamine** therapy in adults, the calculated reporting rate was 1.79 cases per million prescriptions dispensed.

Rate ratios comparing reporting rates for **amphetamine** versus **methylphenidate** ranged from 2.3 (pediatric sudden deaths) to 7.6 (adult sudden deaths), and were consistently greater than 1 in all categories studied, showing numerically higher rates for **amphetamine**. However, inference of risk from these results is limited as they are

generally <3-fold and are based on comparisons of small numbers, thus lacking statistical robustness.¹⁵

It should also be noted that, for **methamphetamine** and **dexmethylphenidate**, IMS estimates of drug utilization during the five year period from 1999 through 2003 show relatively little drug use compared to **amphetamine** and **methylphenidate**. Thus, if even one case had qualified for inclusion in this case series (regardless of patient age), the reporting rate for the event would be 6.1 per million **methamphetamine** prescriptions dispensed, or 2.9 per million **dexmethylphenidate** prescriptions dispensed, substantially exceeding the reporting rates for **amphetamine** or **methylphenidate**. Because of this, conclusions about the relative safety of these two less frequently used stimulants should not be reached on the basis of this analysis.

IV. DISCUSSION / LITERATURE REVIEW

A. PEDIATRIC AGE GROUP (1-18 YEARS)

Six of the 12 pediatric sudden death cases during therapy with **amphetamine** described potential cardiac risk factors including undiagnosed cardiac abnormalities (e.g., bicuspid aortic valve, idiopathic hypertrophic subaortic stenosis) or positive family history of ventricular arrhythmia. Development of cardiac hypertrophy was considered to be related to chronic **amphetamine** therapy and to have contributed to sudden death (collapse while running with full cardiac arrest) in one pediatric case (3887728-7).

Cardiac risk factors were described in three of the **methylphenidate** cases and include one case with congenital cardiac malformation (abnormal origin of left coronary artery subject to compression by the aortic root), one case of cardiac hypertrophy, and a history of syncope in one case.

Unusual and unexplained accumulation of drug resulting in toxic levels during usual therapeutic dosing also appears to have played a role in several of the pediatric sudden

¹⁵ Taubes G. Epidemiology faces its limits. *Science* 1995;269(14):164-9.

death cases (ISR#s 3789506-6, 3978812-8, both patients taking **amphetamine**; and, ISR# 3986870-X, in which patient was taking **methylphenidate**).

The urinary excretion of amphetamine is known to be dependent on urine pH;¹⁶ however, variations in urine pH associated with accumulation of toxic amphetamine levels have not been described in published literature, based on a Medline search. A recent review of potential drug interactions with psychostimulants¹⁷ states that **amphetamine** has been “involved in apparent pharmacodynamic interactions and could be influenced by medications affecting cytochrome P450 (CYP) 2D6.” The authors found that **methylphenidate** “appears to be more often implicated in pharmacokinetic interactions suggestive of possible metabolic inhibition, although the mechanisms still remain unclear.” A single dose pharmacokinetic study with **methylphenidate**¹⁸ showed a lack of involvement of CYP2D6 in the metabolism of **methylphenidate**, and concluded that drugs that are inhibitors of CYP2D6 when taken concurrently with **methylphenidate** should not affect its plasma concentration. Since little information was provided in the case reports, and no similar cases were found in published literature, no conclusions can be made at this time as to the mechanism or potential clinical importance of stimulant accumulation in children taking apparently normal doses of drug.

Estimates of the incidence of sudden death in young persons range from 1.3 to 8.5 per 100,000 patient-years, with “males consistently outnumbering females.”¹⁹ Incidence densities (rates per person-time) are provided here for context and are not intended to be compared to prescription-based reporting rates as calculated in this consult. Comparable to some of the clinical factors (potential risk factors) found in this case series, in a review of pediatric sudden death from cardiac causes, Liberthson²⁰ states that, after the first year and through the third decade of life, the “most common cardiac causes of sudden death include myocarditis, hypertrophic cardiomyopathy, coronary artery disease, congenital

¹⁶ Anggard E, Jonsson LE, Hogmark AL, et al. Amphetamine metabolism in amphetamine psychosis. *Clin Pharmacol Ther* 1973; 14: 870-880.

¹⁷ Markowitz JS, Patrick KS. Pharmacokinetic and pharmacodynamic drug interactions in the treatment of attention-deficit hyperactivity disorder. *Clin Pharmacokinet* 2001; 40(10): 753-72.

¹⁸ DeVane CL, Markowitz JS, Carson SW, et al. Single-dose pharmacokinetics of methylphenidate in CYP2D6 extensive and poor metabolizers. *J Clin Psychopharmacol* 2000 Jun; 20(3): 347-9.

¹⁹ Liberthson RR. Sudden death from cardiac causes in children and young adults. *N Engl J Med* 1996; 334(16): 1039-1044.

coronary-artery anomalies, conduction-system abnormalities, mitral –valve prolapse, and aortic dissection.” Extrapolation of these data suggests that “each year several thousand Americans under the age of 20 years die suddenly from cardiac disorders.”²¹ Because sudden death may be an outcome of these conditions alone, it is difficult at this time to assess the additive risk associated with stimulant therapy in this population of patients.

Driscoll²² determined the incidence of pediatric sudden death during the 32 year period from 1950 to 1982 in Olmstead County, Minnesota by a review of death certificates for all residents of that county who were between the ages of 1 and 22 years when they died. Of 515 death certificates reviewed, 12 (2.3%) recorded sudden unexpected death, resulting in an incidence of 1.3 per 100,000 patient-years. The subjects ranged in age from 3 to 20 years (median 13); 8 of the 12 were male. Of the 12 deaths, 4 were definitely cardiac-related and 3 were probably cardiac-related. The cause of death was unknown in the remaining 5 cases. Three of the 12 patients had a history of syncope; 2 of the 3 had syncope during exercise, and both died while exercising. Risk factors identified by Driscoll which he considered warranted thorough evaluation were 1) exercise-associated syncope; 2) nonvasodepressor syncope; 3) a family history of sudden unexpected death; or 4) a family history of hypertrophic cardiomyopathy.

In his review of pediatric sudden death, Liberthson recommends prompt cardiac evaluation for children or young adults with “exertional chest pain not affected by movement, inspiration, or palpation and without an apparent noncardiac cause, particularly if the patient has a high-risk cardiac disorder, a family history of sudden death, or exertion-related, unexplained syncope that is unheralded or preceded by palpitation.”²³ It would clearly seem prudent that any of these conditions should be fully evaluated prior to initiation of stimulant therapy, and certainly if onset is noted during stimulant therapy. It is not known to what extent the presence of cardiac risk factors in children receiving stimulant therapy may increase the risk of sudden death.

²⁰ Liberthson RR. *op cit.*

²¹ Liberthson RR. *op cit.*

²² Driscoll DJ, Edwards, WD. Sudden unexpected death in children and adolescents. *JACC* 1985; 5(6): 118B-121B.

²³ Liberthson RR. *op cit.*

B. ADULT AGE GROUP (19+ YEARS)

The risk of sudden death among the population aged 35 years and older is on the order of 1-2 per 1000 per year; between the ages of 40 and 65 years, there is a marked increase, with coronary artery disease as the most important cause.²⁴

A published review²⁵ of 61 prospective observational epidemiological studies of blood pressure and mortality (N=1,000,000) determined that “throughout middle and old age, usual blood pressure is strongly and directly related to vascular (and overall) mortality, without any evidence of a threshold down to at least 115/75 mmHg.” During middle age (40-69 years), the authors found that “each difference of 20 mmHg usual systolic blood pressure (or, approximately equivalently, 10 mmHg usual diastolic blood pressure) is associated with more than a twofold difference in the stroke death rate, and with twofold differences in the death rates from ischemic heart disease and from other vascular causes.” The usual DBP was therefore strongly and positively related to risk not only among those individuals who might be considered hypertensive, but also among those who would usually be considered normotensive. Chronic elevation of blood pressure of this magnitude is thus associated with an increased risk for cardiovascular diseases.

Pre-existing hypertension was described in three of the five adult sudden death cases during **amphetamine** therapy, which suggests that this may be an important risk factor for stimulant-associated sudden death in the adult population. A history of coronary artery disease and unspecified dysrhythmia was also present in one of the cases. No information about underlying risk factors was reported in the adult sudden death case during **methylphenidate** therapy.

²⁴ Janse, MJ. A brief history of sudden cardiac death and its therapy. *Pharmacol and Therapeutics* 2003; 100: 89-99.

²⁵ MacMahon S, Peto R, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; 360:1903-13.

V. CONCLUSION / RECOMMENDATION

A. PEDIATRIC AGE GROUP (1-18 YEARS)

Sudden death and serious cardiovascular adverse events including stroke have been reported in association with **amphetamine** and **methylphenidate** at usual doses in the treatment of children with ADHD. Limitations of available information and methods do not allow a direct comparison of reporting rates of sudden death during stimulant therapy with background rates of sudden death in the general pediatric or adult populations. Although calculated reporting rates for death, sudden death, or nonfatal cardiovascular SAEs including stroke do not exceed one case per million prescriptions dispensed, it is not known to what extent under-reporting of cases may result in an underestimate of the incidence of these events.

Because **dexmethylphenidate** and **methamphetamine** have been prescribed much less often than **amphetamine** and **methylphenidate**, as shown by IMS drug utilization projections, conclusions about the relative safety of these two stimulant therapies cannot be made on the basis of this analysis.

The rare occurrence of pediatric sudden death during stimulant therapy of ADHD is an issue that warrants close monitoring. This case series of pediatric sudden deaths includes reports of undiagnosed structural cardiac abnormalities and positive family history of ventricular arrhythmias. Since these are well-described independent risk factors for pediatric sudden death, the contribution from stimulant therapy cannot be quantified. Under the assumption that there is an independent association between stimulant therapy and pediatric sudden death, it would be prudent for approved product labeling to recommend that clinicians consider the benefit versus risk of stimulant therapy in patients with established structural cardiac abnormalities.

B. ADULT AGE GROUP (19+ YEARS)

Sudden death and serious adverse events including hypertension, myocardial infarction, or stroke have been reported in association with **amphetamine** and **methylphenidate** at usual doses in the treatment of adults. A potential risk factor identified in this analysis for the adult population is hypertension. Physiologic studies^{26, 27} have demonstrated an increase in blood pressure and heart rate during stimulant therapy. How these changes affect the population using these medications is still not clear. AdvancePCS drug utilization data show considerable off-label use of amphetamine salt products and methylphenidate in adults; 11.5% of amphetamine use and 17.2% of methylphenidate use is in those over 40 years of age.²⁸

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure²⁹ states that the risk of cardiovascular disease begins with a blood pressure of 115/75 mm Hg and doubles with each increment of 20/10 mm Hg. Since hypertension is the most common primary diagnosis in America, it is important to consider the burden of cardiovascular illness that would result from chronic and widespread utilization of stimulant among the adult population.

Further evaluation of how these products affect long term cardiovascular outcomes is recommended.

²⁶ Stowe C, Gardner S, Gist C, Schulz E, Wells T. Twenty-four hour ambulatory blood pressure monitoring in male children receiving stimulant therapy. *Ann Pharmacother* 2002; **36**: 1142-1149.

²⁷ Matochik JA, Nordahl, TE, Gross M, Semple WE, King C et al. Effects of acute stimulant medication on cerebral metabolism in adults with hyperactivity. *Neuropsychopharmacol* 1993; **8**(4): 377-386.

²⁸ ODS Consult, Division of Surveillance, Research and Communication Support, HFD-410, "CNS Stimulant Drug Use and Duration of Therapy Review", March 1, 2004.

²⁹ Chobanian AV, Bakris GL, Black HR, et al. National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 Report. *Hypertension* 2003; **42**: 1206-1252.

APPENDIX A

AMPHETAMINE (including ADDERALL[®] and ADDERALL XR[®])

ADDERALL AND OTHER AMPHETAMINES

A comprehensive search of the AERS safety database was conducted to identify all reports with a fatal outcome in which ADDERALL, Dexedrine, or any other brand or generic formulation of amphetamine or dextroamphetamine were considered to be a suspect drug. Datalock for this search was December 31, 2003. A total of 149 cases meeting these criteria were found. Of these, 114 cases were excluded from further analysis for the following reasons:

- In seven cases the suspect drug was Eskatrol (a combination product containing amphetamine and prochlorperazine): ISR numbers 9575-9, 66943-7, 72256-X, 72821-X, 79512-X, 411071-1, 417799-1
- Eighteen reports were identified as duplicates: ISR numbers 3086467-2, 3471045-3, 3562120-3, 3671472-5, 3677969-6, 3731168-8, 3788756-2, 3972359-0, 3982225-2, 3756564-4, 3859036-1, 4055716-6, 4092127-1, 3692401-4, 4111983-1, 4258509-X, 4256552-8; and one ISR number (3459227-8) corresponded with two different case numbers (3437056 and 3437058)
- In 79 cases the decedent had ingested many drugs at the same time in a setting of drug abuse (33 cases), suicide (26 cases), or for undetermined reasons (20 cases)
- In three cases (979052-7, 65644-9, 4220030-2), death occurred as a result of illicit amphetamine abuse (with no other drugs identified)
- In three cases the patient did not die (4019482-2, patient's child died in MVA while patient was driving; 796947-8, patient's wife had miscarriage; 4205656-4, intra-uterine death after maternal exposure to amphetamine)
- In three cases, phentermine or fenfluramine were suspect drugs (two cases of fatal pulmonary hypertension: 1923045-X and 1987322-9, and one case reported as fatal coronary artery disease: 3355565-8)
- In one case (3981827-7) no amphetamine was taken (miscoded case)

In the remaining 35 cases, suspect amphetamine-containing drug was identified in the AERS database as: ADDERALL (24 reports), amphetamine (1), Biphetamine (1), Dexedrine (8), and dextroamphetamine (1). Patient age was reported in all but one case, and ranged from seven to 77 years. The majority of these 35 reports (57%) described children ≤ 19 years of age. Four reports described patients between seven and ten years of age (inclusive). Patient age at the time of death was eleven years in three cases, twelve years in three cases, thirteen years in three cases, fourteen years in two cases, fifteen years in two cases, sixteen years in two cases, and nineteen years in one case. Patient age was between 20 and 30 years in four cases, between 31 and 40 years in two cases, between 41 and 60 years in five cases, and older than 60 years in three cases. Patient gender was female in eight cases, male in 26 cases, and not reported in one case. Country of origin was the US for all 35 reports.

The majority (80%) of these 35 reports were received during the past five years. Seven reports were received between 1970 and 1997, three were received in 1999, five in 2000, nine in 2001, three in 2002, and eight of these 35 reports were received in 2003.

A narrative summary of each of these 35 cases is presented below. Reports are identified as follows: ISR number / country of origin (case number) (dup - ISR number for duplicate cases, if any).

ARRHYTHMIA

366947-0/US (4460691): An attorney reported that a 34 year old female developed an unspecified cardiac arrhythmia and died after approximately nineteen years of therapy with “a diuretic, synthetic thyroid preparation and an amphetamine” for the treatment of obesity. For approximately five years prior to her death, the specific amphetamine was Biphphetamine (resin complexes of amphetamine and dextroamphetamine), dose not specified. Concomitant medications included Synthroid and Lasix (dose and duration of therapy not specified). No additional information was provided.

CARDIAC ARREST

1731747-3/US (5381331): A physician reported that a 47 year old female collapsed, was found to be in ventricular fibrillation, and could not be resuscitated after approximately one year of therapy with Dexedrine 40 mg daily for the treatment of ADHD and two months of therapy with Effexor 37.5 mg three times daily for the treatment of depression. Concomitant medications included Inderal (dose not reported) and unknown “herbal medicines”. The patient was previously “physically healthy” with no prior cardiac history. Autopsy toxicology studies showed venlafaxine level 1,052 ng/mL and desmethylvenlafaxine level 220 ng/mL (reference ranges not provided). No additional information was provided.

3887728-7/US (3776530): A newspaper reporter and a medical examiner reported that a 14 year old male developed shortness of breath while running, followed by collapse and full cardiac arrest after approximately four years of therapy with ADDERALL (dose not specified) for the treatment of ADHD. The patient collapsed during exercises for his high school ROTC class. Prior therapy included Ritalin (dose and duration of therapy not reported). Autopsy showed the heart weighed 315 grams. The coroner stated that the expected cardiac weight for this child’s body weight is 206-299 grams, and the expected cardiac weight for the child’s age is 213-237 grams. Heart blood amphetamine level was 0.22 mg/L. Mild ventricular hypertrophy was noted, and was concentric, with no definite septal asymmetry noted. Microscopic examination showed “equivocal evidence of myocardial cell hypertrophy.” Postmortem diagnosis was “Sudden collapse and death of 14 year old male during exercise class at school; past history of cardiac murmur diagnosed as a functional murmur; short history of dyspnea prior to terminal collapse; cardiac hypertrophy; pulmonary congestion and edema; no evidence of trauma; history of treatment with ADDERALL (amphetamine) for attention deficit disorder, treatment lasted several years; toxicological examination (heart blood) positive for amphetamine.” The coroner concluded that the cause of death was “cardiac hypertrophy, years, due to chronic amphetamine toxicity, years, due to ADDERALL therapy, years.” The coroner commented that “the subject died as a result of a cardiac arrhythmia due to amphetamine-related cardiac hypertrophy. The level of amphetamine in the blood at the time of death was higher than would be generally expected with a therapeutic dose.”

4041466-9/US (3889978): An attorney reported that a 76 year old female with a history of irritable bowel syndrome, urinary incontinence, osteoarthritis, hypertension, headaches, hiatal hernia, depression, anxiety, memory deficits, chronic fatigue syndrome, deep vein thrombosis, pulmonary embolism, peptic ulcer disease, and obesity, developed dizziness, and was later found dead lying face down in the hall, after four months of therapy with Lotronex 1 mg twice daily for the treatment of diarrhea-predominant irritable bowel syndrome, and Dexedrine 5 mg twice daily for the treatment of fatigue (duration of therapy not specified). The patient’s physician had recently advised her to decrease her dose of Dexedrine because of hypertension. Concomitant medications included citalopram, venlafaxine, ranitidine, lansoprazole, donepezil, methylcellulose, oxybutynin, verapamil, warfarin, allopurinol, thyroxin, losartan, Celecoxib and Excedrin. The death certificate indicated the cause of death as cardiac dysrhythmia and arrest due to pre-existing coronary artery disease.

