Safety Review

Follow up review of AERS search identifying cases of sudden death occurring with drugs used for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

Drugs:	Amphetamine/dextroamphetamine (including Adderall ® and Adderall XR®); methylphenidate; atomoxetine and pemoline)
NDAs:	11-522, 21-303, 21-121,21-259,21-475,21-419,10-187,21-284, 18-029, 21-411 and generic products.
Sponsor:	Various
Subject:	Postmarketing safety review of sudden deaths during treatment with drugs used to treat ADHD.
Date:	February 28, 2006
Reviewer:	Lourdes Villalba, M.D., Medical Officer, Safety Team, DPP
Team Leader:	Judy Racoosin, M.D., M.P.H., Team Leader, Safety Team, DPP

1. Executive Summary

The current review complements a prior review by the Office of Drug Safety (ODS) of sudden death associated with the use of central nervous system stimulants (amphetamine and dextroamphetamine -including Adderall and Adderall XR®-, methylphenidate, methamphetamine and dexmethylphenidate) in the Adverse Event Reporting System (AERS). AERS reporting rates of sudden deaths encompassing January 1, 1992 through December 31, 2004 were estimated based on drug use data. With small differences between product-specific rates, the estimated rates of sudden death found in this review for all drugs used to treat ADHD are below the background rates of sudden death reported in the literature, for both adults and children.

2. Current review

2.1 Background

A prior review (dated April 27, 2004) by Dr. Kate Gelperin of the Office of Drug Safety (ODS) addressed death, sudden death and cardiovascular serious adverse events associated with the use of central nervous system stimulants (amphetamine and dextroamphetamine -including Adderall and Adderall XR®-, methylphenidate, methamphetamine and dexmethylphenidate) in Adverse Event Reporting System (AERS) reports from January 1, 1999 through December 31, 2003. **Seventeen** sudden death cases were identified with amphetamine and dextroamphetamine (A/DA) (one with Dexedrine® and 16 with Adderall/Adderall XR®) and **eight** were identified with methylphenidate (MP) treatment. Of these, twelve and seven were in the pediatric age range (< 19 years) for Adderall/Adderall XR® and MP, respectively. Six out of the

twelve Adderall/Adderall XR® and four out of the seven MP pediatric sudden death cases occurred in patients with structural cardiovascular abnormalities or other potential risk factors for sudden death. No cases of sudden death were found with methamphetamine and dexmethylphenidate.

A separate review (dated August 13, 2004) by Dr. Lisa Jones of the Division of Neuropharmacological Drug Products (DNDP) analyzed and compared the risk of sudden death in patients treated with Adderall and Adderall XR ® based on Dr. Gelperin's analysis and the Sponsor (Shire) analysis. The sudden death reporting rates were 0.5 and 0.6 cases per one million prescriptions dispensed in Dr. Gelperin's and Shire's reports, respectively (Table 18 of Dr. Jones' review). Both analyses appear to indicate that sudden death with Adderall and Adderall XR® is rare in persons using the medications therapeutically.

Based on Drs. Gelperin and Jones' reviews, the following paragraph was added to the WARNINGS section of the Adderall XR® label:

> **"Sudden Death and Pre-existing Structural Cardiac Abnormalities:** Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR generally should not be used in children or adults with structural cardiac abnormalities."

2.2 Current review

The current review addresses reports of sudden death for A/DA and MP before January 1999 and after December 2003. Sudden deaths are also reviewed for two other drugs used in the treatment of ADHD: pemoline (Cylert®) and atomoxetine (Strattera®) from the time of their approval (January, 1975, and November, 2002 respectively) until February 2005. Of note, MP and A/DA derivatives are Category II controlled substances. Atomoxetine, a norepinephrine reuptake inhibitor, has been marketed and labeled as a non-stimulant ADHD drug and is not scheduled as a controlled substance. Pemoline is a Category IV controlled substance. Cylert® was withdrawn from the market in May 2005 and generic pemoline products were withdrawn in October 2005.

