

MEMORANDUM

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

DATE: June 14, 2005

FROM: Kathleen M. Phelan, R.Ph., Safety Evaluator
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THROUGH: Mark Avigan, M.D., C.M., Director
Div. of Drug Risk Evaluation, HFD-430

TO: Solomon Iyasu, MD, MPH., Team Leader
Div. of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: Adverse events with methylphenidate products other than Concerta in pediatric patients during the first year after granting of pediatric exclusivity for Concerta. (December 4, 2003 – January 4, 2005)

PID# D050249

DRUGS:

Trade Name	NDA #	First Approval	Sponsor
Ritalin	N 10-187	Dec 5, 1955	Novartis
Ritalin SR	N 18-029	Mar 30, 1982	Novartis
Concerta	N 21-121	Aug 1, 2000	Alza
Metadate CD	N 21-259	Apr 3, 2001	Cell Tech Pharms
Ritalin LA	N 21-284	Jun 5, 2002	Novartis
Methylin oral soln	N 21-419	Dec 19, 2002	Mallinckrodt Baker
Methylin Chewable	N 21-475	Apr 15, 2003	Mallinckrodt

Executive Summary

The 1-year post-pediatric exclusivity postmarketing adverse event review of Concerta (OROS methylphenidate tablets, NDA 21-121)¹ found that psychiatric adverse events may not be adequately labeled. The Office of Pediatric Therapeutics requested a review of adverse events reported with methylphenidate dosage forms other than Concerta during the same 1-year period to determine whether AERS adverse event profiles differ qualitatively between dosage forms. Ninety-seven unduplicated cases for methylphenidate products other than Concerta were found. One case was a dispensing error with no ingestion and is not discussed in this review.

¹ March 18, 2005, Kathleen M. Phelan, R. Ph., PID# D040058

The remaining 96 cases comprise 56 immediate-release methylphenidate cases, 4 of which are strongly confounded, and 40 extended-release methylphenidate cases, 3 of which are strongly confounded. There was one death with extended-release methylphenidate. Autopsy found brain edema but did not specify a cause of death.

As with Concerta, neuropsychiatric adverse events are the most reported adverse events with other methylphenidate products. There are fewer psychiatric adverse events reported with other methylphenidate (MPH) products than with Concerta and many are described in less detail, presenting a less severe impression than the psychiatric adverse events reported with Concerta. However, from these data it is not possible to determine whether the effects of Concerta truly differ from those of other methylphenidate products because various factors affecting spontaneous adverse event reporting could account for differences. The area of concern raised by the Concerta review, neuropsychiatric effects, is reinforced by this review. Cardiovascular and cerebrovascular effects are previously identified concerns.

AERS receives reports of adverse events submitted spontaneously by health care professionals and consumers to the product manufacturers or directly to the FDA. The main utility of spontaneous reporting systems, such as AERS, is to identify potential drug safety issues. There are inherent limitations to voluntary or spontaneous reporting systems, such as underreporting and duplicate reporting; and, for any given report, there is no certainty that the reported suspect products caused the reported adverse events. Thus, case counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

Because of the common and extended use of these drugs, additional study of their effects in children is warranted. AERS reviews of these issues may help to illuminate and prioritize directions for study.

Reason for Review

The 1-year post-pediatric exclusivity postmarketing adverse event review of Concerta (OROS methylphenidate tablets, NDA 21-121) found adverse events that may not be adequately labeled. Specifically, serious psychiatric adverse events were reported in pediatric patients with no previously diagnosed psychiatric illness other than that being treated with methylphenidate. Concerta labeling reports serious psychiatric adverse events as exacerbations of pre-existing psychiatric illness rather than newly arising events. The Office of Pediatric Therapeutics requested a similar review of methylphenidate dosage forms other than Concerta to determine whether adverse event profiles differ qualitatively between dosage forms.

AERS Search criteria

AERS Search performed on April 4, 2005

- Drugs: all methylphenidate dosage forms (see chart above)
- Age range: 0 to 17 years
- FDA received dates: December 5, 2003 (Concerta Pediatric Exclusivity granted) through January 5, 2005 (One year from Pediatric Exclusivity date plus one month to allow time for reporting)

Case Selection

The above search found 261 reports. Concerta cases, duplicates, and reports for patients older than 16 years were eliminated and the remaining 97 cases were reviewed. One case reported a dispensing error without ingestion of drug and was removed. The remaining 96 cases were divided into immediate-release methylphenidate and extended-release methylphenidate using the following factors:

Immediate-release if

- dosing was more frequent than once per day,
- OR dose was a multiple of 5 but not 10,
- OR methylphenidate was initiated very recently
 - AND no other factors implied extended-release,
- OR dose included ½ of a tablet,
- OR the drug was called “Ritalin” and there was no information on dose or dosing frequency;

Extended-release if

- drug name included suffix indicating extended-release formulation,
- OR dosing was once per day,
- OR dosage is described as “daily”
 - AND dose was a multiple of 10
 - AND no other factors implied immediate-release.