4069419-5/US (4050182-9): A pediatrician reported that a 19 year old female developed chest pain, dyspnea, cardiac arrest, heart failure, cardiomyopathy, persistent vegetative state, and subsequently expired after taking an unknown amount of ADDERALL, and possibly some unknown "over the counter diet pills". The pediatrician stated that her patient, a "straight-A" student, obtained ADDERALL "on her own", and "possibly to help her study for finals week at college". The reporter didn't know how much ADDERALL her patient took or for how long, as she did not prescribe this for her. On _____, the student woke up her roommate complaining that her chest hurt and she couldn't breathe. She collapsed. She was defibrillated twice at the scene and intubated. She was taken to the hospital with congestive heart failure. A catheterization showed a 20% ejection fraction. The first ECG showed slow junction escape rhythm and then ventricular tachycardia. She was diagnosed with biventricular cardiomyopathy. She was "down for about eighteen minutes". Her condition was described as "persistently vegetative". An intra-aortic balloon was placed, and a gastrostomy tube was inserted. The tracheotomy was capped. She was transferred to another hospital. Results of a myocardial biopsy and viral titer were not reported. The toxicology screen was "positive for amphetamine only". The reporter stated "there was ADDERALL in the room". It is unknown how much ADDERALL the patient took. Information about the identity or amount taken of "over the counter diet pills" was not available. The patient had no history of cardiac problems and took no other medications. A police investigation was ongoing. Supplemental information indicated the patient subsequently died.

4151000-0/US (3974885) (dup 4111983): A physician reported via a sales representative that a 42 year old male with a history of hypertension, obstructive sleep apnea, and dysrhythmia (unspecified), developed chest pain, ventricular fibrillation (witnessed in the hospital emergency room), asystole, and subsequently expired despite resuscitation efforts, after approximately nine months of therapy with ADDERALL XR 15 mg daily intermittently for the treatment of ADD. The patient weighed 239 pounds. Concomitant medications included hydrochlorothiazide and quinapril. An autopsy was not done. The reporter considered that the events were probably related to ADDERALL therapy.

CEREBROVASCULAR ACCIDENT

135872-2/US (4357946): A male patient (age not specified) developed a severe headache and clinical symptoms suggestive of cerebral aneurysm during therapy with Dexedrine 60 mg daily for the treatment of narcolepsy (duration of therapy not specified). As he was being prepared for an angiogram, he had a catastrophic episode suggesting rupture of the aneurysm and died shortly thereafter. The angiogram was not completed, and an autopsy was not done.

3004170-1/US (3003088): A physician reported via a sales representative that a 51 year old male experienced a fatal stroke in _____ after approximately three years of therapy with ADDERALL 20 mg three times daily for the treatment of ADD. Medical history included a "possible history of cardiovascular problems". No additional information was provided.

DROWNING

3459227-8/US (3437058) (dup 3471045): A physician reported that a 10 year old male drowned while swimming in shallow water after seven months of therapy with ADDERALL 20 mg daily for the treatment of ADHD. He had been unsuccessfully treated in the past for ADHD with paroxetine, sertraline, and bupropion. On _____ at approximately 4:30 pm he drowned while swimming with other campers in a shallow pond. He had been taking ADDERALL as prescribed and was taking no other medications. It was reported that his mother turned her back for a moment to get a camera and when she looked again he had disappeared. Twenty-two minutes later his body was recovered in the deepest part of the pond, which was seven to eight feet deep. The patient was an athletic boy who played soccer and baseball, and had no medical history other than ADHD. A neurologist had recorded a weight of 77 pounds and height of 54 inches on _____. The pediatrician reported that the boy was approximately 50th percentile for both height and weight. An autopsy showed findings "consistent with a fresh water drowning. The causes predisposing to the drowning are unclear. There may have been exhaustion. The stomach was noted to contain a large amount of food, suggesting a recently eaten meal. The possibility that stomach cramps impaired the swimmer is also suggested. There is no evidence of any traumatic injury to the deceased which would suggest a loss of consciousness or incapacity to facilitate the drowning." Drug screen analysis showed a whole blood

amphetamine level of 229 ng/mL and urine amphetamine level of >12,500 ng/mL. The coroner stated that “it is my opinion that the whole blood level amphetamine reading is a little high for a therapeutic range. However, it is too low to have had any likely role in loss of control, either motor or sensory.”

HEAT STROKE

3789498-X/US (3706375) (dup 3788756-2): A medical examiner reported that a 14 year old male died of complications from heat exhaustion, dehydration, and near-drowning after several weeks of therapy with ADDERALL 30 mg daily for the treatment of ADHD. Concomitant medications included divalproex sodium 775 mg daily for the treatment of post traumatic stress disorder. Medical history included depression, possibly psychotic symptoms, but no other significant medical or surgical history. Weight was 205 pounds. The patient was living at a tent based facility for troubled youth near _____ On the day of his death, the temperature at the boot camp was between 109 to 111 degrees Fahrenheit. The patient was reportedly given 50 mg of ADDERALL instead of his usual 30 mg dose. According to the reporter, “the patient was being punished and was told to sit in the dirt for two to three hours.” Access to water was reportedly restricted. The patient became delirious and began eating dirt. He was taken to a hotel and was put in a bathtub. He was found face down in the bathtub. He was still breathing when taken out of the bathtub. He was lethargic and his pulse was 160 to 180. No body temperature was taken. Emergency services were called. He was found to be in asystole and was air-transported to a hospital. The patient was dead on arrival at the hospital. ADDERALL was considered a suspect medication. Autopsy results identified the cause of death as complications from near-drowning and dehydration due to heat exposure. The patient died approximately four to five hours after first becoming delirious.

MYOCARDIAL INFARCTION

3195487-9/US (3206763): A physician reported that a 62 year old male experienced a fatal myocardial infarction while shoveling snow after thirteen days of therapy with ADDERALL 15 mg daily (10 mg in the morning and 5 mg in the evening) for the treatment of ADD. The patient was dead at the time EMT personnel arrived. The patient had not taken any ADDERALL on the day of his death (_____). His last dose was taken on the previous day at approximately 3:30 pm. The dose of ADDERALL had been titrated from a starting dose of 5 mg daily for three days to a total daily dose of 15 mg on _____. The patient was seen by his physician on _____ and “denied any comorbid health conditions”. Blood pressure at that time was 155/95 and weight was 210 pounds. No cardiovascular function tests were performed. The patient did not take any other prescription, herbal, or over the counter drugs. Past medical history included alcoholism (no alcohol use over the past nine years), and “poor dietary habits”.

3391203-6/US (3385135): A physician reported via a sales representative that a 56 year old male with a history of hypertension and hypercholesterolemia experienced a fatal myocardial infarction during therapy with Dexedrine 15 mg twice daily for the treatment of ADHD. Dexedrine therapy was initiated in January 1997, then was switched to Ritalin at the patient’s request on two different occasions in mid-1997 for three months and in early 1999 for two months; however, the patient requested on both occasions to be switched back to Dexedrine “as it was more efficacious”. An ECG was noted to be normal in 1997. Concomitant medications included Vasoretic (enalapril + hydrochlorothiazide) and “another unidentified agent” for hypertension which had been diagnosed in 1985. Family history was positive for coronary artery disease. The patient was a nonsmoker, and cholesterol levels were never >250.

4223562-6/US (4029308) (dup 4258509-X): A reviewing psychiatrist in a legal case reported that a 12 year old male with a history of bipolar disorder, oppositional defiant disorder, and other unspecified conditions, experienced a fatal myocardial infarction during therapy with ADDERALL immediate release formulation 15 mg twice daily. Total duration of therapy was not specified, but the reporter stated that the dose had been increased to 15 mg twice daily “several months prior to his death”. The child collapsed after playing basketball at about 5 pm. His “cardiac enzymes were increased at the 1 am blood draw”. At 5:30 am on _____, the “wall of his heart blew out and CPR was performed”. The child died. An autopsy showed “aberrant origin of right main coronary around aorta and embedded in fibrous tissue”. The reporter stated that the child had experienced “palpitations and dizziness at the lower dose”, and there had been “at least one episode of tachycardia during treatment (not followed well)”.

Reportedly, his “general practitioner had wanted cardiac studies but did not share this information with the prescribing psychiatrist”. The child had a pre-existing cardiac malformation which was not known. No information was provided pertaining to concomitant medications.

PULMONARY EMBOLISM, ARDS

348504-5/US (4445683): A 77 year old female developed acute severe shortness of breath and was admitted to a hospital after “many years” of therapy with Dexedrine Spansules 15 mg daily for the treatment of narcolepsy. Other concomitant medications included Monocid. About ten days prior, she had visited her doctor for bronchitis, and was given penicillin, Novafed-A, and cough syrup. At the time of admission, the patient appeared extremely ill, somewhat emaciated, with normal blood pressure, temperature 101, and weighing 110 pounds (her usual weight). Rales, rhonchi and wheezes were heard throughout both lung fields. Admitting diagnoses included acute bronchitis, acute pneumonitis, narcolepsy, degenerative arthritis, and questionable diabetes. The patient’s hospital course was “steadily downhill” with numerous complications including anemia requiring blood transfusion, pneumonia treated with multiple antibiotics, encephalopathy, hypoxia requiring mechanical ventilation, hypotension, poor urine output, paroxysmal atrial tachycardia with bundle branch block treated with verapamil and lanoxin, pulmonary edema, pulmonary emboli treated with heparin, and thrombocytopenia. On the twelfth hospital day, the patient arrested and developed ventricular tachycardia. Attempts at resuscitation were not successful. Past medical history included hospital admission four years prior for acute urinary infection and septicemia. Autopsy showed (provisional anatomic diagnosis): mild cardiomegaly (440 grams); cardiac mural thrombus, apex of left ventricle, etiology undetermined; multiple pulmonary infarcts; pulmonary embolus; severe pulmonary edema; possible bronchopneumonia; coronary atherosclerosis, moderate; aortic arteriosclerosis, moderate; hydrothorax, left (700 mL); peripheral edema, moderate; adrenal hypoplasia; arterial and arteriolar nephrosclerosis. A comment on the autopsy report stated “the mural thrombus of the left endocardium does not explain the patient’s multiple pulmonary emboli in that the foramen ovale is not patent. The multiple pulmonary emboli are presumed to be thromboemboli from the right side of the heart.”

RHABDOMYOLYSIS

3224225-6/US (3214508) (dup 3086467-2): A hospital pharmacist and an attorney reported that a 14 year old male developed acute rhabdomyolysis and subsequently expired after approximately four weeks of therapy with Dexedrine 35 mg daily, decreased to 25 mg daily due to nausea, for the treatment of ADHD. Previous therapy for ADHD included methylphenidate (dose and duration of therapy not reported). On _____, the patient was playing basketball when he went up for a shot and was undercut, landing on his left shoulder and left hip. The next day he was taken to a hospital ER with complaints of myalgia and joint pain and diagnosed with probable viral syndrome. Three days later, the child was again taken to the hospital with complaints of worsening pain all over. X-rays were negative and he was treated with Tylenol with codeine, and Motrin. On _____ the child was seen by a doctor due to inability to put weight on his legs, pain in his legs and arms, and dark urine. He was admitted to a hospital for possible rhabdomyolysis. At the time of admission, CK was 234,000 and urinalysis showed 4+ proteinuria with large amounts of blood and negative myoglobin. On _____ the patient was noted to have a heart rate of 161 and respirations 30, and continued to complain of pain. He became agitated with BP 183/138, and then became unresponsive with gasping respirations and then apnea. Resuscitation attempts were unsuccessful. An autopsy was performed the next day. Final anatomic diagnoses were: 1) massive diffuse acute and subacute rhabdomyolysis and active interstitial myocarditis – most consistent with viral or post-viral etiology; 2) acute hyperkalemic episode; 3) multiple enzymatic abnormalities secondary to rhabdomyolysis; 4) congested lungs (post resuscitative state); 5) probable early acute tubular necrosis – myoglobin casts present; 6) reactive lymphadenopathy; 7) minimal cerebral edema, most consistent with acute terminal state and resuscitative measures. The pathologist stated that he was later notified by the reporting attorney that the deceased had been taking Dexedrine at the time of the events, which neither he nor the other physicians had been aware of. He concluded that this was vital information and would alter his interpretation of the findings. The diagnosis and cause of death were amended as 1) massive diffuse acute and subacute rhabdomyolysis – most consistent with associated dextroamphetamine intake. Cause of death: acute and subacute massive rhabdomyolysis associated with dextroamphetamine intake.

SUDDEN DEATH

3534227-8/US (3505904) (dup 3562120): A psychiatrist reported via a sales representative that a 22 year old female was “found dead in the community home in which she lived” in _____ after four months of therapy with ADDERALL 20 mg daily for the treatment of ADD and one year of therapy with Wellbutrin (bupropion) 225 mg daily (indication not reported). The cause of death was unknown but it did not appear that any physical harm was done to her. Medical history and other concomitant medications were not reported. Results of an autopsy were not reported.

3555682-3/US (3521975): A newspaper article and the father of the patient reported that a 15 year old male collapsed while playing basketball on _____, and was subsequently pronounced dead at the hospital after approximately three years of therapy with ADDERALL 20 mg for the treatment of ADD. The child’s father stated that the cause of death was explained to him as “an arrhythmia caused by an increased density of the muscle around the heart”, and that “neither the family physician nor the medical examiner considered ADDERALL a suspect in his son’s death.” Since his son had been asymptomatic, “the condition remained undiagnosed”. The child had “appeared healthy during a recent sports physical.” His son was an honor student with no history of drug abuse. Medical history included an unspecified “heart murmur” which had been diagnosed at age nine months, which was followed by the physicians until it was felt to have “resolved” at age two years. There is no family history of cardiac disease.

3613516-2/US (3569797): A physician reported that a 15 year old male died suddenly after 18 months of therapy with ADDERALL 20 mg daily for the treatment of ADHD. There were no concomitant medications. Autopsy showed “no gross major organ abnormalities, including his heart. A toxicology screen was negative. The only significant post-mortem finding, based on tissue assay, was neutropenia. The patient had no prior history of neutropenia.” No additional information was provided.

3686984-8/US (3625300) (dup 3671472-5 and 3677969-6): A physician reported via a sales representative that a 28 year old patient developed flu-like symptoms and chest pain, and died suddenly, during therapy with ADDERALL and Celexa (citalopram). No additional information was provided.

3753892-3/US (3678776) (dup 3731168-8): A pediatrician reported that a 16 year old male died suddenly after two years of therapy with ADDERALL 40 mg daily for the treatment of ADD and one to two years of therapy with Zyprexa (olanzapine) 5 mg daily for the treatment of ADHD and personality disorder. On _____, he was found dead on the floor beside his bed. The autopsy showed hepatic steatosis. The reporting physician considered that there may have been an interaction between the two medications, but there was no evidence of an interaction.

3782505-X/US (3701541) (dup 3859036-1): A pediatrician reported that a 13 year old male collapsed while working at his computer and died suddenly after taking a single dose of ADDERALL 20 mg for the treatment of ADHD. He had been seen by a physician for a physical exam the previous day, with complaints of school problems and was diagnosed with ADHD. Blood pressure and heart rate were normal. Weight was 118 pounds. He was active in sports. The patient took a single dose of ADDERALL 20 mg at 10:30 am, complained of tiredness about midday, and collapsed at his computer in late afternoon. A pulse was present when emergency personnel arrived, but he was pulseless at the hospital. An autopsy showed idiopathic hypertrophic subaortic stenosis (IHSS), “apparently a genetic disorder”, and an enlarged heart “filling complete chest”. The number of ADDERALL tablets was correct in the remaining drug supply. No concomitant medications were reported. Final pathology report and drug screening results were not provided. The reporting physician considered that the cause of death was cardiomegaly (unrelated to ADDERALL), and arrhythmia possibly caused by ADDERALL.

3789506-6/US (3706321): A physician reported that an 11 year old male with a history of insulin dependent diabetes “went to bed and never woke up” after four years of therapy with ADDERALL 10 mg twice daily for the treatment of ADHD. The last dose had been taken two days prior to the child’s death. Concomitant medications included insulin only. The coroner reportedly told the child’s physician that the amphetamine level was “out of sight (900-1000)”. The child had no known renal or hepatic abnormalities.

3811155-1/US (3723113): A pediatrician reported that a 7 year old male with a history of heart murmur died suddenly during therapy with ADDERALL (dose, duration of therapy, and indication not reported). The child was

found dead in his bed on _____ . Autopsy showed bicuspid aortic valve and no other abnormalities. The "tox screen was negative for amphetamines". The coroner considered that the child died of an arrhythmia.

3818607-9/US (3727777): A pharmacist reported via a sales representative that a 10 year old male died suddenly during therapy with ADDERALL (dose, duration of therapy, and indication not reported). The pharmacist stated that three or four years ago she heard that a 10 year old boy collapsed and died on a soccer field, possibly in _____ . The child had reportedly been taking ADDERALL since he was two years old. The pharmacist didn't remember the source of the information, and was unable to provide additional information.

3978812-8/US (3844047) (dup 3982225): A physician reported that an 11 year old male died suddenly during therapy with ADDERALL 20 mg daily (duration of therapy, and indication not reported). The reporting physician also provided information from an article in the _____ . According to the article, the patient collapsed during activities at a camp. He had been taking ADDERALL 20 mg daily "for some time". An autopsy and toxicology testing showed that he "died as a result of an elevated level of the prescription drug ADDERALL." Blood level of the drug at the time of death was 210 ng/mL, with toxic levels considered to be ≥ 150 ng/mL. The number of tablets of the drug remaining in the child's prescription bottle was correct according to the number purchased and his medication schedule. The remaining tablets were sent for independent analysis, which confirmed that the concentration of the drug in each of the tables tested was consistent with product labeling. The coroner stated that the elevated level of ADDERALL found in the blood was the result of "his body's apparent inability to properly metabolize and dispose of the medicine normally, resulting in a buildup of the drug that ultimately reached a toxic level sufficient to cause arrhythmia and death."

4112853-5/US (3614279) (dup 3692401-4): A case report in published medical literature described an 8 year old male who developed a fatal cardiac arrhythmia after approximately eighteen months of therapy with imipramine, and three months of therapy with dextroamphetamine for the treatment of ADHD. At the time of his death, the child was taking imipramine 100mg twice daily (6.9 mg/kg/day), and dextroamphetamine 10mg daily. The recommended dose of imipramine was noted by the author to be 5 mg/kg/day. Previous therapy included methylphenidate, prior to the initiation of dextroamphetamine. The patient was playing basketball when he suddenly clutched his chest saying his "chest hurt", and collapsed. At the hospital he was noted to be in full cardiac arrest. Resuscitation efforts were unsuccessful. At the time of ADHD diagnosis at age 7 years, the child was in generally good health with no history of cardiovascular or other significant health problems. Prior to initiation of imipramine, an ECG was noted to be normal. Autopsy results indicated a "toxic amount of imipramine and desipramine in his system." Imipramine level was 480 ng/mL and desipramine level was 740 ng/mL. The death certificate stated death was caused by "cardiac arrhythmia caused by imipramine intoxication." *Citation:* Varley CK, 2000, "Sudden death of a child treated with imipramine", J Child and Adolescent Psychopharmacol, Vol 10 (4), pages 321-325.