2.2.1 Methods

The updated search of the AERS safety database was conducted by Kate Phelan, ODS Safety Evaluator, with a datalock of February, 2005. The criteria used for the search was "Death" as the outcome. I conducted the hands-on review of cardiovascular-related deaths. Reports were excluded for further review if the death was caused by multi-drug overdose, if drug abuse was reported or if death was most likely due to another condition or drug. The definition of sudden death used for this review was the World Health Organization definition (death that is instantaneous or occurs within 24 hours of an acute collapse), the same used in Drs. Gelperin and Jones' reviews. Cases were included in reporting rates if the FDA receipt date was between January 1992 and February 2005.

Cases of sudden death from the first 2 months of 2005 were included in reporting rates based on the assumption that the events occurred several weeks or months prior to the FDA receipt date

AERS reporting rates of sudden death encompassing January 1, 1992 through December 31, 2004 were estimated based on the projected number of prescriptions dispensed by retail pharmacies (IMS Health, National P Audit Plus™). Because of the background rates for sudden death range so substantially by age, the reporting rates were stratified by age to make a more appropriate comparison to background rates. Age breakdowns were not available for the year 1992, so percentages of drug exposure by age group (0-18, >18) were calculated based on data from 1993-2004, and applied to the projected number of prescriptions for the 1992-2004 time period.

2.2.2 Findings

The updated search revealed three additional cases of sudden death with A/DA (one case before 1999 and two after 2003) and ten cases with MP (all before 1999), making a total of **twenty** cases with A/DA and and **eighteen** cases with MP. Additionally, there were **seven** reports of sudden death with atomoxetine and no cases with pemoline. Of note, most of these spontaneous adverse event reports were incomplete and confounded by concomitant medications and comorbidities.

2.1 Update of sudden deaths with amphetamine/dextroamphetamine (Table 1)

There were two pediatric (13 and 14 year-old boys) and one adult (38 year-old female) cases of sudden death with A/DA at therapeutic doses. Of the pediatric cases, one had an autopsy that did not show structural predisposing factors and the other one had no autopsy. The former case involved Dexedrine (amphetamine) alternating with Ritalin® for 7 years. The latter involved Adderall XR® taken for 3 years. The adult case showed extensive mitral valve prolapse and alcoholic liver damage in a woman who had taken Adderall XR® along with Dexedrine® for an unknown period. It is difficult to attribute causality to A/DA treatment in any of these cases.

In summary: These three cases in addition to the previous seventeen cases described by Dr. Gelperin make a total of twenty (fourteen pediatric and six adult) cases of sudden death with A/DA reported to AERS. Of these twenty cases, seventeen were reported with Adderall/ Adderall XR®; one with Dexedrine®; one with Adderall® and Dexedrine®; and one with Dexedrine® and methylphenidate).

Of the fourteen pediatric cases of sudden death, six had structural cardiovascular abnormalities or predisposing factors for sudden death (described in Dr. Gelperin's review).

Table 1. Update of sudden death with amphetamine/dextroamphetamine at therapeutic doses before January 1999 and from January 2004 through February 2005)

	ISR#/(date of FDA receipt)	Age (years)	Sex	Duration of Rx	Suspect Drug	Dose	Past MHx	Cause of death	Comment
1	341069 (5/84)*	13	M	7 years	Dexedrine MP	15 mg am/ 5 mg pm unknown	ADHD	Sudden death	Patient had been taking amphetamine alternating with Ritalin for several years. He suddenly collapsed while going to school with friends. Autopsy: adrenal medulla atrophy. No mention of cardiovascular abnormality.
2	4571913* (1/05)	14	M	3 years	Adderall XR	15 mg	ADHD No CV Hx	V Fib	At school had flickering movements ("not seizure") and collapsed. Monitor showed V. Fibrillation. He was resuscitated and went into coma. Monitor showed PVC's. He died 10 days later. "No arrhythmia". No autopsy.
3	4472525* (10/04)	38	F	Unknown	Adderall XR Dexedrine	20 mg am 10 mg pm	MVP	Sudden death	Woke up short of breath and died. Autopsy: extensive Mitral Valve Prolapse and alcoholic liver damage

* Reported by heath care provider (physician, nurse or pharmacist).
MP- methylphenidate

The following case was not included in the above table or in the reporting rate calculations. A 47 year old female was taking Dexedrine® 40 mg daily for 14 months for ADHD along with verapamil and herbal medicines. Venlafaxine 37.5 mg daily was added to treat depression. Two days into the venlafaxine treatment she developed ventricular fibrillation and died. Toxicology testing found toxic levels of venlafaxine. Although this is not a clear case of multi-drug overdose, death might be explained by venlafaxine toxicity. This case was not included in the current analyses.

2.2 Sudden death with Methylphenidate

There were ten reports of sudden death with methylphenidate before January 1999 and no new cases from January 2004 through February 2005. The cases include nine males and one female, ages 7 to 77 years. Of the ten cases, seven were in the pediatric age range (<19 years) with ages between 7 to 15 years and three were in adults (ages 39, 42 and 77 years old). Of the pediatric cases, one mentioned a possibility of MP overdose (ISR #556955). One of the cases was in a patient taking concomitant atomoxetine (ISR# 4488221), one was taking concomitant Dexedrine® (ISR# 3410069, included in Table 1) and another was in a patient using a clonidine patch (ISR # 1656104). Of note, seven of the ten cases lacked information on duration of MP treatment, and the other three occurred seven to ten months into treatment.

Five of the seven pediatric cases had an autopsy. Of these, two showed structural cardiac abnormalities that are likely to have preceded MP treatment (ISR#1570235 and 1656104), one was "inconclusive", one showed adrenal atrophy but did not mention CV abnormalities and one was reported to have been done but did not mention CV abnormalities. Of the three adult cases, one had a history of a cardiac murmur but none of the patients had an autopsy.

Therefore, altogether, there were fourteen pediatric and four adult sudden death cases reported with methylphenidate in AERS for the reporting period of January 1992 to February, 2005. Of the pediatric cases, seven were described in Dr. Gelperin's review and seven in this updated review). Of those fourteen pediatric cases, six had a documented structural cardiovascular abnormality that may have increased the risk of death (four in Dr. Gelperin's review and two in this review).

Table 2. Update of sudden death with methylphenidate (MP) at therapeutic doses before January 1999 and from January 2004 and through February 2005.

ISR/FDA date of receipt		Age (years)	Sex	Duration of Rx	Suspect Drug	Dose	Past MHx	Cause of death	Comment
1	556955* (9/86)	12	M	10 months	MP (Ritalin SR)	20 mg	-	Sudden death	Possible accidental overdose
2	769097* (1991)	8	M	Unknown	MP	30 mg	ADHD	Sudden death	Autopsy done: results inconclusive
3	1570235* (12/94)	13	M	Unknown	MP	Unknown	-	Cardiac arrhyth	Autopsy: multiple abnormalities, heart hypertrophy, tricuspid valve anomalies and other anatomic variations. MP blood levels were normal
4	1799045* (6/96)	13	M	9 months	MP	20 mg tid	ADHD	Cardiac arrest	As per reporter, the coroner stated that cause of death was cardiac arrest. Reporter did not mention CV abnormalities.
5	1656104 (2/95)	7	M	Unknown	MP Clonidine	Unknown Unknown	ADHD, premature birth (34w) Heart murmur	Sudden death.	Felt ill at school. Lied down for a while and felt better; found unresponsive 15 min later. Paramedics found Ventricular Fibrillation. Autopsy: dilated heart, R>L without hypertrophy. Congestive heart failure. Fibrosis of mitral valve papillary muscles c/w perinatal hypoxia. Normal Clonidine levels. MP level "elevated but below toxic". Mode of death: natural.

Table 2. Cont. Update of sudden death with methylphenidate (MP) at therapeutic doses before January 1999 and from January 2004 and through February 2005.

	ISR/date of receipt	Age (years)	Sex	Duration of Rx	Suspect Drug	Dose	Past MHx	Cause of death	Comment
6	2003854 (7/97)	15	M	Unknown	MP	30 mg	"Complex medical history"	Arrhythmia	Also on prednisone and carbamazepine. Admitted for phlebitis, suffered a "coronary attack". No autopsy.
7	483489* (9/87)	39	M	Unknown	MP	40 mg	Narcolepsy Non specific T and ST changes	Sudden death	Body builder. History of apical & L parasternal systolic murmurs. Found dead with Ritalin alongside the body. Toxicology report: negative.
8	705007* (1990)	77	F	Unknown	MP	20 mg	Depression	Unknown	Patient had two separate episodes of 10- second period asystole with syncope within the first week of treatment. On follow up, she had died. No autopsy.
9	4488221* (10/04)	42	M	2 months 7 months	Atomoxetine MP (Concerta)	80 mg qd 36 mg day	ADHD CAD/HTN Family Hx of CAD	Coronary artery disease	Day of death c/o chest pain, drove himself to ER, collapsed and died. Autopsy: blockage of two coronary arteries. Old myocardial infarction. (See narrative).
10	341069 (1984)	13	M	Unknown	MP/ Dexedrine	Unknown	ADHD	Sudden death	See Table 1. No CV abnormalities mentioned on autopsy.