4163447-7/US (3985139) (dup 3972359-0): A pediatrician reported via a sales representative that a 12 year old male died suddenly on _____ after taking a single dose of ADDERALL XR 10 mg for the treatment of ADHD. Previous treatment for ADHD included Ritalin (methylphenidate) for about four years (dose not reported). Medication was changed to ADDERALL XR 10 mg, and the child took his first dose on _____ . At about 4 pm that day, he collapsed while running cross country. He had run about one to two miles. He could not be revived. Autopsy results were not reported. Family history was positive for maternal arrhythmia (ventricular tachycardia treated with implanted defibrillation and ablation) which the child's mother had developed about three years prior. The death certificate indicated the cause of death was sudden cardiac death.

SUICIDE (amphetamine only without other concomitant drugs)

6254-9/US (4231847): A health professional reported that a 23 year old female committed suicide by ingesting an unknown amount of amphetamine. She was admitted to a hospital with fever and convulsions, dilated pupils, hyporeflexia, and decorticate posture. Six hours after admission she developed hypothermia and decreased blood pressure, and subsequently expired "despite supportive care".

SUICIDE BY HANGING

3471046-5/US (3442770): A non-health professional reported that a 25 year old male with a history of depression and substance abuse (alcohol and cocaine) committed suicide by hanging after approximately three weeks of therapy with ADDERALL (dose and indication for therapy not reported). Concomitant medications included venlafaxine (dose and duration of therapy not reported) for the treatment of bipolar disorder. An autopsy had not been done at the time of the report. A post-mortem blood screen was negative for amphetamines. The patient was to have taken ADDERALL one tablet per day (dose not specified), but nine tablets were accounted for after the suicide. The original quantity from his first prescription should have been exhausted nine days prior to his death. There was no indication of a refill.

4049232-5/US (3897496): A physician reported via a sales representative that a 13 year old male committed suicide by hanging during therapy with ADDERALL for the treatment of ADHD (dose and duration of therapy not reported). He apparently had shown no indication that he might commit suicide, but after having an argument with his mother in _____ he went to his room and hanged himself. No additional information was provided.

3838254-2/US (3741293): An attorney and the father of the patient reported that a 12 year old male committed suicide by hanging on _____ during therapy with ADDERALL 30 mg daily for the treatment of ADHD. ADDERALL therapy was started in April 2000 when the patient was diagnosed with ADHD in sixth grade. A psychologist who evaluated him at that time diagnosed him with "ADD" and said he should be "monitored for depression". A neurologist prescribed ADDERALL based on the psychologist's evaluation, and suggested stopping ADDERALL over the summer, which was done. ADDERALL was resumed on August 1 (dose and duration of therapy not reported). The boy became "withdrawn from family and friends, his speech slowed, he seemed to us clearly depressed", however the psychologist did not change his therapy. The boy went to a seventh grade party, came home angry because he wasn't allowed to stay overnight with friends, and hanged himself with his belt from his chinup bar in his room. Autopsy was reportedly "negative for drugs".

3847231-7/US (3746163): A registered nurse who is also the patient's mother reported that an 11 year old male with a history of psychotic episodes committed suicide by hanging during therapy with Dexedrine 10 mg daily for the treatment of ADHD. Prior therapy included ADDERALL (dose not specified), which had been started three or four months prior, and was discontinued when Dexedrine 5 mg daily was started around August 2000. Dexedrine was increased to 10 mg daily in late _____. On _____, after taking his morning Dexedrine dose the child played with his friends outside. He came inside around noon and told his stepfather "his head felt funny, and he was hearing someone talking but no one was there." Approximately 30 minutes later, his mother found him dead in his bedroom. He had hung himself.

SUICIDE WITH GUN

4070563-7/US (3916202): A plaintiff's attorney reported that a 16 year old male with a history of major depression committed suicide with his father's gun during therapy with ADDERALL XR 30 mg daily (indication not specified) and clonidine (dose, duration of therapy, and indication not specified). ADDERALL XR 30 mg daily was started in February 2002 and stopped at the end of May 2002. It was restarted "on the first Monday in _____. On Monday, _____ his father found his deceased son's body in the house."

UNDERLYING DISEASE PROGRESSION

777013-4/US (4822093): A pharmacist reported that a 58 year old male with a history of progressive widely metastatic lymphoma status post recent radiation therapy and chemotherapy expired due to disease complications after two days of therapy with Dexedrine 2.5 mg daily for appetite enhancement. Concomitant medications included Elavil, mitoxantrone, morphine, Motrin, Promod, Restoril, Valium, and vinblastine. The patient weighed 152 pounds, height 73 inches. The patient had been diagnosed with T cell lymphoma ten years prior, and had undergone six cycles of cyclophosphamide, doxorubicin, vincristine and prednisone, and had sustained a complete remission for nine years. Subsequently, the disease relapsed, and despite aggressive therapy, the patient developed bone marrow, skin, and retroperitoneal lymph node involvement, and died due to unspecified disease complications.

4074653-4/US (3919502) (dup 4092127-1): A dentist and a physician's assistant (the patient's sister) reported via a sales representative that a 36 year old female with a history of osteosarcoma since age 15, tachycardia, severe

depression, prior suicide attempts, and cardiomyopathy caused by adriamycin, experienced abdominal pain, nausea, cardiac arrest, anoxia, encephalopathy, subarachnoid hemorrhage, respiratory failure requiring mechanical ventilation, and subsequently expired after removal from the ventilator after two months of therapy with ADDERALL 45 mg daily and Elavil (amitriptyline) 200 mg nightly. ADDERALL therapy was reportedly prescribed "to enhance the pain medications she was taking." Concomitant medications included Toradol (ketorolac tromethamine), Effexor-XR (venlafaxine), Ativan (lorazepam) and methadone. The patient had been scheduled for testing for an accessory pathway prior to the onset of the events due to her severe tachycardia. The cause of death was reported as a result of a "combination of ADDERALL and Elavil with a known cardiomyopathy."

TABLE A1 – ALL AMPHETAMINE REPORTS WITH A FATAL OUTCOME

ISRNUM	CK	CSENUM	RECVDATE	AGE	SEX	CNTRY	VERBDR1	CAUSE OF DEATH
6254	9	4231847	1-Apr-1970	23	F	US	AMPHETAMINE	suicide
30382	5	4255835	1-Jul-1971	24	F	US	MDI	MDI - unk
35118	X	4260571	1-Feb-1971	46	M	US	RITALIN	MDI - abuse
54984	5	4280228	1-Sep-1973	24	M	US	MDI	MDI - unk
64084	6	4289060	1-Aug-1974	24	F	US	MDI	MDI - unk
65644	9	4290620	1-Oct-1974	21	M	US	AMPHETAMINE	overdose of amphetamine (illicit)
70550	X	4295260	1-Apr-1975	33	M	US	MDI	MDI - unk
91497	9	4315842	1-May-1977	U	M	US	MDI	MDI - unk
122765	X	4345737	1-Oct-1981	27	M	US	PROPOXYPHENE	MDI - abuse
135872	2	4357946	18-Mar-1982	U	M	US	DEXEDRINE	CVA
348504	5	4445683	6-May-1985	77	F	US	DEXEDRINE	pulmonary embolism, ARDS
366947	0	4460691	17-Oct-1985	34	F	US	BIPHETAMINE	arrhythmia
389827	3	4480321	17-Apr-1986	28	F	US	MDI	MDI - suicide
389832	7	4480326	29-Apr-1986	32	M	CA	MDI	MDI - abuse
777013	4	4822093	24-Sep-1991	58	M	US	DEXEDRINE	underlying dis prog (cancer)
783601	1	4828047	23-Oct-1991	35	F	US	MDI	MDI - unk
796947	8	4840334	10-Dec-1991	U	Unk	US	DEXEDRINE	wife had miscarriage (pt did not die)
979052	7	5002546	17-May-1993	37	F	US	DEXEDRINE	amphetamine IVDA
1731747	3	5381331	27-Mar-1996	47	F	US	DEXEDRINE	cardiac arrest
1784764	1	5432781	24-Jul-1996	59	F	US	MDI	MDI-abuse
1923045	X	5566962	14-May-1997	56	F	FR	FENFLURAMINE	pulmonary HTN
1964911	9	5607704	21-Aug-1997	47	F	US	MDI	MDI - unk
1987322	9	3061247	17-Sep-1997	50	F	SE	PHENTERMINE	pulmonary HTN, right heart failure
1989199	4	3063054	23-Sep-1997	41	Unk		MDI	MDI - suicide
3004170	1	3003088	3-Dec-1997	51	M	US	ADDERALL	CVA
3082387	8	3039083	21-May-1998	30	M	AU	MDI	MDI - suicide
3086467	2	3785908	23-Apr-1998	13	M	US	DUP	dup of 3224225-6
3136176	6	3149402	28-Sep-1998	40	M		MDI	MDI - abuse
3136673	3	3151666	30-Sep-1998	44	M		MDI	MDI - abuse
3137048	3	3147761	30-Sep-1998	29	M		MDI	MDI - abuse
3137331	1	3151316	1-Oct-1998	42	M		MDI	MDI - abuse
3137333	5	3747133	1-Oct-1998	34	M		MDI	MDI - suicide by hanging
3137566	8	3154288	2-Oct-1998	26	M		MDI	MDI - abuse
3137725	4	3154896	2-Oct-1998	42	M		MDI	MDI - abuse
3195487	9	3206763	10-Feb-1999	62	M	US	ADDERALL	MI
3224225	6	3214508	22-Mar-1999	13	M	US	DEXEDRINE	rhabdomyolysis, myocarditis (dup of 3086467-2)
3355565	8	3323626	22-Sep-1999	53	M	US	PONDIMIN	coronary artery disease
3380738	8	3352494	25-Oct-1999	29	M	US	MDI	MDI - unk
3391203	6	3385135	8-Nov-1999	56	M	US	DEXEDRINE	MI
3459227	8	3437058	18-Feb-2000	10	M	US	ADDERALL	drowning (dup of 3471045)
3471045	3	3442765	6-Mar-2000	10	M	US	DUP	dup of 3459227
3471046	5	3442770	6-Mar-2000	25	M	US	ADDERALL	suicide by hanging
3493803	1	3462155	27-Apr-2000	31	M	US	MDI	MDI - unk
3495314	6	3468273	1-May-2000	38	F	US	MDI	MDI - unk
3534227	8	3505904	24-Jul-2000	22	F	US	WELLBUTRIN	sudden death (dup of 3562120)
3555682	3	3521975	22-Aug-2000	15	M	US	ADDERALL 10	sudden death
3562120	3	3528625	30-Aug-2000	22	F	US	DUP	dup of 3534227
3613516	2	3569797	17-Nov-2000	15	M	US	ADDERALL	sudden death
3651350	8	3595025	22-Jan-2001	43	Unk	US	MDI	MDI - suicide
3671472	5	3615158	28-Feb-2001	28	Unk	US	DUP	dup of 3686984-8 and 3677969-6
3677969	6	3619816	9-Mar-2001	28	Unk	US	DUP	dup of 3671472-5 and 3686984-8
3686984	8	3625300	21-Mar-2001	28	Unk	US	ADDERALL 10	sudden death (dup of 3671472-5 and 3677969-6)
3692401	4	3631576	28-Mar-2001	8	M	US	DUP	dup of 4112853
3727819	4	3658858	23-May-2001	33	M	US	MDI	MDI - abuse
3731168	8	3992759	30-May-2001	16	M	US	DUP	dup of 3753892-3
3740662	5	3666652	15-Jun-2001	36	M	US	MDI	MDI - abuse
3753892	3	3678776	6-Jul-2001	16	M	US	ADDERALL 10	sudden death (dup of 3731168-8)
3756584	4	3680762	11-Jul-2001	27	F	US	DUP	dup of 3983860
3782505	X	3701541	23-Aug-2001	13	M	US	ADDERALL	sudden death, cardiomegaly (dup of 3859036-1)
3788756	2	3706113	5-Sep-2001	14	M	US	DUP	dup of 3789498
3789498	X	3706375	7-Sep-2001	14	M	US	DIVALPROEX SODIUM	heat stroke
3789506	6	3706321	7-Sep-2001	11	M	US	ADDERALL	sudden death
3796445	3	3696535	19-Sep-2001	17	M	US	MDI	MDI - unk (self inflicted gunshot wound)
3806619	0	3720991	8-Oct-2001	40	F	US	MDI	MDI - suicide
3806654	2	3720215	8-Oct-2001	40	F	US	MDI	MDI - suicide
3807084	X	3719159	8-Oct-2001	26	F	US	MDI	MDI - suicide
3811155	1	3723113	17-Oct-2001	7	M	US	ADDERALL	sudden death, arrhythmia
3818607	9	3727777	31-Oct-2001	10	M	US	ADDERALL	sudden death
3820707	4	3729084	5-Nov-2001	23	Unk	US	MDI	MDI - unk
3820856	0	3729218	5-Nov-2001	30	Unk	US	MDI	MDI - unk

3838254	2	3741293	10-Dec-2001	12	M	US	ADDERALL 30 MG	suicide by hanging
3841798	0	3741129	18-Dec-2001	50	F	US	MDI	MDI - abuse
3841915	2	3743107	18-Dec-2001	48	M	US	MDI	MDI - abuse
3847231	7	3746163	28-Dec-2001	11	M		DEXEDRINE	suicide by hanging
3859014	2	3756499	22-Jan-2002	50	F	US	MDI	MDI - abuse
3859036	1	3756783	24-Jan-2002	13	M	US	DUP	dup of 3782505-X
3868962	9	3763985	12-Feb-2002	29	M	US	MDI	MDI - unk
3869404	X	3780953	13-Feb-2002	36	M	US	MDI	MDI - abuse
3871070	4	3787348	13-Feb-2002	24	F	US	MDI	MDI - unk
3872406	0	3785523	13-Feb-2002	41	F	US	MDI	MDI - suicide
3873180	4	3791314	13-Feb-2002	25	M	US	MDI	MDI - abuse
3873182	8	3791319	13-Feb-2002	31	M	US	MDI	MDI - abuse
3876168	2	3788254	13-Feb-2002	47	M	US	MDI	MDI - suicide
3876726	5	3795576	13-Feb-2002	43	M	US	MDI	MDI - abuse
3877728	5	3784869	13-Feb-2002	19	M	US	MDI	MDI - abuse
3887728	7	3776530	22-Mar-2002	14	M	US	ADDERALL	cardiac arrest
3908209	8	3788612	26-Apr-2002	36	F	US	MDI	MDI - suicide
3913591	1	3792648	7-May-2002	15	F	US	MDI	MDI - abuse
3960442	5	3863528	2-Aug-2002	41	Unk	US	MDI	MDI - suicide
3960443	7	3863558	2-Aug-2002	35	Unk	US	MDI	MDI - suicide
3972359	0	3839135	5-Sep-2002	12	M	US	DUP	dup of 4163447-7
3978812	8	3844047	18-Sep-2002	11	M	US	ADDERALL	sudden death (dup of 3982225)
3981827	7	3821634	26-Sep-2002	71	F	AT	NAPROXEN	no amphetamine taken (miscoded case)
3982225	2	3846299	25-Sep-2002	11	M	US	DUP	dup of 3978812
3983860	8	3709991	2-Jun-2002	27	F	US	MDI	MDI - suicide (dup of 3756564)
3985077	X	3847746	27-Sep-2002	18	M	US	MDI	MDI - abuse
3987909	8	3850078	9-Oct-2002	23	Unk	US	MDI	MDI - unk
3989966	1	3851291	8-Oct-2002	20	Unk		MDI	MDI - unk
3991217	9	3833415	9-Oct-2002	30	M		MDI	MDI - abuse
3999590	2	3858600	23-Oct-2002	31	Unk	US	MDI	MDI - suicide
4003497	4	3860834	31-Oct-2002	63	Unk	US	MDI	MDI - suicide
4015720	0	3869791	20-Nov-2002	21	Unk	US	MDI	MDI - abuse
4015736	4	3869690	20-Nov-2002	63	Unk	US	MDI	MDI - suicide
4019482	2	3873175	4-Dec-2002	34	F	US	ADDERALL	pt's child died in MVA (dup of 4055716)
4028005	3	3880202	17-Dec-2002	70	Unk	US	MDI	MDI - abuse
4041466	9	3889978	13-Jan-2003	76	F	US	ALOSETRON	cardiac arrest
4044740	5	3892465	21-Jan-2003	24	Unk	US	MDI	MDI - suicide
4045638	9	3892951	21-Jan-2003	63	Unk	US	MDI	MDI - suicide
4047204	8	3894848	23-Jan-2003	21	Unk	US	MDI	MDI - abuse
4049232	5	3897496	28-Jan-2003	13	M	US	ADDERALL	suicide by hanging
4051521	5	3899942	3-Feb-2003	50	Unk	US	MDI	MDI - suicide
4055716	6	3903948	12-Feb-2003	34	F	US	DUP	dup of 4019482
4057368	8	3905815	12-Feb-2003	70	Unk	US	MDI	MDI - unk
4057546	8	3905754	12-Feb-2003	36	F	US	MDI	MDI - abuse
4069419	5	3915418	4-Mar-2003	19	F	US	ADDERALL	cardiac arrest
4070563	7	3916202	4-Mar-2003	16	M	US	ADDERALL XR	suicide with gun
4074653	4	3919502	11-Mar-2003	36	F	US	ADDERALL	underlying dis prog (cancer) (dup of 4092127)
4080624	4	3894869	20-Mar-2003	63	F	US	MDI	MDI - suicide
4080630	X	3892941	20-Mar-2003	31	Unk	US	MDI	MDI - suicide
4092127	1	3933051	8-Apr-2003	36	F	US	DUP	dup of 4074653
4111983	1	3947954	13-May-2003	42	M	US	DUP	dup of 4151000
4112853	5	3614279	15-May-2003	8	M	US	IMIPRAMINE	sudden death, imipramine intoxication (dup of 3692401)
4131952	5	3953869	11-Jun-2003	43	M	US	MDI	MDI - abuse
4151000	0	3974885	16-Jul-2003	42	M	US	ADDERALL XR	cardiac arrest (dup of 4111983)
4163447	7	3985139	1-Aug-2003	12	M	US	ADDERALL XR	sudden death (dup of 3972359-0)
4171696	7	3991767	18-Aug-2003	29	Unk	US	MDI	MDI - unk
4171819	X	3991813	15-Aug-2003	17	Unk	US	MDI	MDI - abuse
4189337	1	3989211	11-Sep-2003	21	M	GB	MDI	MDI - suicide by hanging
4202672	3	4013869	29-Sep-2003	34	M	US	MDI	MDI - suicide
4204610	6	4028792	3-Oct-2003	23	M	US	MDI	MDI - abuse
4215682	7	4011538	21-Oct-2003	45	F	US	MDI	MDI - unk
4188922	0	4002842	19-Jun-2003	41	M	US	MDI	MI-suicide
4205656	4	4016920	6-Oct-2003	22	F	US	ADDERALL	in utero exposure
4213775	1	4022751	17-Oct-2003	17	M	US	MDI	MDI-abuse
4220030	2	4027022	24-Oct-2003	19	F	US	ADDERALL	illicit use - abuse
4223562	6	4029308	29-Oct-2003	12	M	US	ADDERALL	fatal MI (dup of 4258509-X)
4258509	X	4055073	23-Dec-2003	12	M	US	ADDERALL	dup of 4223562-6
4241769	9	4039482	24-Nov-2003	16	M	US	MDI	MDI-abuse (dup of 4256552-8)
4256552	8	4051946	19-Dec-2003	16	M	US	MDI	dup of 4241769-9
4254534	3	4049179	17-Dec-2003	19	M	US	MDI	MDI-abuse
4258513	1	4055092	23-Dec-2003	17	M	US	MDI	MDI-suicide

*Seven (7) excluded cases in which Eskatrol was a suspect drug are not included in this table.