* Reported by health care provider (physician, nurse, pharmacist). MP= methylphenidate.

The following narratives and comments relate to two patients included in Table 2.

ISR # 705007 was a 77 year old woman. She had documented periods of asystole and syncope within a week of starting methylphenidate. On follow up, she had died.

> *Comment: This patient is somewhat atypical as compared to the other cases of sudden death with methylphenidate (a 77 year old female vs. boys or men in their 40's). She may have had some underlying arrhythmia such as sick sinus syndrome or some degree of heart block, although there is no mention of such a history in the report. The role that methylphenidate may have played in this death is unclear.*

ISR# 4488221 (submitted 10/04) was a 42 year old male with history of coronary artery disease, hypertension and family history of coronary artery disease. He started atomoxetine on 8/5/04. He had been on Concerta ® for seven months before his death. He started with 18 mg/day on 3/31/04, with increases up to 72 mg/day by 6/2/04. He experienced insomnia, dyspepsia, irritability and edginess, and the dose was decreased to 36 mg/day. Then two months prior to his death, atomoxetine was added (on 8/5/04). He received 25 mg/day for 7 days, 50 mg/day for 7 days then 75 mg/day for seven days. On 9/22/04 the dose was increased to 80 mg. At that doctor's visit he had no complaints of palpitations, chest pain insomnia or fatigue. On 10/3/04 he awoke in the morning with complaints of "funniness" in his chest and chest pain. He drove himself to the hospital and collapsed at arrival to the ER. After an unspecified length of time he arrested and died. According to the autopsy report, the patient died of arteriosclerotic CV disease and natural causes. He had significant blockage of two major arteries and evidence of an old myocardial infarction (MI).

> *Comment: Although this patient had prior CV risk factors and an autopsy-confirmed MI, the role of methylphenidate and atomoxetine in this death is unclear. This case is also included in Table 3 for atomoxetine.*

Two cases of drowning <u>not included among the ten described above</u>, are worth noting:

ISR 1636930, reported 7/95, 3 year-old female with history of fetal alcohol syndrome and mild mental retardation, receiving Ritalin 2.5 mg TID for ADHD for unknown period drowned in the company of others. Reporting terms are: death, convulsions, ataxia. The physician did not feel Ritalin was implicated. There was no autopsy.

ISR 483811-1, received 2/05, from Greece. A 15 year-old male received Ritalin 10 mg/ day for speech disorder. On February 2005 while swimming in the community pool, the patient drowned after half an hour of swimming and during an attempted dive. The mother stated that he took his dose (one tablet) of Ritalin that morning. The reported causality is stated as unknown. No autopsy.

> *Comment: In these two cases the patient could potentially have had an arrhythmia preceding the drowning although there is no mention of such a*

possibility in the reports. In the first case, the patient could have had a seizure preceding the drowning. There were no autopsy reports for these cases.

In summary: There were ten additional reports of sudden death with methylphenidate in this review, including three adult and seven pediatric cases. That makes a total of fourteen pediatric and four adult cases. None of them appears solely or directly related to methylphenidate. Six of the 14 pediatric sudden deaths occurred in children with structural cardiovascular abnormalities that likely preceded the use of methylphenidate (two in this review and four in Dr. Gelperin's review).

2.3 Sudden deaths with atomoxetine (Table 3)

A total of seven cases of sudden death were reported in three children and four adults taking atomoxetine at therapeutic doses, from November 2002 to February, 2005.