TABLE A2 – NON-EXCLUDED DEATH REPORTS

ISRNUM	CK	CSENUM	RECVDATE	AGE	SEX	CNTRY	VERBDR1	DAILY DOSE	CAUSE OF DEATH
6254		9 4231847	1-Apr-1970	23	F	US	Amphetamine	NR	suicide
135872		2 4357946	18-Mar-1982	U	M	US	DEXEDRINE	60 mg	CVA
348504		5 4445683	6-May-1985	77	F	US	DEXEDRINE	15 mg	pulmonary embolism, ARDS
360947		0 4460891	17-Oct-1985	34	F	US	BIPHETAMINE	NR	arrhythmia
777013		4 4822093	24-Sep-1991	58	M	US	DEXEDRINE	2.5 mg	underlying dis prog (cancer)
1731747		3 5381331	27-Mar-1996	47	F	US	DEXEDRINE	40 mg	cardiac arrest
3004170		1 3003088	3-Dec-1997	51	M	US	ADDERALL	60 mg	CVA
3195487		9 3206763	10-Feb-1999	62	M	US	ADDERALL	15 mg	MI
3224225		6 3214508	22-Mar-1999	13	M	US	DEXEDRINE	35 mg	rhabdomyolysis, myocarditis (dup of 3086467-2)
3391203		8 3385135	8-Nov-1999	56	M	US	DEXEDRINE	30 mg	MI
3459227		8 3437058	18-Feb-2000	10	M	US	ADDERALL	30 mg	drowning (dup of 3471045)
3471046		5 3442770	6-Mar-2000	25	M	US	ADDERALL	NR	suicide by hanging
3534227		8 3505904	24-Jul-2000	22	F	US	ADDERALL	20 mg	sudden death (dup of 3562120)
3555682		3 3521975	22-Aug-2000	15	M	US	ADDERALL	20 mg	sudden death
3613516		2 3569797	17-Nov-2000	15	M	US	ADDERALL	20 mg	sudden death
3686984		8 3625300	21-Mar-2001	28	Unk	US	ADDERALL	NR	sudden death (dup of 3671472-5 and 3677969-6)
3753892		3 3678776	6-Jul-2001	16	M	US	ADDERALL	40 mg	sudden death (dup of 3731168-8)
3782505	X	3701541	23-Aug-2001	13	M	US	ADDERALL	20 mg	sudden death, cardiomegaly (dup of 3859036-1)
3789498	X	3706375	7-Sep-2001	14	M	US	ADDERALL	50 mg	heat stroke (dup of 3788756-2)
3789506		6 3706321	7-Sep-2001	11	M	US	ADDERALL	20 mg	sudden death
3811155		1 3723113	17-Oct-2001	7	M	US	ADDERALL	NR	sudden death, arrhythmia
3818607		9 3727777	31-Oct-2001	10	M	US	ADDERALL	NR	sudden death
3838252		2 3741293	10-Dec-2001	12	M	US	ADDERALL	30 mg	suicide by hanging
3847231		7 3746163	28-Dec-2001	11	M	US	DEXEDRINE	10 mg	suicide by hanging
3887728		7 3776530	22-Mar-2002	14	M	US	ADDERALL	NR	cardiac arrest
3978812		8 3844047	18-Sep-2002	11	M	US	ADDERALL	20 mg	sudden death (dup of 3982225)
4041466		9 3889978	13-Jan-2003	76	F	US	DEXEDRINE	10 mg	cardiac arrest
4049232		5 3897496	28-Jan-2003	13	M	US	ADDERALL	NR	suicide by hanging
4069419		5 3915418	4-Mar-2003	19	F	US	ADDERALL	NR	cardiac arrest
4070563		7 3916202	4-Mar-2003	16	M	US	ADDERALL XR	30 mg	suicide with gun
4074653		4 3919502	11-Mar-2003	36	F	US	ADDERALL	45 mg	underlying dis prog (cancer) (dup of 4092127)
4112853		5 3614279	15-May-2003	8	M	US	Dextroamphetamine	10 mg	sudden death, imipramine intoxication (dup of 3692401)
4151000		0 3974885	16-Jul-2003	42	M	US	ADDERALL XR	15 mg	cardiac arrest (dup of 4111983)
4163447		7 3985139	1-Aug-2003	12	M	US	ADDERALL XR	10 mg	sudden death (dup of 3972359-0)
4223562		6 4029308	29-Oct-2003	12	M	US	ADDERALL	30 mg	MI (dup of 4258509-X)

TABLE A3 – NON-EXCLUDED SERIOUS NONFATAL CARDIOVASCULAR
AND CEREBROVASCULAR REPORTS (1999-2003)

	A	B	C	D	E	F	G
1	3907898	25-Apr-2002	7	M	HO	PERICARDIAL EFFUSION, COLLAPSE, EDEMA, INCREASED BLOOD PRESSURE, INCREASED WBC	ADDERALL, PALMOCOT, CLARITIN
2	4048785	28-Jan-2003	7	M	LT, HO	SYNCOPE, CYANOSIS	ADDERALL XR, COUMADIN, DIGOXIN, LASIX
3	4112507	14-Apr-2003	7	M	HO	HYPERTENSION	ADDERALL
4	3863062	31-Jan-2002	9	M	HO	DYSYPNEA, ABDOMINAL PAIN, AGITATION, VOMITING	ADDERALL
5	3656612, 3687974	29-Jan-2001	9	M	RI	CHEST PAIN, DYSYPNEA, PREMATURE ATRIAL CONTRACTIONS	ADDERALL
6	3499982	15-May-2000	10	F	RI	HEADACHE, HYPERTENSION (130/100)	ADDERALL, DEPAKOTE, CLONIDINE, ZYPREXA, SERZONE
7	3715950	30-Apr-2001	10	M	HO	HYPERTENSION (177/117)	ADDERALL
8	4019516	4-Dec-2002	10	M	HO	AGITATION, DYSYPNEA, HALLUCINATIONS	ADDERALL, DEXTROMETHORPHAN
9	4112953	13-May-2003	10	M	HO	DYSYPNEA, ABDOMINAL PAIN	ADDERALL
10	3669229	21-Feb-2001	11	M	LT	RESPIRATORY ARREST, BRADYCARDIA, POSSIBLE SEIZURE, LEFT VENTRICULAR HYPERTROPHY	ADDERALL, ALBUTEROL, FLOVENT, SEREVENT
11	4078778, 4098128	19-Mar-2003	12	M	LT, HO	HYPERTENSION (189/99)	ADDERALL XR
12	3416579	8-Dec-1999	13	F	HO	RECURRENT AV NODAL RE-ENTRY TACHYCARDIA	ADDERALL, ZOLOFT
13	3806827, 3879596	5-Oct-2001	13	M	LT, HO	SUB-ARACHNOID HEMORRHAGE, SEIZURE	ADDERALL, ZOLOFT
14	3985830	7-Oct-2002	14	M	HO	ARRHYTHMIA, ABNORMAL BEHAVIOUR	ADDERALL, ZOLOFT
15	3606660	3-Nov-2000	15	M	RI	SYNCOPE, HYPERTENSION (138/110), CHEST PAIN	ADDERALL, ALEVE
16	3475900	15-Mar-2000	16	F	HO	THROMBOEMBOLIC STROKE, FLACCID PARALYSIS	ADDERALL, PAXIL
17	3516759	20-Jun-2000	16	M	HO	CONFUSIONAL STATE, TACHYCARDIA, FEVER, TACHYPNEA	ADDERALL, DEPAKOTE, PROZAC, SEROQUEL, SYNTHROID
18	4179651	26-Aug-2003	17	M	HO	MYOCARDIAL INFARCTION	ADDERALL, NORVASC
19	3731376	31-May-2001	19	F	HO	CHEST PAIN, WOLFF-PARKINSON-WHITE SYNDROME	ADDERALL
20	4043846, 4188715	21-Jan-2003	21	M	HO	MYOCARDIAL INFARCTION	DEXEDRINE, DEPAKOTE
21	3521046	28-Jun-2000	26	F	HO	SYNCOPE, DIZZINESS, SOMNOLENCE	DEXEDRINE, CELEXA
22	3308907	22-Jul-1999	34	M	HO	PAROXYSMAL VENTRICULAR TACHYCARDIA	DEXEDRINE, WELLBUTRIN
23	4107651	7-May-2003	37	F	LT, HO	MYOCARDIAL INFARCTION	DEXEDRINE
24	4178681, 4220033	2-Sep-2003	38	M	LT, HO	HYPERTENSION (160/100), SYNCOPE, DYSYPNEA, DILATED CARDIOMYOPATHY	ADDERALL, EFFEXOR
25	3646707	11-Jan-2001	39	F	HO	STROKE	ADDERALL
26	3532719, 3526409	20-Jul-2000	40	M	LT	CARDIAC ARREST, VENTRICULAR FIBRILLATION	ADDERALL
27	4229881	7-Nov-2003	42	F	LT, HO	CHEST PAIN, HYPERTENSION (189/119)	ADDERALL, WELLBUTRIN
28	3667094	15-Feb-2001	43	M	HO	CHEST PAIN, DYSYPNEA, HYPERTENSION (180/110), CARDIOMYOPATHY, STROKE, MEDICATION ERROR	ADDERALL, RITALIN, PERCOCET, XANAX
29	4070969	4-Mar-2003	50	F	HO	CEREBROVASCULAR ACCIDENT	ADDERALL, ATENOLOL, NORVASC, AGGRENOLX, SPIRONOLACTONE
30	3787042	31-Aug-2001	54	M	LT, HO	MYOCARDIAL INFARCTION	ADDERALL
31	4172296, 4214792	18-Aug-2003	56	M	LT	ATRIAL FIBRILLATION	ADDERALL XR
32	3821633	6-Nov-2001	57	M	HO	MYOCARDIAL INFARCTION	ADDERALL, VIOXX
33	3193647	8-Feb-1999	58	M	LT, HO	MYOCARDIAL INFARCTION, CARDIAC ARREST, VENTRICULAR TACHYCARDIA	DEXEDRINE, VIAGRA
34	3817356	30-Oct-2001	58	M	LT, HO	CARDIOMYOPATHY	ADDERALL
35	4147742	11-Jul-2003	adult	M	HO	CHEST PAIN, DYSYPNEA, PREMATURE VENTRICULAR CONTRACTIONS	ADDERALL XR

APPENDIX B

METHYLPHENIDATE

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Appendix B: Methylphenidate Deaths

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REVIEW OF METHYLPHENIDATE SPONTANEOUS REPORTS WITH A FATAL OUTCOME

A search of the AERS safety database was conducted on November 25, 2003 for all cases with a fatal outcome in which methylphenidate (Ritalin, Concerta, Metadate) was identified as a suspect drug. A total of 160 cases met the criteria with an additional 3 found in the literature. Of these 163, 117 were excluded from further analysis for the following reasons:

- 2 cases of Accident: ISR 3751030, 654080
- 1 case of Homicide: ISR 1772964
- 4 cases of In Utero Exposure: ISR 599083, 3839772, 4183095, 21350
- 3 cases of IV Drug Abuse of methylphenidate: ISR 1548670, 3209268 (cerebral hemorrhage after injection of Ritalin), 4250967
- 28 cases of Multiple Drug Ingestion Abusers (not necessarily drug overdose deaths): ISR 3895299 (small cardiac defect on autopsy), 35118, 46090, 97309, 131238, 155913, 788777, 788778, 789406, 789415, 789809, 1 unreported case from literature (Parran, Jasinski), 796597, 796598, 796599, 1580727 (cardiac arrest after snorting Ritalin & drinking ETOH), 3115530, 3352445, 3649689, 3755727, 3761064, 3928278, 3940940 (electromechanical dissociation 1 day after abuse), 3959112, 3982891, 3987210 (drug abuser found dead at home), 4102312, 1579973
- 12 cases of Multiple Drug Ingestion Suicide completions: ISR 1522154, 1744847, 3306831, 3352444, 3813651, 3877738, 3959865, 3978460, 3997826, 4150385, 4240737, 4242524
- 2 cases of Unintentional Multiple Drug Ingestion deaths: ISR 135243 (adverse interaction between phentermine, phenylpropylamine, & parnate), 3324016 (died 4 days after administration of xylocaine jelly; was on multiple meds)
- 1 case of Medication Error: ISR 3760268 (methadone 5 mg dispensed instead of methylphenidate & child died of toxicity)
- 6 cases were not real cases: ISR 34562 (request for Ritalin for animal studies), 93243 (not a case), no mention of methylphenidate for 3604026, 3604028, 3604029, 3604030
- 3 cases the patients did not die: ISR 796843 (patient shot and killed another child), 3741505 (addicted to crack and killed another child), 3775981 (methylphenidate was discontinued because of contraindication with Effexor)
- 1 case of Pulmonary Embolism: ISR 1777320 (patient was on Ortho-cept)
- 2 cases of Pulmonary Hypertension: ISR 3032689, 3056072 (both patients were on Pondimin)
- 1 case of Trauma: ISR 769097 (splenic rupture)
- 6 cases of Underlying Disease Progression: ISR 656006, 789405, 1372493, 1705847, 3112488, 4002281
- 5 cases of Unknown etiology: ISR 130555 (patient was a Ritalin abuser), 3965811, 4035002 (no information given), 4050776 (not suspected to be medication related), 4132138 (no details given)
- 2 Missing cases: ISR 120697, 1343012
- 38 Duplicates: ISR 3766038, 4138233, 3616770, 3894289, 4034273, 4035868, 608906, 46979, 3756640, 497346, 4018172, 4054470, 4163841, 4165416, 4112929, 4117123, 4103211, 3999617, 3999628, 4162496, 3822813, 3827883, 4009219, 4054409, 1797836, 1680461, 1784758, 1842644, 3240724, 3446728, 4030508, 3783538, 4005531, 3120455, 4226201, 4202430, 4237465, 4241392

46 cases remained (44 reported to AERS, 2 from the literature).

Below is a table that shows the fatal category outcomes and whether they were considered cases.

	Total Methylphenidate Deaths	Cases
Accident	2	
Cardiac		
Arrest	2	2
Ischemic heart disease	1	1
MI	2	2
Myocarditis	1	1
Cerebral hemorrhage	1	1
Drowning	1	1
Homicide	1	
In utero exposure	4	
IV drug abuse of methylphenidate	3	
Liver necrosis	1	1
Malignant hyperthermia / NMS	2	2
Medication error	2	1
Methylphenidate overdose	2	2
Multiple Drug Ingestion		
Abuse	28	
Accidental poisoning	1	1
Suicide	12	
Unintentional	2	
Not a case	6	
Patient did not die	3	
Pulmonary embolism	1	
Pulmonary hypertension	2	
Seizure	1	1
Sudden death	19	19
Suicide	7	7
Trauma	1	
Underlying disease progression	6	
Unknown	9	4
Missing	2	
Duplicates	38	
total	163	46

AERS captured 160 cases but an extra 3 cases were found in literature.

All Methylphenidate Fatal Outcomes Spreadsheet

ISR	AGE	SEX	DUR OF MP TX	SUSPECT DRUGS	DOSE OF MP	PMH	CAUSE OF DEATH	COMMENT	capsule	case
3751030, 3766038	U	Female	?	provigil, corticosteroids	?	fatigue, back pain	Accident	possible steroid psychosis (seen chasing imaginary cat), found dead in a canyon.	Y	N
654080	52	Female	15 yrs	Desoxyn, Diuril, Tagamet	40 QD	HTN, myocarditis, mitral valve disease, ulcer, depression	Accident	head injury (struck by truck). Hospitalized for aphasia, syncope. Had L cerebral artery thrombosis followed by infarction. Increased intracranial P.	Y	N
3986870	9	Female	2 months		18 QD	asthma	Cardiac - arrest	9 days before death had ENT surgery. Developed flu sxs, admitted to hospital w/ increased cough. Coded & died. Autopsy- increased methylphenidate level 156 ng/ml.	Y	Y
4121941, 4138233	13	Male	6 yrs		20 QD	Learning disorder, deafness	Cardiac - arrest	autopsy- normal.	Y	Y
3489120, 3616770, 3894289, 4034273, 4035868	14	Male	10 yrs		20 TID	ADHD	Cardiac - ischemic heart disease	complained of chest pain. Autopsy-small vessel damage. No preexisting hrt disease.	Y	Y
4169310	U (30s)	Male	?	mirtazipine	60-80 QD	depression, diabetes, L below knee amputation, obesity (500 lbs), cardiac problem	Cardiac - MI	had cardiac episode, resuscitated, died weeks later. Had cardiac hx.	Y	Y
515040	50	Female	? Years	None	?	narcolepsy	Cardiac - MI	EKG showed MI, arrested and could not be resuscitated.	Y	Y
573890	15	Male	5 yrs		65 QD	Father had pleurodynia (virus) 2 wks before death	Cardiac - myocarditis	hospitalized w/ lactic acidosis, ARF, tachy, tachypnic, cyanotic. Died 14 days later. Autopsy-eosinophilic myocarditis	Y	Y
1916772	13	Male	1 dose	?	100mg x1		cerebral hemorrhage	took 10 pills, had stroke.	Y	Y
1618983	3	Female	?		2.5 TID	ADD, mild mental retardation, fetal alcohol syndrome	Drowning	seizure, drowned.	Y	Y
1772964	43	Male	1 episode				homicide	Ritalin overdose (child on medication). Police chase, cornered, lunged at police with knife, shot & killed.	N	N

599083, 608906	0	?	entire pregnancy		30 QD	mother treated with Ritalin for 12 years for narcolepsy, cataplexy	In utero exposure	34 yo female had abortion 2ndary to cardiac malformation found on U/S. Had healthy child 2 yrs prior while on Ritalin. Autopsy of fetus revealed hypoplastic left heart & Ebstein's anomaly with massive dilated right atrium, pulmonary atresia & intact ventricular septum.	N	N
3839772	1 day	Male	during first trimester	benadryl, tetracycline	?		In utero exposure	exposure early 1st trimester. born at 41 wks, at 20 hrs became apneic, cyanotic, tremulous, asystole, died. Case form literature (Soul et al, Time course of changes in diffusion-weighted magnetic resonance...., Pediatrics, 108 (5) p 1211-14, 2001).	N	N
4183095	6 hours	Female	in utero 10-13, 17-30 wks	distalgesic	?		In utero exposure	in utero exposure of infant, respiratory distress at birth and died 6 hours later.	N	N
21350	1 day	?	?		20 Q 3 hrs	narcolepsy	In utero exposure	27 yo female gave birth to an infant who died after 1 day 2ndary to hyaline membrane disease. Mom had prior normal pregnancy while on Ritalin.	N	N
3209268	U	Unk	?	?	? IV	?	IV drug abuse of methylphenidate	could be a duplicate but not enough detail to determine.	Y	N
1548670	26	Male	?		? IV	ADD	IV drug abuse of methylphenidate		Y	N
4250967	30	Female	?	Paroxetine	?	Drug abuser	IV drug abuse of methylphenidate	crushed methylphenidate and in a water mixture, injected herself. Died of an irregular heartbeat. Methylphenidate level 23 ug%.	N	N
3122062	14	Male	2+ months	pemoline	20 QD	ADHD	Liver necrosis	jaundice, increased LFTs, encephalopathic. Biopsy- >90% hepatocellular necrosis. Transplanted, rejected, retransplanted. ARF, cerebral edema, died.	Y	Y
3171158	41	Male	5 days	Risperidone, sodium valproate	20 QD	Depression, epilepsy	malignant hyperpyrexia	unwell during trip, rigid, fever 40 C, hypoxemic, DIC, multiple organ failure, died.	Y	Y

1631220	67	Male	?	Risperdal, Paroxetine, Lithium, Clonazepam, Venlafaxine	?	COPD, depression, dementia, CHD	malignant hyperthermia or NMS	hospitalized for depression, had seizure, increased CPK. CT scan showed cerebral infarct. T 110.6 F, ARF, BP dropped & died.	Y	Y
3895299	15	Male	years		?		MDI-abuse	collapsed at home, autopsy- small cardiac defect.	Y	N
351118	46	Male	?	Ritalin, Talwin, Dextroamphetamine IV	?	Schizophrenia	MDI-abuse	? OD. Found syringe of dextroamphetamine & pentazocine next to body. Died of a convulsion.	N	N
46090, 46979	U elderly	Male	?	Ritalin, MP, Heroin	?	Drug Abuser, Pulmonary disease	MDI-abuse		Y	N
97309	28	Male	?	Methadone	?	Drug Abuser	MDI-abuse	cerebral anoxia 2ndary to pulm edema & congestion	Y	N
131238	26	Female	9 months	Heroin IV	IV	drug abuse, pulm hypertension 2ndary talc induced granulomatosis	MDI-abuse	From case series. Pulmonary granulomatosis of IV drug abuser. Found comatose at home. Died days later (Brown et al, 67 gallium scanning in talc-induced pulmonary granulomatosis, Chest, 77(4), p. 561, Apr 1980).	N	N
155913	29	Female	?		? IV	Pulm hypertension	MDI-abuse	drug abuser. This may be the missing case from Parran, Jasinski case series (see # 789405 - underlying disease progression) but not enough information in case series to determine (reporters are also different).	N	N
788777	35	Female	?		? IV	Drug abuse, emphysema	MDI-abuse	from case series. Lung talc granulomas found on autopsy (Schmidt et al, Panlobular emphysema in young intravenous ritalin abusers, Am Review of Resp Diseases, 143 (3), p. 649-56, 1991).	N	N
788778	39	Female	?		? IV	Drug abuse, emphysema	MDI-abuse	from Schmidt case series. Lung talc granulomas found on autopsy.	N	N
789406	33	Male	?		? IV	Drug abuse, emphysema	MDI-abuse	from Schmidt case series.	N	N
789415	35	Male	?		? IV	Drug abuse, emphysema	MDI-abuse	from Schmidt case series.	N	N
789809	U	Unk	?		? IV	drug abuse	MDI-abuse	from Parran, Jasinski case series.	N	N

3987210	31	Male	?	oxycodone, diazepam, doxepin, fluoxetine, cocaine	10 QD	drug/ETOH abuse, bipolar	MDI-abuse	found dead at home.	N	N
4102312, 4112929, 4117123	16	Male	?	norpropoxyphene, fentanyl, marijuana	?	drug abuse	MDI-abuse		N	N
3115530	U Adult	Male	?	Hypertension med, ETOH, sudafed	?		MDI-abuse	took 48 sudafed 30mg tabs, ritalin, hypertension med, & possibly ETOH. ? suicide.	N	N
3352445	U Adult	Female	?	desipramine, ETOH	?	?	MDI-abuse	15-20 methyl phenidate tabs, 10 desipramine tabs, ETOH	N	N
3959112	30	Male	?	luvox, toledomin, amoxan, paxil	?		MDI-abuse	amoxapine OD suspected. Admitted to ICU w/ ARF, cerebral infarction, seizures. Died of neuroleptic malignant syndrome.	N	N
3649689	45	Female	?	meprobamate, amisulpride	?	drug abuse	MDI-abuse	Overdose of meprobamate and amisulpride in a drug abuser.	N	N
1579973	U	Male	?	ETOH	?	Psychosis, prior LSD abuser	MDI-abuse, trauma	snorted ritalin, psychotic, ran naked through campus, blow to head & died.	N	N
1889044	6	Female	1 dose	Tofranil, oxycodone	?		MDI-accidental poisoning	given a mix of ritalin, tofranil, oxycodone in grape juice as cough med by mom. Found dead.	Y	Y
1522154	25	Male	?	Desipramine	10 TID	ADD, depression	MDI-suicide	ingested 60 tabs of desipramine & ritalin	N	N
1744847	31	Male	?	Tylenol, ASA, Loratabs	100-200 tabs x1		MDI-suicide	took 100-200 tabs of ritalin. Malignant hyperthermia, asystole.	Y	N
3306831	39	Female	?	Ibuprofen, Tylenol	1.2 gm x 1		MDI-suicide	took methyl phenidate 1.2 gm, ibuprofen 12 gm, Tylenol 10 gm. Cardiopulmonary arrest.	N	N
3352444	36	Female	?	alprazolam, lorazepam, l throxine	?		MDI-suicide		N	N
3813651, 4103211	16	Unk	?	hydroxyzine, amitriptyline	?		MDI-suicide		N	N
3877738	45	Male	?	oxycodone, tylenol, bupropion, mepredine,	?		MDI-suicide	cerebral/ lung edema, cardiomegaly, RVH	N	N

3959865	18	Unk	?	?	amitriptyline, hydroxyzine	?			MDI-suicide		N	N
3978460, 4237465	35	Unk	?	?	bupropion, venlafaxine				MDI-suicide		N	N
3997826, 3999617, 3999628, 4162496	42	Male	?	?	bupropion		depression, suicide attempts		MDI-suicide	found face down in mountains, resp/renal failure, stroke in hospital.	Y	N
4150385	33	Male	?	?	Benadryl, Cocaine, Tylenol				MDI-suicide		N	N
4240737	42	Female	?	?	Bupropion		?		MDI-suicide	Bupropion and methylphenidate overdose. Found unresponsive and taken to ER. Seizing upon arrival and died 3 hours later.	N	N
4242524, 4241392	38	?	?	?	Trandolapril/Vera pamil		?		MDI-suicide	intentional suicide using methylphenidate and trandolapril/Verapamil.	N	N
135243	42	Female	?	10 BID	Parnate		Depression		MDI-unintentional	Took diet med with phenylpropanolamine. In ER received ergotamine.	Y	N
3324016	67	Female	3 months	?	xylocaine jelly, cipro, ms contin, coloxyl w/ senna, dothiepin, panadol, gastrogel				MDI-unintentional	developed confusion & visual hallucination after the administration of xylocaine jelly and died 4 days later.	N	N
1879846	88	Male	1 dose	5 mg x 1	ASA, Benazepril, Furosemide, Sertraline, Heparin, Sinemet, Glipizide, Metolazone		diabetes		med error	presented to hospital w/ proximal weakness & CHF. Given methylphenidate instead of metolazine. Became confused, lethargic, CT scan of head was negative. Unknown cause of death.	Y	Y
3760268, 3822813, 3827883, 4009219	8	Male	?	?	Methadone				med error	pharmacist filled methadone 5 mg instead of methyl phenidate 5 mg. child died of methadone toxicity.	N	N

3733545	13	Male	4 yrs	wellbutrin, seroquel	?		depression, ? Abuse	Methylphenidate overdose	living in foster home, mother died 6 months before of cancer.	Y	Y
4054405, 4054409	42	Unk	?		?			Methylphenidate overdose - intentional	literature case - can't find case in article.	Y	Y
34562	U	Unk						Not a case	request for ritalin for animal studies.	N	N
3604026	82	Male		salmeterol				Not a case	no mention of methylphenidate taken for this case.	N	N
3604028	57	Female		salmeterol				Not a case	no mention of methylphenidate taken for this case.	N	N
3604029	65	Male		salmeterol				Not a case	no mention of methylphenidate taken for this case.	N	N
3604030	87	Male		salmeterol				Not a case	no mention of methylphenidate taken for this case.	N	N
93243	Child-ren	Unk	?	?	?	?	?	Not a case	Not a specific case.	N	N
796843	15	Male	?		?	?	?	patient did not die	patient shot & killed another adolescent.	N	N
3741505	13	Male	5 months		?	?	drug addict	patient did not die	patient taken off med after 5 months due to side effects. To get same effect, became addicted to crack. Became violent & 2 yrs later killed someone.	N	N
3775981	U	Unk	?	effexor	?	?	?	patient did not die	pharmacist informed psychiatrist that deaths occurred with MP & effexor so MP D/C'd.	N	N
1777320, 1797836	47	Female	?	Ortho-cept, Effexor	?		Depression	pulmonary embolism		Y	N
3032689	29	Female	4.5 months	Pondimin	20 TID			pulmonary hypertension	meds D/C'd after pulmonary hypertension diagnosed.	N	N
3056072	39	Female	5 months	pondimin, klonopin, lasix, lithium, methyltestosterone, synthroid, triazolam	20 TID		Obesity, intermittent DOE, bipolar affective, hypothyroid	pulmonary hypertension	dx by cath, died of pulm htn & pneumonia.	Y	N
3997822	42	Female	?	bupropion, chlordiazepoxide/clidinium, singular, levothyroxine	?			seizure	actively seizing upon arrival in ER, died 3 hrs later.	Y	Y

1557196	7	Male	?	Clonidine	?	ADD, heart murmur, premature birth	Sudden death	unresponsive in class. Found in Vfib. Autopsy-chronic mitral regurg, CHF, cerebral edema.	Y	Y
1770090	13	Male	9 months		10 TID x 3 months, then 20 TID x 6 months	None	Sudden death		Y	Y
3240721, 1680461, 1784758, 1842644, 3240724	10	Male	4 yrs	Catapress TTS-2	10 BID	ADD, Tic disorder, previous syncopal episodes	Sudden death	collapsed after swimming, seizure. Autopsy-congenital cardiac malformation capable of causing ischemia/arrhythmia. Described in case 4 of Cantwell et al., J Am Acad Child Adolesc Psychiatry, 36(4):539-44, 1997. Also see case 1781818 (sudden death) for case report that includes this case.	Y	Y
1504208	13	Male	?		?	?	Sudden death	autopsy- heart hypertrophied, anomalies of tricuspid valve.	Y	Y
3775962, 3446728	11	Female	4 yrs, 3 months		25 & 15 QD	ADHD	Sudden death	found dead in bed. Per coroner, no congenital hrt disease.	Y	Y
451578	39	Male	4 yrs		40 QD	nonspecific T & ST changes; systolic murmur	Sudden death	body builder; taking MP for narcolepsy.	Y	Y
4143391	13	Female	9 months	zyrtec	36 QD	allergies	Sudden death	no history of heart problems.	Y	Y
544470	12	Male	4 yrs		?		Sudden death	collapsed & died. Autopsy- idiopathic dilated cardiomyopathy.	Y	Y
1963252	15	Male	1.5 yrs	Prednisone, Tegretol	30 QD	hypopituitarism	Sudden death	admitted to hospital for phlebitis, had coronary event.	Y	Y
4115324, 4226201	13	Male	10 months		18 QD	single syncopal episode while on Concerta	Sudden death	collapsed at camp.	Y	Y
705007	77	Female	7 days		20 QD	?	Sudden death	syncopal episode w/ slow HR x 2. asystole.	Y	Y
4027547, 4030508	59	Male	?	zoloft	60 QD	restless leg. smoker, ETOH	Sudden death	died suddenly. 6 months prior found to have ventricular extrasystoles & couplets by a cardiologist.	Y	Y
307979	13	Male	6 yrs 3 months	diamphetamine	?	ADD	sudden death	collapsed & could not be revived. Autopsy showed thin adrenals, almost absent medulla.	Y	Y

363488	76	Male	5 doses	chloral hydrate, haldol	60 QD	Alzheimers	sudden death	started for senile withdrawn depression. D/C'd 2ndary to agitation, died 36 hrs later.	Y	Y
1781818	9	Female	3 yrs	Prozac, Clonidine	20 TID	ADD, OCD, fetal alcohol syndrome, neuro impairment	sudden death	died after grand mal seizure. Literature (Swanson et al., J Child Adolesc Psychopharm 5(4):301-304, 1995) also described 3 other cases. See case 1680461 (sudden death) & 2 cases below.	Y	Y
	8	Female	?	Clonidine	?		sudden death	had anesthesia, See case 1781818 for lit source.	Y	Y
	7	Male	?	Clonidine	45 QD		sudden death	heart murmur, fibrotic cardiac scarring, See case 1781818 for lit source.	Y	Y
4106370	12	Female	?			ADHD, migraines, skating accident 1 yr prior	sudden death	found in bathtub, pronounced dead at hospital. Not clear whether she had seizures after skating accident.	Y	Y
4183882	12	Male	3 months	budesonide, fluticasone, inflammide	20 QD	asthma	sudden death	collapsed at school, no convulsions.	Y	Y
127220	48	Male	2 yrs	Tylenol #4, Fiorinal, Pertofrane	20 QD	Alcoholism, Depression	Suicide	shot himself	Y	Y
769098	18	Male	?		?	ADD	suicide	no detail on how it was completed.	Y	Y
3525243	62	Male	1 week	clonazepam	10 BID	Panic Disorder, MI, dementia, social stress	suicide	started meds in psych hospital. Shot himself 4 days after discharge.	Y	Y
3661388	14	Male	?	Zoloft	36 QD	ADHD, depression	suicide	father & maternal great grandfather also committed suicide.	Y	Y
3680933, 3783538	U	Female	7 yrs	Prozac	?		suicide	per attorney, patient addicted to meds that caused personality & behavioral changes.	Y	Y
3976076	U elderly	Female	2 weeks		20 QD	bipolar	suicide	hung herself.	Y	Y
4001702, 4005531	16	Male	4 yrs, 8 months		30 QD	ADHD	suicide	hung himself. D/C'd Ritalin 1 wk prior.	Y	Y
769097	8	Male	?		30 QD	ADD	trauma	splenic rupture, unrelated to medication.	N	N
656006	69	Male	4 days	desipramine	10 QAM	bladder CA	Underlying disease progression	put on MP temporarily until desipramine took affect. Died of GI bleed.	N	N

789405	U	Unk	?				?	Hep B	Underlying disease progression	from case series (Parran, Jasinski, Intravenous methylphenidate abuse, Archives of Int Med, 151 (4), p 781-3, 1991 Apr).	N	N
1372493	33	Male	1 dose	Biatin, Lamprene, Neupogen, Procrit, Foscamet, Pentam, Florical			5 mg	AIDS, depression	Underlying disease progression	3 hrs after taking Ritalin had seizure. Had nystagmus at ER, tx w/ Dilantin. Admitted & died 9 days later 2ndary to PCP (AIDS). Had pneumocystosis, cytomegalovirus, leukopenia.	N	N
1705847	9	Male	3.5 yrs				5-10 BID	premature at 5 months, mother used ETOH, crystal methamphetamine, cigs during pregnancy.	Underlying disease progression	hepatoblastoma	N	N
3112488, 3120455	10	Male	14 months				55 QD		Underlying disease progression	hepatic tumor, death unrelated to medication.	N	N
4002281	65	Female	3 days	megace, decadron, toradol, humalin, arimidex			5 BID	metastatic breast CA to brain & bone	Underlying disease progression	unrelated to medication.	N	N
130555	U	Unk	?	?			?	Ritalin Abuse	unknown	Patient was a Ritalin abuser.	N	N
738806	U	Male	?	?			?	?	unknown	found dead w/ empty bottle of MP & ritalinic acid.	Y	Y
1696046	50	Male	?				?		unknown	? Overdose, increased blood level at 430 pg/l.	Y	Y
3509918	17	Male	2 years				40 QD		unknown	found dead in woods. Was on ritalin, empty bottle found on him but no trace of ritalin found in blood.	Y	Y
1504202	U elderly	Unk	?	TCA			?	depression, CAD	unknown		Y	Y
3965811	74	Male	?	bromocriptine, maprotiline			?	depression	unknown	severely depressed, tried multiple meds, ECT, hospitalized. Case from literature - see capsule summary.	Y	N
4035002	U	Male	?				?		unknown	Appears to be a duplicate but not enough information to specify case. Father reports son died while on methylphenidate.	N	N

4050776	U elderly	Male	?		20 QD		unknown	not suspected to be medication related.	Y	N
4132138	20	Female	?		?	?	unknown	no details given.	N	N
120697	12	Male						missing	N	N
1343012	7	Unk						missing	N	N