Of the three pediatric sudden deaths (in patients 2 and ½ to 12 years old), one case occurred three days after atomoxetine *discontinuation* and had an autopsy that showed lymphocytic myocarditis, consistent with a viral infection (ISR# 436895). This case is very unlikely to be related to atomoxetine therapy. The other two pediatric cases were confounded by toxic levels of olanzapine (ISR# 4161070) or a possible seizure preceding the death (ISR#4572167). The cases occurred six weeks to four months into atomoxetine therapy. None of these patients had a prior cardiovascular history or cardiovascular structural abnormalities.

The adult cases also had confounders. They were either in patients taking unknown doses of multiple medications or who had one or more pre-existing risk factors for cardiovascular death. One of these cases (ISR# 4572119) may have been related to intentional or unintentional overdoses. Three other cases had predisposing factors for sudden death such as a family history of myocardial infarction at an early age (ISR# 4378206), mitral valve prolapse (ISR# 4434006) and autopsy proven blockage of the coronary arteries in a patient who had been on methylphenidate for seven months prior to starting atomoxetine (ISR# 4488221 already described in Table 2). For those adult cases with known duration of exposure, death occurred two to seven months into atomoxetine treatment. Duration of treatment was unknown for two cases.

Table 3. Sudden death with atomoxetine (Strattera®) at therapeutic doses (since approval –November 2002, to April, 2005)

	ISR# (date of receipt)	Age (years)	Sex	Duration of Rx	Suspect Drug	Dose	Past MHx	Cause of death	Comment
1	4161070* (8/03)	2 1/2	F	3 months	Atomoxetine Olanzapine	20 mg qd, then 30 qd 2.5 mg bid	ADHD/bipolar Apneic episodes as a baby. Hx of questionable absence seizures.	Sudden death. Olanza-pine toxicity	Day of death felt sleepy. Did not take meds. Died in her sleep. Autopsy: no morphologic abnormalities. Toxicology: therapeutic level of atomoxetine but toxic levels of olanzapine.
2	436895* (5/04)	12	M	4 months	Atomoxetine	40 mg bid	ADHD	Sudden death.	Prior Rx with MP & amphetamines. Stopped atomoxetine because of nausea. Autopsy consistent with viral infection. (See narrative)
3	4572167* (2/05)	8	M	6 weeks	Atomoxetine	10 mg qd titrated up to 40 mg qd over 6 weeks	ADHD	Sudden death	Autopsy: No structural CV abnormalities. Official cause of death was Sudden Unexplained Death in Childhood accompanied by Peribronchiolar chronic inflammation. Levels of atomoxetine were therapeutic. (See narrative)
4	4434006* (8/04) 4456279 (9/04)	45	F	Unknown	Citalopram Atomoxetine Olanzapine Pramipexole	40 mg qd 80 mg qd	ADHD/ major depression	Sudden death	No significant personal history of CV disease. "Normal CV workup" sometime prior to starting treatment. Sudden death at work. EMS monitor showed VFib. Autopsy showed mitral valve prolapse.

Table 3. Sudden death with atomoxetine (Strattera®) continuation									
	ISR	Age	Sex	Duration	Suspect drug	Dose	Past Med Hx	Cause of death	Comments
5	4488221* (10/04)	42	M	2 months 7 months	Atomoxetine Concerta®	80 mg qd 36 mg day	ADHD CAD & HTN Family Hx of CAD	Coronary artery disease	MP started 3/04; atomoxetine started 8/04. Day of death c/o chest pain, drove himself to ER, collapsed and died. Autopsy: blockage of two coronary arteries. Old myocardial infarction. (See narrative).
6	4572119* (1/05)	41	F	Unknown 7 months Unknown Unknown Unknown	Olanzapine Atomoxetine Sertraline Fluoxetine Celecoxib	35 mg qd 40 mg qd 300 mg qd 20 mg qd	Schizoaffective and bipolar disorder	Sudden death	She was on olanzapine 35 mg qd. Started atomoxetine 25 mg in 11/03, increased to 40 mg in 12/03. Found dead at home on 7/6/04 with "high blood levels" but appropriate number of pills left. Medical examiner felt it could have been suicide but the reporter (psychiatrist) disagreed.
7	4378206* (6/04)	41	M	4 months	Atomoxetine	40 mg bid	ADHD, RA, thyroid disorder.	Sudden death	Died suddenly while at work. Family history of father died of MI at early age. Also on levothyrox MTX, Tramadol, Sertraline. No autopsy.