Methylphenidate Cases

ISR	CK	CSENUM	RECVDATE	AGE	SEX	CNTRY	VERBDR1
127220	9	4349942	17-Dec-1980	48	Male	US	RITALIN
307979	8	4416766	9-Apr-1984	13	Male	US	RITALIN
363488	1	4457997	23-Sep-1985	76	Male	US	RITALIN
451578	4	4535196	2-Mar-1987	39	Male	US	RITALIN
515040	2	4590401	23-Mar-1988	50	Female	US	RITALIN
544470	8	4616220	27-Sep-1988	12	Male	US	RITALIN-SR
573890	0	4642637	14-Mar-1989	15	Male	US	RITALIN
705007	3	4758183	14-Nov-1990	77	Female	US	RITALIN
738806	2	4788028	8-Mar-1991	U	Male	US	METHYLPHENIDATE
769098	6	4815011	27-Aug-1991	18	Male	US	RITALIN
1504202	3	5162477	30-Sep-1994	U	Unk	US	RITALIN
1504208	4	5162483	30-Sep-1994	13	Male	US	RITALIN
1557196	9	5212781	13-Feb-1995	7	Male	US	RITALIN
1618983	1	5271947	26-Jul-1995	3	Female	US	RITALIN
1631220	7	5283722	31-Jul-1995	67	Male	US	METHYLPHENIDATE
1696046	7	5346546	3-Jan-1996	50	Male	US	RITALIN
1770090	3	5418564	2-Jul-1996	13	Male	US	RITALIN
1781818	0	5429941	19-Jul-1996	9	Female	US	METHYLPHENIDATE
1879846	X	5525052	22-Jan-1997	88	Male	US	METHYLPHENIDATE
1889044	1	5533954	6-Mar-1997	6	Female	US	RITALIN
1916772	1	5560873	7-Apr-1997	13	Male	GB	RITALIN
1963252	3	5606117	25-Jul-1997	15	Male	US	RITALIN
3122062	4	3139767	25-Aug-1998	14	Male	US	RITALIN
3171158	X	3180991	16-Dec-1998	41	Male	US	METHYLPHENIDATE
3240721	1	3123579	15-Apr-1999	10	Male	US	RITALIN
3489120	6	3456934	18-Apr-2000	14	Male	US	RITALIN (METHYLPHENIDATE)
3509918	5	3464396	5-Jun-2000	17	Male	Can	RITALIN-SR
3525243	0	3495177	3-Jul-2000	62	Male	US	RITALIN
3661388	2	3607283	6-Feb-2001	14	Male	US	CONCERTA
3680933	4	3622025	14-Mar-2001	U	Female	US	RITALIN
3733545	8	3634786	1-Jun-2001	13	Male	US	CONCERTA (METHLPHENIDATE HCL)
3775962	6	3696266	13-Aug-2001	11	Female	US	RITALIN / 25&15 MGS / NOVARTIS
3976076	2	3841376	13-Sep-2002	elderly	Female	US	RITALIN LA (METHYLPHENIDATE HYDROCHLORID
3986870	X	3842527	2-Oct-2002	9	Female	US	CONCERTA (18 MG SUSTAINED RELEASE TABLET
3997822	8	3847433	22-Oct-2002	42	Female	US	CONCERTA (SUSTAINED RELEASE TABLET) (MET
4001702	1	3859323	10/29/2002	16	Male	US	RITALIN-SR (METHYLPHENIDATE HYDROCHLORID
4027547	4	3879775	16-Dec-2002	U	Male	DE	RITALIN-SR (METHYLPHENIDATE HYDROCHLORID

4054405	1	3903633	7-Feb-2003	42	Unk	US	METHYLPHENIDATE
4106370	6	3944251	1-May-2003	12	Female	US	CONCERTA (SUSTAINED RELEASE TABLET) (MET
4115324	5	3883603	20-May-2003	13	Male	US	CONCERTA (SUSTAINED RELEASE TABLET) (MET
4121941	9	3949206	2-Jun-2003	13	Male	GB	METHYLPHENIDATE(METHYLPHENIDATE HYDROCHL
4143391	1	3968393	8-Jul-2003	13	Female	US	CONCERTA 36 MG
4169310	X	3982165	18-Aug-2003	30s	Male	US	RITALIN
4183882	0	3991585	11-Sep-2003	12	Male	ZA	RITALIN
from lit			19-Jul-1996	8	Female	US	METHYLPHENIDATE(METHYLPHENIDATE HYDROCHL
from lit			19-Jul-1996	7	Male	US	METHYLPHENIDATE(METHYLPHENIDATE HYDROCHL

The following epidemiologic characteristics were determined for the cases.

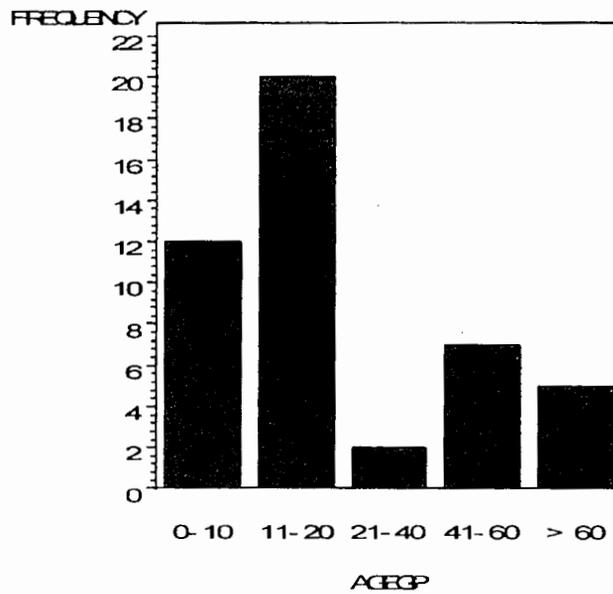
1. Age

Mean = 26.4 ± 22.9

Median = 14.0

Range = (3, 88)

4 not reported

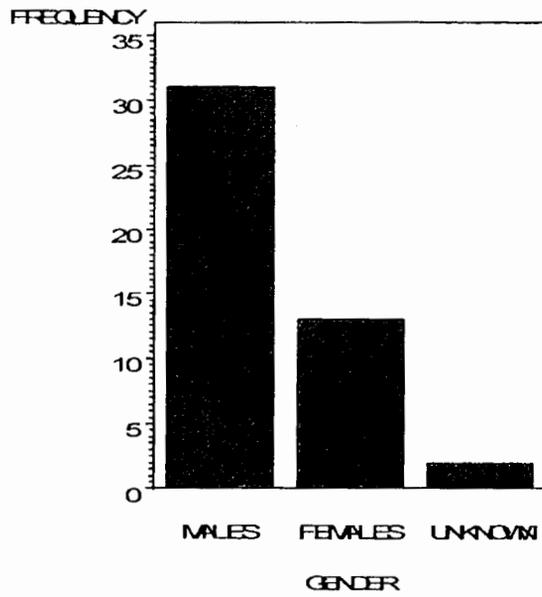


2. Gender

Male = $31 / 46 = 67.4 \%$

Female = $14 / 46 = 28.3 \%$

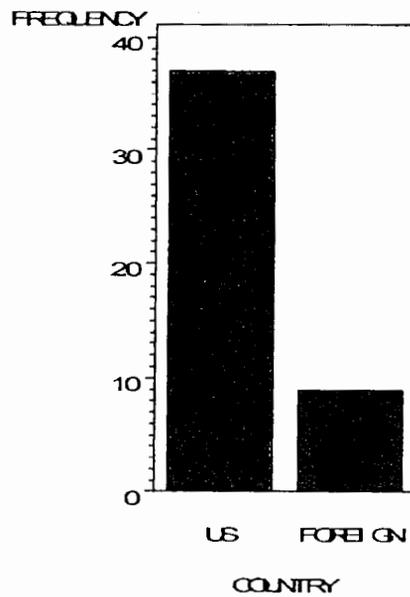
Not reported = $2 / 46 = 4.3 \%$



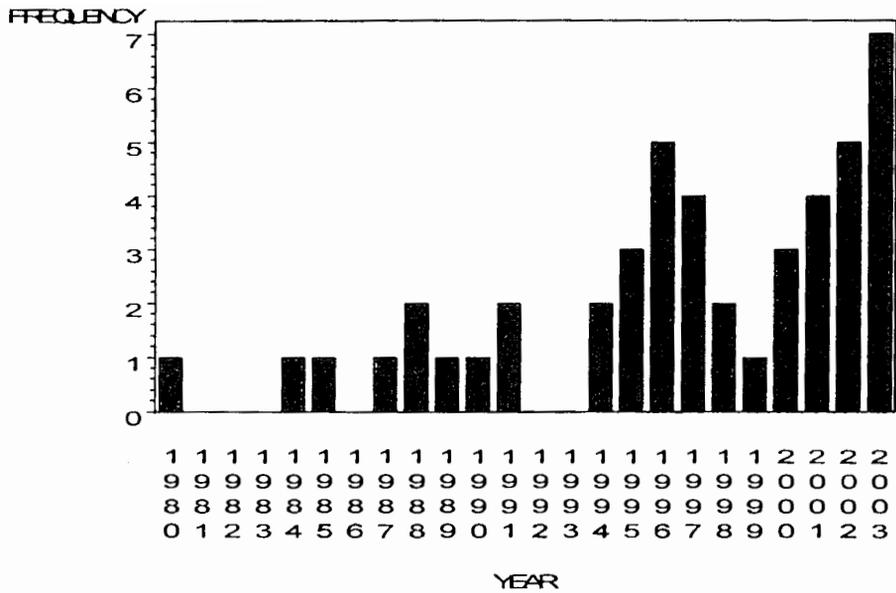
3. Location

US = $37 / 46 = 80.4\%$

Foreign = $9 / 46 = 19.6\%$

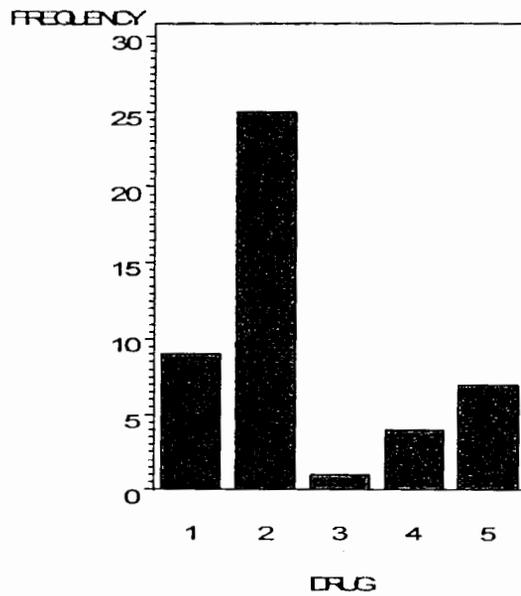


4. Year Reported



5. Formulations

1 = Methylphenidate	9 / 46 = 19.6 %
2 = Ritalin	25 / 46 = 54.3 %
3 = Ritalin-LA	1 / 46 = 2.2 %
4 = Ritalin-SR	4 / 46 = 8.7 %
5 = Concerta	7 / 46 = 15.2 %



A narrative summary of each of the cases is presented below.

Cardiac

3986870/US

Arrest

A pharmacist and a physician reported that a 9 year old female with a history of ADHD, asthma, chronic otitis media, and surgical placement of tubes in her ears nine days prior, was admitted to the hospital for sinusitis, vomiting, and increasing respiratory symptoms. After hospital admission, the child was reportedly given IV fluids and three hours later experienced cardio-respiratory arrest and expired. Medications included Concerta, cefuroxime axetil, ceftriaxone, albuterol, loratadine, and fluticasone propionate. Concerta 18 mg daily had been initiated two months prior for the treatment of ADHD. At the time of hospital admission, the methylphenidate level was 156 ng/mL (therapeutic range is 3.7 – 6.8 ng/mL according to the reporter), and blood glucose was 402 mg/dL, SGOT 132 U/L, and SGPT 42 U/L. The child's grandmother stated that there were no additional tablets missing from the bottle of Concerta. The pharmacist reported that no Concerta shells were found in the bowel at autopsy. The official autopsy report was unavailable.

4121941, 4138233/ Foreign

Arrest

A physician reported a 13 year old male with a history of ADHD, learning disorder, and deafness collapsed at school due to cardiac arrest. He had been taking methylphenidate for 6 years and had recently switched to a long-acting form of the medication. Upon collapse at school, he was resuscitated but pupils remained fixed and dilated. Two days later he suffered another cardiac event and died. The autopsy showed no cardiac abnormalities by gross examination. Viral studies for myocarditis were negative. ECGs between cardiac events indicated late repolarization syndrome which may be associated with ion channel abnormalities. The toxicology screen was negative.

3489120, 3616770, 3894289, 4034273, 4035868/ U.S.

Ischemic heart disease

A physician's office, coroner, and lawyer report that a 14 year old obese male weighing 198 lbs died while taking methylphenidate 20 mg TID for 10 years. The report mentions a literature report but the source was not provided. The physician providing the report did not care for the patient but received information about the case from the patient's father (also a physician). Per the father, the autopsy revealed small vessel damage of the heart and the heart weighed approximately 402 grams. The patient did not have preexisting heart disease but did complain of chest pain for an unknown period of time prior to death. The patient's methylphenidate level was 6.5 ng/ml. Autopsy results stated the "patient died of acute coronary insufficiency due to ischemic heart disease complicating long term use of methylphenidate."

4169310/ U.S.

MI

A physician reported the death of a male in his 30s with a history of diabetes, left below the knee amputation, cardiac disease, obesity (500 lbs), and depression. The patient had a coronary event, was resuscitated and hospitalized, and subsequently died weeks later. The patient was on methylphenidate 80 mg QD for depression and was reduced to 60 mg at an unknown time. The patient had cardiac problems and his cardiologist wanted to discontinue methylphenidate but the patient insisted on continuing due to the positive effects on his depression. No autopsy was performed.

515040/ U.S.

MI

A physician reported the death of a 50 year old female with a history of narcolepsy. The EKG showed infarction. The patient arrested and could not be resuscitated. No other information was provided.

573890/ U.S.

Myocarditis

A physician reported the death of a 15 year old male with a history of ADHD. The patient was on Ritalin 65 mg QD for approximately 5 years. The patient was hospitalized with lactic acidosis, renal failure, tachycardia, tachypnea, and cyanosis. Chest X ray and ECG were normal. He died 14 hours after hospitalization. The drug screen was negative and the autopsy revealed eosinophilic infiltrates in the myocardium. The patient's father had a pleurodynia (a viral syndrome) approximately 2 weeks prior to the patient's reaction.

Cerebral hemorrhage

1916772/ Great Britain

A physician reported the death of a 13 year old male who took ten 10 mg Ritalin tablets supplied by a child on Ritalin. The boy was admitted to the hospital in an agitated state. 4.5 hours after admission the patient had a respiratory arrest and was thought to have increased intracranial pressure. CT scan of the head confirmed this and also revealed a subarachnoid hemorrhage. Care was withdrawn later that day. No Ritalin was detected in the blood 10 hours post ingestion.

Drowning

1618983/ U.S.

A physician reported the death of a 3 year old female with a history of ADHD, mild mental retardation, and fetal alcohol syndrome. The patient was taking Ritalin 2.5 mg TID. The physician reported seizure activity and ataxia. The child drowned in the presence of others.

Liver necrosis

3122062/ Foreign

A physician reported the death of a 14 year old male with a history of ADHD. Initially, the patient was treated with methylphenidate alone, then pemoline (37.5 mg QD) alone for 16 months. Then, the patient was treated with both pemoline and methylphenidate (20 mg QD) for 2 months preceding presentation. The patient then experienced acute illness including fatigue, anorexia, and 1-2 kg weight loss. Both pemoline and methylphenidate were stopped but jaundice developed 10 days prior to hospital admission. Exam revealed an enlarged liver and pertinent labs included AST 2265, ALT 3332, total bilirubin 349, direct bilirubin 281, alkaline phosphatase 237, prothrombin time 21 seconds. He became encephalopathic and required intubation. Liver biopsy revealed greater than 90% hepatocellular necrosis with inflammatory changes, cholestasis, occasional giant hepatocytes, and prominent eosinophils. Iron and copper stains were negative. Peripheral eosinophilia was evident. Orthotopic liver transplantation was performed 1 week after admission and graft necrosis caused by hyperacute rejection necessitated retransplantation. This was complicated by ARF and the patient died with severe cerebral edema and uncus herniation 2 days later (from literature Marotta et al., Pemoline hepatotoxicity in children, J Pediatr 1998, 132, 894-7). The article suggests that pemoline and methylphenidate may act synergistically to cause liver damage.

Malignant hyperthermia or NMS

3171158/ Japan Malignant hyperpyrexia

A pharmaceutical company reported the death of a 41 year old obese (220 lb) male with a history of epilepsy and mental retardation. In _____ the patient was started on sodium valproate due to epilepsy. 4 months later, the patient went on a trip to Okinawa where he became less energetic and experienced facial muscle twitching. 11 days later, the patient returned home and was started on methylphenidate, cetraxate hydrochloride, and risperidone. 5 days later the patient began vomiting and had a decreased level of consciousness. He was brought to the ER and was hospitalized. His temperature at this time was 40 C. Rigidity of the arms and legs and hypoxemia were noted. The patient was started on cefmetazole sodium, clindamycin, and antipyretics. The patient's temperature remained above 40 C and DIC occurred. Dantrolene sodium had no effect and the patient died 2 days after hospitalization. A physician familiar with the case doubted an infectious cause. Relevant labs included WBC > 16,000 and CPK values of 1218, 1930, 3555. The patient was believed to have a syndrome of malignant hyperpyrexia.

1631220/ U.S. NMS

A physician reported the death of a 67 year old male with a history of chronic pulmonary disease, heart disease, dementia, and depression who was residing in a personal care boarding home. The patient was admitted to the hospital with worsening symptoms of depression and Parkinsonian symptoms. At the time of admission, the patient was taking Risperidal, Methylphenidate, Paroxetine, Lithium, and Clonazepam. All medications except Lithium were discontinued upon admission. The patient was treated with Venlafexine 75 mg QD for depression and Bzotropine 1 mg QD for the Parkinsonian symptoms. 5 days later Risperidal 1 mg daily was restarted. On day 8 the patient became confused, tremulous and agitated possibly due to the extrapyramidal effects of Risperidal. The Risperidal was discontinued but the patient continued to deteriorate over the next 2 days and developed muscle rigidity and jerky movements. On day 10 he had a tonic-clonic seizure. The patient's temperature was 40.2 C.

Phenobarbital 130 mg IV was initiated and he was transferred to the ICU. Temperature increased to 43 C and CPK was 823 u/L. Fluids, ice packs, and cooling blankets were initiated. Phenytoin was added for seizure control, Dantrolene and Bromocriptine for NMS, and Dopamine for BP control. Two days after the onset of NMS, the patient experienced kidney failure and blood pressure was difficult to control and the patient expired.

MDI-accidental

1889044/ U.S.

A lawyer reports the death of a 6 year old female. The child was allegedly forced by her mother to drink a drug cocktail of Ritalin, Tofranil, and oxycodone in grape juice. The child was found dead after consuming the mixture. The mother gave the mixture as a cough remedy. 2 of her other children were also given the mixture and they did not suffer adverse reactions.

Medication error

1879846/ U.S.

The Drug Information Center from the Health Sciences Center reported the death of an 88 year old male due to a medication error. The patient presented to the hospital for proximal weakness evaluation and congestive heart failure. He was on multiple medications including ASA, Benazepril, Furosemide, Sertraline, Heparin, Sinemet, Glipizide, and Metolazone. At the hospital the patient was inadvertently given Methylphenidate 5 mg instead of Metolazone 5 mg. The patient became agitated, confused, lethargic and was not oriented to person, place, or time. A CT scan of the head was negative. An infectious workup including UA, pleural effusion tap, and CBC with differential were within normal limits. The patient died 5 days after admission to the hospital.

Overdose of Methylphenidate

3733545/ U.S.

A physician reported the death of a 13 year old obese (195 lbs) male with a history of ADHD, depression, and possible abuse. The patient was on Concerta 54 mg QD for 3-4 years, Wellbutrin 100 mg QD for 3-4 years, and Seroquel which was discontinued 2 months prior to his death. The patient was living in a foster home and may have been depressed. His sister and her boyfriend may have been abusing him and his mother died of cancer 6 months prior to his death. The patient is thought to have taken a Concerta overdose the night before his death. His aunt awoke him in the morning and the patient insisted on sleeping more. A short time later he was found unresponsive. Resuscitation was unsuccessful. Additional toxicology screening including opioids, benzodiazepines, volatiles, and carbon monoxide were negative. An autopsy listed the cause of death to be "Ritalin intoxication". Autopsy revealed pulmonary edema and congestion, moderate cardiac ventricular dilation, and hepatic steatosis. The patient was seeing a psychiatrist on a monthly basis and did not appear depressed at his last visit.

4054405, 4054409/ U.S.

A literature report from the American Journal of Emergency Medicine (Litovitz et al) reported the death of a 42 year old patient who ingested an unknown amount of methylphenidate and died. The case could not be located in the article and no other information was available.

Seizure

3997822/ U.S.

A toxicologist reported in the published literature the death of a 42 year old female with an unknown medical history. The patient was found unresponsive and was transferred to a local emergency room. She was actively seizing upon arrival, was intubated, and was given IV alprazolam and phenytoin which failed to control the seizures. Activated charcoal was administered. The patient was taking bupropion SR, methylphenidate, clordiazepoxide/clidinium, Singulair, and levothyroxine. The patient died in the ER 3 hours after arriving (case published in the American Journal of Emergency Medicine).

Sudden death

1557196/ U.S.

An autopsy report describes the death of a 7 year old male with a history of premature birth at 34 weeks, ADHD, and a heart murmur. He was on both Ritalin and Clonidine. He was at school when he complained of feeling ill. He lay down for a few minutes and then returned to class. Shortly afterwards he was found unresponsive. Paramedics arriving at the scene found no vital signs and a heart monitor showed ventricular fibrillation. Attempts to resuscitate him were unsuccessful. Autopsy revealed fibrosis of the mitral valve papillary muscle consistent with perinatal hypoxic injury, evidence of CHF, 4 chamber dilatation of the heart (right greater than left), peritoneal effusion, and moderate cerebral edema.

1770090/ U.S.

A physician reported that a 13 year old male with a history of ADHD died suddenly from suspected cardiac arrest. The patient was on methylphenidate 10 mg TID for 3 months and was subsequently increased to 20 mg TID for 5-6 months prior to the fatal event. The patient was on imipramine prior to starting methylphenidate. An autopsy was performed but results are not available.

3240721, 1680461, 1784758, 1842644, 3240724/ U.S.

2 physicians (1 treating) and 1 psychologist reported the death of a 10 year old male taking methylphenidate 10 mg BID concurrently with clonidine patch (.2 mg Q 5 days). The patient had a history of treated ADHD since kindergarten and had been started on clonidine within 6 months of his death to treat tics that had developed with higher doses of methylphenidate. The patient had a history of exercise induced syncopal events with subsequent normal ECG, normal EEG, and a normal head CT scan. While swimming, the patient complained of feeling faint. After resting, the child swam again, passed out, and appeared to experience a tonic-clonic seizure. Cardiopulmonary resuscitation was unsuccessful. The autopsy revealed a congenital cardiac malformation that was thought to be capable of causing transient ischemia and arrhythmia. His left coronary artery originated in the right sinus of Valsalva and was subject to compression by the aortic root. The left coronary artery orifice was stenotic. Clonidine blood levels were within normal limits and there was no evidence of ischemic changes. (for more details see Case 4 of Cantwell et al., Case Study: Adverse Response to Clonidine, Cantwell et al., J. Am. Acad. Child Adolesc. Psychiatry, 36:4, April 1997)

1504208/ U.S.

A pathologist reported that a 13 year old male died during football practice secondary to a suspected cardiac arrhythmia. The autopsy revealed a hypertrophied and enlarged heart with anomalies of the tricuspid valve. Methylphenidate was present within a therapeutic range. It is unknown how long the patient had been taking the medication.

3775962, 3446728/ U.S.

A mother reports the death of her 11 year old daughter who was taking methylphenidate for ADHD for 4 years and 3 months. One day prior to her death, her doctor changed her dose from 20 mg QAM and 15 mg Q lunch to 25mg QAM and 15 mg Q lunch. According to her mother, the child seemed "out of it" on the first morning of the dose increase but seemed fine after school. The following morning, the child was found dead in bed. The mother states that the autopsy did not reveal cardiac abnormalities and that the coroner described death due to cardiac arrhythmia.

451578/ U.S.

A physician reported that a 39 year old male bodybuilder was found dead with a Ritalin 20 mg tablet found alongside the body. The patient was taking Ritalin 20-40 mg QD for 4 years to treat narcolepsy. At least 2 years prior to death, the patient was diagnosed with non-specific T and S-T changes on an ECG which was still present shortly before his death as well as apical and left parasternal systolic murmurs. The reporting physician did not believe that the patient overdosed and thought that he may have "gone into an arrhythmia or had an acute coronary."

4143391/ U.S.

An unknown reporter states that a 13 year old female with a history of ADHD and seasonal allergies died in her sleep due to a cardiac arrhythmia. The patient had been taking Concerta 36 mg QD for 9 months and had been on Zyrtec for an unknown period of time. She had no prior cardiac history and autopsy was not mentioned.

544470/ U.S.

A physician reported the sudden death of a 12 year old male with a history of ADHD while riding his bicycle. The patient was taking Ritalin-SR 20 mg QD and there is discrepancy as to the length of therapy. One report claims 11

months of drug treatment while others state 4 years. An autopsy revealed a markedly enlarged heart weighing 320 grams (normal = 124 grams) and marked dilatation of all chambers of the heart. In addition, there was congestive atelectasis of the lungs.

1963252/ U.S.

A physician reported that a 15 year old male with a history of hypopituitarism died from a "coronary attack" while hospitalized for the treatment of phlebitis. He had been taking Ritalin, Prednisone, and Tegretol for over 1.5 years and was in the hospital for one week prior to the event. An autopsy was not performed.

4115324, 4226201/ U.S.

A physician reported that a 13 year old male with a history of ADHD experienced sudden cardiac death while at camp. The patient was started on Concerta 18 mg QD for 1 month and was then titrated up to 36 mg QD. Six months after initiating treatment the patient had a syncopal event. ECG performed on that day was normal. Ten months after starting Concerta the boy suffered polymorphic ventricular tachycardia and could not be resuscitated. Autopsy results were not reported.

705007/ U.S.

A physician reported the death of a 77 year old female with a history of depression treated with Ritalin 20 mg QD for 7 days. The patient had 2 episodes of syncope secondary to bradycardia. An ECG captured a 10 second interval of asystole associated with one of the syncopal events. Details on the death and other concomitant medications and comorbidities were not reported.

4027547, 4030508/ Germany

A physician reported that a 59 year old male with a history of restless leg syndrome suffered sudden cardiac death while at a stadium. The patient was being treated with Ritalin SR 60 mg QD and Zoloft 100 mg QD for an unspecified period of time for restless leg syndrome. The patient also drank alcohol and smoked cigarettes but quantities were not noted. Six months prior to his death, the patient made an appointment with a cardiologist to rule out "primary cardiac illness" and ECG revealed ventricular extra-systoles and couplets but no other abnormalities. An autopsy was not performed.

307979/ Germany

A physician reported the unexpected death of a 13 year old male with a history of ADHD. The patient was on his way home from school with friends when he suddenly collapsed in the subway. Resuscitation efforts were unsuccessful. The patient was taking alternate courses of di-amphetamine and Ritalin for 6 years and 3 months. The autopsy revealed macroscopically recognizable alteration of the adrenals with extremely thin, practically absent medulla and normal texture of the cortex. There was almost complete depletion of adrenalin and noradrenalin storage in the adrenals but normal blood values of these 2 substances.

363488/ U.S.

A physician reported the death of a 76 year old male with a history of Alzheimer's Disease. The patient was transferred to a nursing home from an acute care hospital on chloral hydrate and Haldol. Both drugs were discontinued by a psychiatrist who believed the patient was suffering from senile withdrawn depression. Ritalin 20 mg TID was given but discontinued after 5 doses after the patient became agitated. He was given Haldol and Sinequan. The patient died suddenly 36 hours after the last dose of Ritalin. According to the reporter, the autopsy was non-contributory.

1781818/ U.S. & foreign

A psychologist reports in the literature the deaths of 4 children (Table 1, Swanson et al., Clonidine in the treatment of ADHD: questions about safety and efficacy, J of Child & Adolescent Psychopharm, 5 (4), 1995, 301-304).

1. 8 year old female on clonidine .2 mg QD and methylphenidate (no dose specified).
2. 7 year old male on clonidine .1 mg QD and methylphenidate 45 mg QD. The patient had a history of heart murmur and had fibrotic cardiac scarring.
3. 9 year old female on clonidine .9 mg QD and methylphenidate 60 mg QD. She had a history of OCD, Tourette's syndrome, and fetal alcohol syndrome. She was also taking Prozac and the coroner reported high levels at autopsy. The child complained of flu-like symptoms, headache, and nausea. The patient then had several grand mal seizures and died.

4. 10 year old male on clonidine patch and methylphenidate 20 mg QD. He had a history of syncope and undetected cardiac malformation (this case was already described – Cases 1680461, 1784758, 1842644, 3240721, 3240724).

4106370/ U.S.

A newspaper journalist reported the death of a 12 year old girl who was being treated with Concerta for ADHD for an unknown period of time. The patient had a history of migraine headaches and had a skating accident with head trauma 11 months prior to her death. The patient was found in the bathtub approximately 20 minutes after entering with her face partially submerged in water. Cardiopulmonary resuscitation was initiated and she was transported to a hospital. She was pronounced dead one hour after she was found. A police detective speculated that the patient may have experienced seizures after the skating accident but neurological tests at the time of the accident were inconclusive.

4183882/ S Africa

A physician reported the death of a 12 year old male treated with Ritalin SR 20 mg QD for 3 months for ADHD. He was also taking Budesonide, Fluticasone, and Inflammide for the treatment of asthma. The patient was on the playground at school and was about to start playing soccer when he collapsed. He murmured a few words but there were no signs of convulsions. Teachers tried to resuscitate him but he was dead by the time the first doctor saw him. Per the reporting physician, the autopsy showed brain edema but no other abnormalities.

Suicide

127220/ U.S.

A physician reported the suicide death of a 48 year old male who had a history of alcoholism and depression. He was taking Ritalin 20 mg QD for approximately 2 years. He was also on Tylenol #4, Fiorinal, and Pertofrane. Psychological dependence on Ritalin was reported. The patient shot himself.

769098/ U.S.

The suicide death of an 18 year old male was reported via legal channels. No details were provided.

3525243/ U.S.

A non-health professional reported the death of a 62 year old male with a history of panic disorder, heart disease including MI, dementia, and social stress. The patient was admitted to a psychiatric hospital for panic attacks and depression. Ritalin 10 mg BID was started at this time. 4 days after admission, Klonopin 1 mg Q8 hours was started. The patient was discharged 1 day later on Ritalin and Klonopin. 4 days later the patient shot himself in the head and died.

3661388/ U.S.

A physician reported the death of a 14 year old male with a history of ADHD. The patient was taking Concerta 36 mg QD for approximately 1 month. He was also taking Zoloft. The patient committed suicide but the report did not explain how. His father and maternal great-grandfather also committed suicide.

3680933, 3783538/ U.S.

A lawyer reported the death of a female of unknown age with a history of depression. The patient was taking Prozac and Ritalin and had been on the drugs for approximately 7 years. The reporter states that the patient became addicted to the drugs and experienced personality and behavioral changes. Depression and anxiety worsened on the medications and the patient committed suicide by an unknown mechanism.

3976076/ U.S.

A physician reported the suicide death of an elderly unknown age female. The patient had a history of bipolar disorder and had reported to improve in all areas of functioning (cognitive, motor, etc.) within the first week of Ritalin therapy. By the end of the second week, she had hung herself.

4001702, 4005531/ U.S.

A nurse reported the suicide death of a 16 year old male with a history of ADHD. The patient was taking Ritalin SR 30 mg QD for 3.5 years. Ritalin therapy was discontinued 1 week prior to the suicide. The report did not explain how the suicide was completed.

Unknown

738806/ U.S.

A toxicologist reported the death of a male of unknown age. The victim was found dead with an empty bottle labeled methylphenidate along with a bottle labeled ritalinic acid. No other details were provided.

1696046/ U.S.

An insurance agent reported the death of a 50 year old male physician who was vacationing in The Ritalin blood level was elevated at 430 pg / l. No other information was available.

3509918/ Foreign

A pharmacist reported the death of a 17 year old male on Ritalin SR 40 mg QD for 2 years for the treatment of ADHD. The patient was found in the woods several days after his death with an empty bottle of Ritalin found close to/on his body. It was calculated that there should have been 28 pills left but no traces of methylphenidate were found in his blood or tissues. Cause of death was reported as exposure to cold weather.

1504202/ U.S.

A pharmacist reported the death of an elderly patient on Ritalin for the treatment of depression. The patient had underlying cardiovascular disease and was also taking an unspecified tricyclic antidepressant. No other information was available.

Narrative summaries of some non-cases are presented below.

Accident

3751030, 3766038/ U.S.

A physician reported the death of a female (unknown age). The patient was a physician and had a history of chronic fatigue and chronic pain. She was on Provigil, Ritalin (for chronic fatigue), and started taking corticosteroids a few days prior to her death for back pain. The treating physician believed the patient experienced steroid psychosis. A witness described the patient jumping a fence while chasing an imaginary cat. The patient was found dead in a canyon behind her home wearing only a pair of shorts. No autopsy was performed.

654080/ U.S.

A physician reported the death of a 52 year old female who had been on Ritalin 40 mg QD for 15 years for the treatment of depression. The patient was struck by a car and suffered a mild head injury. She developed syncope and aphasia and was hospitalized. She had left middle cerebral artery thrombosis followed by cerebral infarction, cerebral edema, and increased intracranial pressure and subsequently died.

IV Drug Abuse of Methylphenidate

1548670/ U.S.

An unknown reporter from the American Association of Poison Control Center reported a case from the literature concerning a 26 year old male who suffered cardiac arrest and subsequent death after injecting Ritalin intravenously (the literature source was not provided). Concomitant medications and medical history is unknown.

3209268/New Zealand

A pharmacist reports the death of a patient who suffered cerebral hemorrhage and death after injection of Ritalin. No other information is available.

MDI

3895299/ U.K. abuse

A physician reported that 15 year old male with a history of ADHD was taking an unknown dose of methylphenidate for many years. He was also suspected of taking other recreational drugs. He collapsed at home one morning and could not be resuscitated. Autopsy revealed a small cardiac defect.

46090, 46979/ U.S. abuse

A pathologist reported the death of an elderly male with a history of chronic drug abuse. He was reported to have injected heroin, methylphenidate, and other drugs. Toxicology examination was negative for Ritalin. The toxicologist reported the death as "acute and chronic right and left heart failure with severe pulmonary hypertension and multiple pulmonary granulomata following chronic intravenous drug abuse". Autopsy revealed multiple bilateral pulmonary talc granulomata, acute passive congestion of the liver, severe right ventricular hypertrophy of the heart, multiple talc granulomata of veins of left arm, and severe pulmonary hypertension.

97309/ U.S. abuse

A pathologist reported the death of a 28 year old male with a history of Ritalin abuse. Final autopsy reported cerebral anoxia due to pulmonary edema and congestion secondary to drug abuse. Methadone, Diazepam, and Desmethyl diazepam were found in the blood in the therapeutic range. No other information was available.

1580727/ U.S. abuse

A physician reported the death of a 19 year old male. The patient went to a party and snorted Ritalin and drank ETOH. The patient presented to the ER at 5:30 AM, collapsed, was hypotensive with tachycardia. Blood alcohol was 0.128, EKG showed findings of MI. Antemortem blood levels showed methylphenidate < 0.05 mg/l, ritalinic acid .4 mg/l, and ethanol 0.10%. Cause of death is reported to be cardiac arrhythmia from methylphenidate ingestion.

3940940, 497346/ U.S. abuse

A physician reported the death of a 25 year old pregnant female with a history of IV Ritalin and Talwin abuse. The patient was admitted via the ER for shortness of breath, low back pain, abdominal pain, and hypotension. Her most recent drug use was the day prior to admission. EKG showed sinus tachycardia and incomplete bundle branch block. An emergency C-section was performed. The patient developed electromechanical dissociation and died.

1744847/ U.S. suicide

A physician reported the death of a 31 year old male who overdosed with 100-200 tablets of Ritalin. The patient presented to the ER with "amphetamine psychosis" and was admitted. Labs also detected levels of acetaminophen, aspirin, and lortabs. Treatment included IV Haldol 2-4 mg Q hour and then 5-10 mg Q hour. Rectal temperature was 107 F. Haldol was discontinued and dantrolene initiated. The patient developed asystole and died.