* Reported by a health care provider (physician, nurse or pharmacist)

The following are narratives from one of the patients described in Table 3.

ISR# 4572167. This 8 year old boy had no personal or family history of CV disease. He was taking no concomitant meds or herbal products. He was taking atomoxetine, 40 mg daily and doing clinically well. The day of his death he was in his usual state of health. He went to have dinner with his grandparents, who had lobster, but he did not have any seafood. On the way back home he napped in the car. He went to bed at 10 PM. At approximately 3 AM in the morning his grandfather heard him coughing and a knee banging the wall in his grandson's room. The boy was alive but not breathing well. He was gasping for air; he aspirated and was incontinent of urine and bowel. The grandfather started CPR although he was not CPR trained. The boy was pronounced dead upon arrival of paramedics at 5:35 am, when he was pulseless, apneic and in asystole. Resuscitation attempts in the ER were unsuccessful. The ER diagnosis was cardiorespiratory arrest. The autopsy and toxicologic examination failed to reveal a cause of death. Microscopic examination of lungs revealed reactive bronchi with increased goblet cells, several vessels were found with fibrin, very prominent bronchial associated lymphoid tissue, patchy chronic interstitial inflammation around bronchioles and vessels in the parenchyma. Child protection services had investigated allegations of physical injuries to the child more than 6 months before the death but there were no current evidence of physical abuse. The official cause of death was "sudden unexplained death in childhood accompanied by pulmonary peribronchiolar chronic inflammation".

> *Comment: it appears that this boy may have been having a seizure (grasping air, knee banging, urine and bowel incontinence) when his grandfather found him, although he did not have a history of having seizures***.**

Two additional cases of sudden death were reported during this reporting period but not included into Table 3 or into the reporting rate analyses.

The following death cases were <u>not included</u> in the analysis:

ISR # 4216036* received by FDA in October, 2003. This was a 35 year old female, who died after taking an unknown dose of atomoxetine for an unknown indication for one week. She was also taking venlafaxine and "other" meds for an unknown period before her death. The reporter, a health care practitioner, stated that the patient was a pharmacist and probably self medicated. This report will be excluded because it is unclear whether this was a case of sudden death (the term used in the report is Death, NOS).

ISR# 4359400 received by FDA in April, 2004. This was a 45 year-old male who had taken atomoxetine for 3 months who died in his sleep. This patient had multiple CV risk factors such as hypertension, congestive heart failure, diabetes, renal disease and alcoholism. At autopsy he was found to have liver cirrhosis, cardiomegaly and amitriptyline was present in blood, although it was not clear who he got this drug from. This case is not included in table 3, because it is considered a case of potential drug abuse.

In summary: There were seven (three pediatric and four adult) reports of sudden death with atomoxetine from November 2002 to February 2005. None of the cases appears solely or directly attributable to atomoxetine at therapeutic doses. The cases were highly confounded. None of the patients had structural cardiovascular abnormalities. However, the extent of the role of atomoxetine in these deaths is difficult to establish.

3. Estimation of reporting rates of sudden death in AERS with drugs used to treat ADHD.

Data on the projected number of total prescriptions dispensed by retail pharmacies (IMS Health, National P Audit Plus™ from January 1992 to December 2004) and the estimated use of these drugs in the pediatric and adult populations (IMS Health, National Disease and Therapeutic Index™, from January 1993 to December 2004 were provided by the Office of Drug Safety (PID# D050204 in April 2005 and PID# D050362 in June 2005, respectively).

Of note, IMS data allows estimation of prescriptions dispensed, not real exposure. As a crude estimate of exposure, in order to transform prescriptions dispensed into patient-years (PYRs), one may assume that each prescription is used for 30 days and then divide the total number of days by 365. Another approach that provides a similar result is to divide the number of prescriptions by 12. The latter approach was used in this review. Event rate estimation using a person-time denominator assumed that the hazard rate of the event is constant over time.

Because the background rates for sudden death range so substantially by age (see Section 4), the reporting rates were stratified by age to make a more appropriate comparison to background rates.

To estimate the number of patients exposed in the adult and pediatric populations, the percentage of Projected Number of total Drug Appearances for the age groups >18 years and 0-18 years (NDTI database) was applied to the patient years of exposure based on the projected number of prescriptions (NPA database). Of note, the projected number of total drug appearances correlates with but does not match the estimated number of prescriptions. Age breakdowns were not available for the year 1992, so percentages of drug exposure by age group (0-18, >18) were calculated based on data from 1993-2004, and applied to the projected number of prescriptions for the 1992-2004 time period.

Table 4 shows AERS reporting rates of sudden death with drugs used for the treatment of ADHD in the pediatric and adult population.

It should be noted that because NPA usage data was only available back to 1992, five AERS reports of sudden death with MP and one case of sudden death with dextroamphetamine occurring prior to 1992 were excluded from the reporting rate calculations. Cases from the first 2 months of 2005 were included in reporting rates based on the assumption that the events occurred several weeks or months prior to the FDA receipt date.

Of note, the reporting rate of sudden death with atomoxetine in the adult population appears to be greater than with Adderall/Adderall XR® and methylphenidate; however, in the pediatric population it seems to be about the same or slightly greater than

Adderall/Adderall XR®. The apparently high reporting rate with atomoxetine in adults may be related to its more recent introduction into the market.

Table 4. Estimated AERS reporting rates of sudden death with amphetamine salts, dextroamphetamine, methylphenidate and atomoxetine in AERS, based on estimated exposure in the pediatric and adult population, from January 1, 1992 to December 31, 2004.

	All populations (pediatric, adult & age undetermined)				Pediatric 0-18 years			Adult >18 years		
	Prescriptions[1]	PYRs[2]	n[3]	Rate per 100,000 PYRs	Exposure PYRs[4]	n	Rate per 100,000 PYRs	Exposure PYRs[4]	n	Rate per 100,000 PYRs
Methylphenidate[4]	110,734,000	9,227,833	13	0.1	7,127,432	11	0.2	1,764,591	2	0.1
Amphetamine & Dextroamphetamine[5]	70,699,000	5,891,583	19[6]	0.3	3,817,929	13	0.3	1,857,056	6[6]	0.3
Amphetamine salts	51,565,000	4,297,083	18	0.4	3,371,702	13	0.4	785,522	5	0.6
Dextroamphetamine	19,134,000	1,594,500	2	0.1	869,833	0	-	645,639	2	0.3
Atomoxetine	9,419,000	784,916	7	0.9	601,246	3	0.5	142,855	4	2.8

[1] IMS Health, National Prescription Audit Plus™ (from January 1992 through December 2004). Provided by ODS, PID# D050204, April 2005)
[2] PYRs estimated by dividing prescriptions dispensed by 12.
[3] n= sudden death events identified in FDA AERS from January 1992 through February 2005.
[4] Total PYRs times the percentage of drug appearances in the age subgroup population (IMS Health, National Disease and Therapeutic Index™ , from January 1993 to December 2004. Provided by ODS, PID# D050362/ADHD, June 2005).
[5] Methylphenidate branded and generic, all formulations, including Concerta ®, Ritalin and Ritalin XR ® Methylin and Methylin ER ®, Metadate ER ® and Metadate CD®.
[6] Amphetamine and dextroamphetamine, branded and generic, all formulations, including Adderall® and Adderall XR ®, Dextrostat® and Dexedrine®. One adult was taking both, amphetamine and dextroamphetamine.

Proprietary IMS Health data not for release outside of FDA without clearance.

4. Background rates of sudden death in the literature

The background rate of sudden death ***in adults*** has been estimated to be approximately **1 per 1,000 PYRs)**, depending on age (0.09 per 1,000 person-years for age 18 to 50 years to 8.5 per 1,000 PYRs for ages >80 years) and gender (age unadjusted rate of 1.1 per 1,000 PYRs in man and 0.75 per 1000 PYRs in women)[1] . Other authors have estimated the overall rate of sudden death to be **53 per 100,000 per year** [2] and **37 per 100,000 PYRs** [3]. When the rate of 37 per 100,000 PYRs was split by gender, the rates were 51 and 23 per 100,000 PYR in men and in women, respectively.