3997826, 3999617, 3999628, 4162496/ U.S. suicide

A physician reported via literature the suicide death of a 42 year old male. The patient had a history of depression and suicidal attempts and reportedly fled home with unknown amounts of methylphenidate and bupropion. He was found 22 hours later in a mountainous area, face down, moaning, cyanotic, and unconscious. He was intubated in the field and found to have gastric contents within the airway. After transport to the hospital he was comatose and in shock, with renal and respiratory failure. Labs on presentation included: ABG: pH 7.36, pCO₂ 35.8, pO₂ 47.6, HCO₃ 20, anion gap 19, BUN 57, Cr 6.1, myoglobin > 10,000, CK 26,400, serum lactate 7, ALT 159, AST 538, serum osmolality 328. The patient was found to have a bupropion level of 2800 nanog/mL. Treatment included artificial ventilation, oral activated charcoal, vasopressors and IV fluids. The patient's neurologic status deteriorated with changes consistent with a cerebral infarct. The patient died 34 hours after being found. Post-mortem examination showed diffuse cerebral edema with tonsillar, uncal and mild right-to-left subfalcine herniation, massive retroperitoneal hemorrhage located at the upper poles of both kidneys, cardiomegaly with left ventricular hypertrophy, congestive hepatosplenomegaly, and mild pulmonary congestion (Litovitz, 2001 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System, American Journal of Emergency Medicine, vol 20, #5, p 391-452).

135243/ U.S. unintentional

A physician reports the death of a 42 year old female. The patient was treated successfully on the inpatient psychiatric service of a hospital with Parmate, Ritalin, and Stelazine. After discharge, the patient went to a "diet

doctor" who gave her medications containing Phenteramine and Phenylpropylamine, both of which are contraindicated with Parnate. 9 days after discharge from the hospital, the patient was treated in an ER for headache and was given 2 cc of Gynergen IM. She expired later that day.

Pulmonary embolism

1777320, 1797836/ U.S.

A physician reported the death of a 47 year old female with a history of depression. The patient was taking Ritalin unknown dose for an unknown period of time as well as Marvelon (Ortho-cept) for 1 month. Death was due to pulmonary emboli. The patient was reported to have visited a clinic several times with a complaint of shortness of breath and chest pain (temporal relationship of these events to death is unknown). There was no previous history of PE, deep vein thrombosis. The patient was non-obese and normotensive.

Pulmonary hypertension

3056072/ U.S.

A physician reported the death of a 39 year old obese (BMI 30.4 kg/m²) female with a history of bipolar disorder, hypothyroidism, S/P TAH, and intermittent DOE since 1990. In the summer of 1995, the patient experienced increased DOE and ascites. Severe pulmonary hypertension was diagnosed via cardiac catheterization. The patient was taking Pondimin 60 mg QD for 7 months, Ritalin 20 mg TID for 5 months, as well as KCl, Klonopin, Lasix, Lithium, Methyltestosterone, Synthroid, Triazolam. The patient was unresponsive to vasodilator treatment and died of complications of pulmonary hypertension and probable acute pneumonia.

3965811/ Japan

A physician reported that a 76 year old male died after treatment for depression. The patient was hospitalized for over 1 year and 4 months with multiple medications used including Setiptiline, Mianserin, Pergolide, Levothyroxine, Maprotiline. Methylphenidate was added but discontinued due to nausea, loss of appetite, and diarrhea. The patient received 9 treatments of ECT due to severe depression. He eventually was discharged from the hospital but readmitted again for depression. He eventually died of unknown causes (for more details see Case 2, Okada et al, Effect of electroconvulsive therapy for senile depression with marked pseudohysterical symptoms: two case reports, Japanese J. of Psychiatric Treatment, 17(6), 757-762).

4050776/ U.S.

A pharmacy representative reported that an elderly male (85-90 years old) died while being treated with Metadate CD 20 mg QD for an unknown reason. The reporter states that the medication had nothing to do with the death but no further information is provided.

Methylphenidate Sudden deaths (23/46 cases were considered sudden deaths by the WHO definition)

ISR	CK	CSENUM	RECVDATE	AGE	SEX	CNTRY	VERBDR1
307979	8	4416766	9-Apr-1984	13	Male	US	RITALIN
363488	1	4457997	23-Sep-1985	76	Male	US	RITALIN
451578	4	4535196	2-Mar-1987	39	Male	US	RITALIN
515040	2	4590401	23-Mar-1988	50	Female	US	RITALIN
544470	8	4616220	27-Sep-1988	12	Male	US	RITALIN-SR
573890	0	4642637	14-Mar-1989	15	Male	US	RITALIN
705007	3	4758183	14-Nov-1990	77	Female	US	RITALIN
1504208	4	5162483	30-Sep-1994	13	Male	US	RITALIN
1557196	9	5212781	13-Feb-1995	7	Male	US	RITALIN
1618983	1	5271947	26-Jul-1995	3	Female	US	RITALIN
1770090	3	5418564	2-Jul-1996	13	Male	US	RITALIN
1889044	1	5533954	6-Mar-1997	6	Female	US	RITALIN
1963252	3	5606117	25-Jul-1997	15	Male	US	RITALIN
3240721	1	3123579	15-Apr-1999	10	Male	US	RITALIN
3489120	6	3456934	18-Apr-2000	14	Male	US	RITALIN (METHYLPHENIDATE)
3775962	6	3696266	13-Aug-2001	11	Female	US	RITALIN / 25&15 MGS / NOVARTIS
3986870	X	3842527	2-Oct-2002	9	Female	US	CONCERTA (18 MG SUSTAINED RELEASE
3997822	8	3847433	22-Oct-2002	42	Female	US	CONCERTA (SUSTAINED RELEASE TABLE
4027547	4	3879775	16-Dec-2002	U	Male	DE	RITALIN-SR (METHYLPHENIDATE HYDROC
4106370	6	3944251	1-May-2003	12	Female	US	CONCERTA (SUSTAINED RELEASE TABLE
4115324	5	3883603	20-May-2003	13	Male	US	CONCERTA (SUSTAINED RELEASE TABLE
4143391	1	3968393	8-Jul-2003	13	Female	US	CONCERTA 36 MG
4183882	0	3991585	11-Sep-2003	12	Male	ZA	RITALIN

**METHYLPHENIDATE NON-EXCLUDED SERIOUS NONFATAL
CARDIOVASCULAR AND CEREBROVASCULAR REPORTS (1999-2003)**

	A	B	C	D	E	F	G
1	3704415, 3875165	13-Apr-2001	7	M	RITALIN, CLONIDINE	palpitations, blurred vision, headache, behavioral changes	LT, HO
2	3718639	7-May-2001	10	M	CONCERTA, ZOLOFT, CLONIDINE	tachycardia (HR=110), fever, lethargy	HO
3	3950092	16-Jul-2002	10	F	CONCERTA	stroke, arteriovenous malformation	HO
4	4057752	12-Feb-2003	10	M	CONCERTA, MIRTAZAPINE	cardiac arrest, ventricular arrhythmia, abnormal heart biopsy	LT, HO
5	4109719	7-May-2003	10	M	CONCERTA, MOTRIN, TYLENOL	loss of consciousness, PVCs, headache	HO
6	4133722	20-Jun-2003	13	F	CONCERTA	QT prolongation, dyspnea, abdominal pain	HO
7	3791057	4-Sep-2001	14	F	CONCERTA, CELEXA, WELLBUTRIN	tachycardia (HR=220)	HO
8	4083568	28-Mar-2003	18	M	CONCERTA, ZESTRIL	syncope, bradycardia	RI
9	3916619, 3917822	14-May-2002	33	F	METADATE, PAXIL, CLOZAPINE	hypertension (BP 140/100), postural hypotension, dizziness, mitral valve prolapse	HO
10	3851100	10-Jan-2002	37	M	METHYLPHENIDATE, ZOLOFT	chest pain, bizarre behavior	LT
11	4189437	22-Sep-2003	41	F	RITALIN	myocardial infarction	HO
12	4246675	3-Dec-2003	45	M	CONCERTA, VIOXX, ROFECOXIB	myocardial infarction	HO
13	3189577	1-Feb-1999	50	M	RITALIN	hypertension, stroke	LT, HO
14	3224294	22-Mar-1999	50	M	RITALIN	ventricular tachycardia, chest pain	LT, HO
15	3932906	12-Jun-2002	74	F	RITALIN, ZOLOFT, LIPITOR, PREVACID	syncope	HO
16	3819864	1-Nov-2001	75	M	METHYLPHENIDATE, CELEXA	supraventricular tachycardia	LT, HO
17	3534580	25-Jul-2000	adult	F	RITALIN	hypertension, myocardial infarction, heart failure	LT
18	3184611	22-Jan-1999	U	Unk	RITALIN	chest pain, increased CK	HO
19	3797912	24-Sep-2001	U	M	METHYLPHENIDATE	syncope	HO

APPENDIX C

METHAMPHETAMINE

ISNRNUM	CK	CSENUM	RECVDATE	AGE	AGE	SEX	REACT1	CAUSE OF DEATH
3267828	5	3274962	21-May-1999	56	Y	F	DRUG TOXICITY	MDI-abuse
3267840	6	3274516	21-May-1999	20	Y	M	DRUG TOXICITY	MDI-abuse
3527410	9	3498255	11-Jul-2000	36	Y	M	OEDEMA	MDI-abuse
3586780	6	3498396	3-Oct-2000	29	Y	M	BRAIN OEDEMA	MDI-unknown
3601198	5	3498379	24-Oct-2000	34	Y	M	COMA	MDI-unknown
3601524	7	3559881	24-Oct-2000	36	Y	M	COMA	MDI-unknown
3601530	2	3498264	24-Oct-2000	29	Y	M	COMA	MDI-unknown
3601532	6	3498268	24-Oct-2000	29	Y	M	COMA	MDI-unknown
3789498	X	3706375	7-Sep-2001	14	Y	M	CARDIAC ARREST	coding error (did not take methamphetamine)
3820678	0	3730772	5-Nov-2001	33	Y	Unk	COMPLETED SUICIDE	MDI-suicide
3841798	0	3741129	18-Dec-2001	50	Y	F	ACCIDENT	MDI-unknown
3841915	2	3743107	18-Dec-2001	48	Y	M	ASPHYXIA	MDI-abuse
3859014	2	3756499	22-Jan-2002	50	Y	F	BRONCHOPNEUMONIA	MDI-abuse
3869404	X	3780953	13-Feb-2002	36	Y	M	ACCIDENTAL OVERDOSE	MDI-unknown
3869414	2	3780963	13-Feb-2002	4	Y	M	OVERDOSE	MDI-unknown
3870499	8	3768267	13-Feb-2002	44	Y	F	OVERDOSE	MDI-unknown
3871066	2	3787338	13-Feb-2002	31	Y	M	OVERDOSE	MDI-unknown
3871070	4	3787348	13-Feb-2002	24	Y	F	OVERDOSE	MDI-unknown
3871097	2	3786933	13-Feb-2002	52	Y	F	ACCIDENTAL OVERDOSE	MDI-unknown
3873180	4	3791314	13-Feb-2002	25	Y	M	OVERDOSE	MDI-unknown
3873182	8	3791319	13-Feb-2002	31	Y	M	ACCIDENTAL OVERDOSE	MDI-unknown
3907055	9	3787962	24-Apr-2002	16	M	M	BRAIN OEDEMA	acetaminophen overdose
3959863	6	3862140	2-Aug-2002	19	Y	Unk	OVERDOSE	MDI-unknown
3978325	3	3843501	19-Sep-2002	35	Y	Unk	NON-ACCIDENTAL OVERDOSE	MDI-suicide
4051521	5	3899942	3-Feb-2003	50	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4091544	3	3932725	8-Apr-2003	48	Y	M	DRUG SCREEN POSITIVE	MDI-abuse (MVA)
4111661	9	3948049	13-May-2003	53	Y	Unk	INTENTIONAL MISUSE	MDI-abuse
4127924	7	3959416	12-Jun-2003	17	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-abuse
4130489	7	3961748	16-Jun-2003	45	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4130928	1	3992764	16-Jun-2003	21	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4130929	3	3961739	16-Jun-2003	53	Y	Unk	MEDICATION ERROR	MDI-unknown
4130931	1	3961746	16-Jun-2003	45	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4137840	2	4005746	19-Jun-2003	22	Y	M	DRUG TOXICITY	MDI-unknown
4142947	X	3968664	3-Jul-2003	43	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4142961	4	3968572	3-Jul-2003	16	M	M	BRAIN OEDEMA	duplicate of 3907055-9
4155426	0	3979302	23-Jul-2003	21	Y	Unk	DRUG ABUSER	MDI-abuse
4158635	X	3982501	30-Jul-2003	21	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4158637	3	3982507	30-Jul-2003	53	Y	Unk	MEDICATION ERROR	MDI-unknown
4183682	1	4001336	2-Sep-2003	43	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-suicide
4202406	2	4013674	29-Sep-2003	27	Y	M	DEATH	MDI-abuse
4224106	5	4028635	30-Oct-2003	39	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4226621	7	4030821	3-Nov-2003	27	Y	Unk	MULTIPLE DRUG OVERDOSE	MDI-unknown
4226641	2	4030797	3-Nov-2003	33	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4227148	9	4031449	4-Nov-2003	39	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4227187	8	4031453	4-Nov-2003	19	Y	Unk	DEATH	MDI-unknown
4227188	X	4031457	4-Nov-2003	40	Y	Unk	DEATH	MDI-unknown
4227281	1	4031485	4-Nov-2003	20	Y	Unk	COMPLETED SUICIDE	MDI-suicide
4227286	0	4031491	4-Nov-2003	29	Y	Unk	DEATH	unknown cause
4227291	4	4031511	4-Nov-2003	27	Y	M	ABNORMAL BEHAVIOUR	massive overdose of methamphetamine
4227300	2	4031516	4-Nov-2003	33	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4227311	7	4031461	4-Nov-2003	27	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4230541	1	4033228	6-Nov-2003	17	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-abuse
4237645	8	4038221	18-Nov-2003	52	Y	M	AORTIC DISSECTION	IVDA - aortic dissection
4237660	4	4038025	18-Nov-2003	28	Y	M	AORTIC DISSECTION	abuse - aortic dissection
4237663	X	4038026	18-Nov-2003	38	Y	F	LABORATORY TEST ABNORMAL	abuse - ruptured aneurysm
4237702	6	4037551	18-Nov-2003	57	Y	M	DRUG LEVEL INCREASED	abuse - ruptured aneurysm
4237718	X	4037968	18-Nov-2003	42	Y	M	AORTIC DISSECTION	overdose - ruptured aneurysm
4237724	5	4037969	18-Nov-2003	27	Y	F	DRUG LEVEL INCREASED	abuse - aortic dissection
4237734	8	4037977	18-Nov-2003	42	Y	M	COMA	abuse - ruptured aneurysm
4237745	2	4037602	18-Nov-2003	33	Y	M	CARDIOMEGALY	abuse - pulmonary HTN
4240645	5	4038989	21-Nov-2003	19	Y	Unk	NON-ACCIDENTAL OVERDOSE	MDI-unknown
4240724	2	4039000	21-Nov-2003	39	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4241274	X	4039285	24-Nov-2003	33	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4245191	0	4041687	28-Nov-2003	17	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4245791	8	4037875	4-Dec-2003	33	Y	Unk	CARDIO-RESPIRATORY ARREST	MDI-unknown
4261521	8	4056300	31-Dec-2003	21	Y	M	MULTIPLE DRUG OVERDOSE	MDI-unknown
4261523	1	4056301	31-Dec-2003	39	Y	M	MULTIPLE DRUG OVERDOSE	MDI-unknown
4262456	7	4059455	31-Dec-2003	27	Y	M	CARDIO-RESPIRATORY ARREST	MDI-unknown

APPENDIX D

IMS DATA

Projected Number of Total Prescriptions Dispensed (TRx)
 by Retail Pharmacies (Chain, Independent, Food Stores, Long Term Care, and Mail Order) in the US
 for Amphetamine Salts (Adderall, Adderall XR, Amphetamine Salts), Dextroamphetamine (Dexedrine, Dextrostat, D-Amphetamine),
 Methylphenidate (Concerta, Metadate CD, Metadate ER, Methylin, Methylin ER, Ritalin, Ritalin LA, Ritalin SR, Methylphenidate HCl),
 and Atomoxetine (Strattera)
 Stratified by Molecule, Automatic Product Summarization, and Product
 Distributed by Moving Annual Total September 1998 to August 2003
 (in thousands; ADD THREE 0's TO EACH FIGURE)



Molecule (Molecule/Trade Name)	1998 TRX (000)	2000 TRX (000)	2001 TRX (000)	2002 TRX (000)	2003 TRX (000)	2003 TRX (%)
METHYLPHENIDATE	11,518	10,911	11,323	12,673	13,086	100.0%
CONCERTA		21	2,944	5,775	6,842	52.3%
METHYLPHENIDATE	8,373	6,975	4,983	3,668	2,784	21.3%
METHYLIN	298	1,478	1,408	1,254	1,090	8.3%
METADATE CD			21	552	714	5.5%
RITALIN LA				5	578	4.4%
RITALIN	2,206	1,841	1,192	764	499	3.8%
METHYLIN ER		2	226	257	309	2.4%
METADATE ER		56	219	211	161	1.2%
RITALIN-SR	640	538	330	188	109	0.8%
AMPHETAMINE Salts	3,465	5,593	6,693	8,135	9,881	100.0%
ADDERALL XR				2,586	6,022	60.9%
AMPHETAMINE SALTS				1,155	2,712	27.4%
ADDERALL	3,465	5,593	6,693	4,394	1,147	11.6%
ATOMOXETINE					1,789	100.0%
STRATTERA					1,789	100.0%
DEXTROAMPHETAMINE	2,264	2,267	1,969	1,619	1,321	100.0%
DEXTROAMPHETAMINE	0	0	45	331	716	54.2%
DEXEDRINE	1,763	1,668	1,394	986	437	33.1%
DEXTROSTAT	501	599	530	302	168	12.7%
DEXMETHYLPHENIDATE				75	266	100.0%
FOCALIN				75	266	100.0%
METHAMPHETAMINE	61	34	24	23	22	100.0%
DESOXYN	61	34	24	23	22	100.0%

SOURCE: IMS HEALTH; National Prescription Audit Plus TM, On-Line
 ORIGINAL FILE: 0311psyc.dvr

Notes:

I Total includes New and Refill prescriptions

There is a trend break for the NPA, LTC channel, beginning with January 2000.

Data from January 2000 forward includes new sample coverage from two leading nursing home providers.

Years 1999 and prior do not include these providers in the sample.

****NOTE: DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH.**

Clearance must be requested from IMS HEALTH through the FDA Office of Drug Safety

A minimum of 48 HOURS is required for clearance by IMS HEALTH**