Estimated rates of sudden death for ***children and adolescents*** have ranged between **1.3 and 8.5 per 100,000 person-years[4, 5].** As noted in Liberthson's review paper on sudden death in the children and young adults, the 8.5 per 100,000 person-years estimate comes from a study in which deaths were counted for the age group 1-30. If one relies only on studies that looked at the age group 1-20, the upper end of the range is **4.6 per 100,000 person-years.**

Despite small differences between product-specific rates, the estimated rates of sudden death found in this review for all drugs used to treat ADHD are below the background rates of sudden death reported in the literature, for both adults and children.

[1] M Straus, G.S. Bleumink, J.P. Dieleman, J. Lei van der, B.H.Ch. Stricker, M.C.J.M. Sturkenboom A, The incidence of sudden cardiac death in the general population. Journal of Clinical Epidemiology, 2004.

[2] Chugh SS, Jui J, Gunson K, Stecker EC, John BT, Thompson B, Ilias N, Vickers C, Dogra V, Daya M, Kron J, Zheng ZJ, Mensah G, McAnulty J Current burden of sudden cardiac death: multiple source surveillance versus retrospective death certificate-based review in a large U.S. community. J Am Coll Cardiol. September 15, 2004 (pg 68-75).

[3] Tokashiki T, Muratani A, Kimura Y, Muratani H, Fukiyama K. Sudden death in the general population in Okinawa: incidence and causes of death. Jpn Circ J. Jan 1999.

[4] Liberthson, RR Sudden death from cardiac causes in children and young adults. N Engl J Med, 1996.

[5] Driscoll DJ, Edwards, WD. Sudden unexpected death in children and adolescents. JACC 1985

4. Conclusions and recommendations

4.1 The rate of sudden death with amphetamine and dextroamphetamine salts, methylphenidate and atomoxetine in this review were below background rates available in the literature (1 to 4.6 per 100,000 PYRs in children & adolescents and approximately 100 per 100,000 PYRs in adult, depending on age and gender). However, no definitive conclusions can be drawn from the analyses of AERS cases due to the following reasons:

a. Limitations inherent to an spontaneous adverse event reporting system (under reporting, incomplete reporting, greater reporting with recently approved drugs versus older drugs, etc),
b. Uncertainties of drug exposure estimates based on number of prescriptions dispensed rather than true exposure,
c. Assumption that the risk of sudden death in association with drug use is constant over time
d. The relatively wide variation of the background rate of sudden death available in the literature

4.2 The current Adderall XR® label carries the following WARNING: "**Sudden Death and Pre-existing Structural Cardiac Abnormalities:** Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR generally should not be used in children or adults with structural cardiac abnormalities." At this time no additional changes are recommended to the Adderall® and Adderall XR® labels regarding sudden death.

Review of methylphenidate cases suggest that six of the fourteen pediatric cases reported to AERS between 1986 and 2004 had some morphologic cardiovascular abnormality that predisposed to the sudden death, suggesting that labeling changes to the Adderall XR® label may apply to methylphenidate.

Given the limitations inherent to the spontaneous reporting system and the smaller exposure, the lack of reported events does not rule out a potential increase in the risk of sudden death with other CNS stimulants. If labeling changes are made to MP, language similar to the Adderall XR® label should be included in the entire class of CNS stimulants used for the treatment of ADHD.

4.3 The overall reporting rate of sudden death with atomoxetine in AERS appeared to be three to nine-fold greater as compared to amphetamine/dextroamphetamine salts and methylphenidate, respectively. This difference is driven by the greater rates reported with atomoxetine in the adult population. However, the reporting rate with atomoxetine in the pediatric population (0.5 per 100,000) was similar to that of A/DA (0.4 per 100,000). None of the atomoxetine cases had congenital cardiovascular abnormalities. All cases had confounders and reporting rates may be greater than with the other ADHD drugs because of its recent introduction into the market (and the associated increased reporting to AERS that occurs with new drugs). No labeling changes are recommended at this time for atomoxetine. Continued surveillance is warranted.

4.4 Potential approaches to adequately assessing the risk of sudden death may include the following: a) conducting a large, simple trial or b) a large epidemiologic observational study. Such approaches are currently being discussed by ODS and DPP.

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/s/

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Requests to add the labeling language regarding sudden death and pre-existing structural cardiac abnormalities currently in Adderall and Adderall XR labeling will be sent to the other CNS stimulants approved for ADHD.