Table 1: Adverse event categories

Ninety-six unduplicated cases that report adverse events with methylphenidate products other than Concerta were found. These 96 cases comprise 56 immediate-release methylphenidate cases and 40 extended-release methylphenidate cases. Summaries of the immediate-release and extended-release methylphenidate cases are in Attachments 1 and 2, respectively. Case distribution is as follows:

AE category	Concerta	Immediate-release methylphenidate	Extended-release methylphenidate
Total	135	56	40
Strongly confounded	19	4	3
Overdose/abuse	3	2	0
Lack of effect	3	10	3
Psychiatric	36	9	7
Neurological	16	7	11
Special Senses	7	0	2
Cardiovascular	20	2	2
Cerebrovascular	2	2	2
Hematological	10	4	0
Gastrointestinal	11	5	0
Skin	0	4	0
Thyroid	1	3	1
Respiratory	0	2	3
Miscellaneous	7	2	6

One report of *in utero* exposure to extended-release methylphenidate was received. The neonate experienced apnea after *in utero* exposure to methylphenidate, paroxetine, flunitrazepam, and alprazolam.

Two reports of overdose with immediate-release methylphenidate were received. In one the ingested overdose was 25 “pills” of unknown strength, in the other, the ingested overdose was 400 mg.

The above table provides a qualitative comparison between Concerta, immediate-release, and extended-release methylphenidate products. It should not be considered a quantitative assessment because of the limitations of a spontaneous reporting system. Many factors, including the length of time a drug has been available and recent publicity, can affect reporting. Also, this review and the Concerta review provide 1-year snapshots of adverse event reporting for these drugs; different time periods might yield different results.

Table 2: Case characteristics

This table displays the characteristics of cases reporting adverse events with methylphenidate (MPH) including cases reporting lack of effect but not including cases in which no adverse event was reported.

Characteristic		Concerta	Immediate-release MPH	Extended-release MPH
Total		135	56	40
Origin	Foreign	77	28	21
	U.S.	58	28	19
Gender	Female	26	12	5
	Male	108	44	33
	Unknown	1	0	2
Age	0-1 year	0	0	1
	2 – 5 years	1	7	2
	6 – 11 years	82	27	23
	12 – 16 years	52	22	14
Outcome selected on MedWatch form (not mutually exclusive)	Death	1	0	1
	Hospitalization	39	9	6
	Life-threatening	5	2	0
	Disability	5	0	4
	Required intervention	1	4	5
	Medically important	69	8	6
	Other	26	32	19
None selected	7	6	2	
Indication	ADHD/ADD/hyperactivity	108	48	30
	Disturbance in attention	2	0	0
	Learning disability	1	0	0
	Oppositional defiant	1	0	0
	Developmental disorder	1	0	0
	Tourette's	1	0	0
	Unknown	21	8	8
Dosage*	Range (mg/day)	18 – 108	5 – 120	7.5 – 60
	Median (mg/day)	36	20	20

*One overdose of immediate-release MPH was 400 mg. In the *in-utero* exposure of extended-release MPH, the mother was taking 100 mg/day.

Summary of case reporting Sudden Death

ISR# 4284879-2, MFR# PHBS2003ZA09019, Foreign, 2003

A 12-year-old boy started Ritalin SR on May 24, 2002 to treat ADHD. He was also using albuterol pump once or twice every 3 months for asthma. In December 2002, wheezing was noted and budesonide was initiated. On July 10, 2003, Ritalin SR was changed to Ritalin LA and intranasal fluticasone was added for allergic rhinitis. On ----- he collapsed on the school playground. He murmured a few words and had no sign of convulsion. Autopsy revealed brain edema and slight inflammation in the lungs. The death was not explained.

Discussion

As with Concerta, neuropsychiatric adverse events are the most reported adverse event category with other methylphenidate products. The psychiatric adverse events reported with methylphenidate (MPH) products other than Concerta, including both immediate- and extended-release products, are described in less detail and present a less severe impression than the psychiatric adverse events reported with Concerta. It must be remembered that these cases represent a 1-year period in the marketing of these products and not a full overview. Also, Concerta is a unique dosage form with no generic equivalents available. Clinicians may have less experience with Concerta than with Ritalin and other methylphenidate products, which have been available longer and have generic equivalents. This may result in differential reporting of adverse events. There is no pharmacological reason to suspect that the effects of Concerta truly differ from those of other methylphenidate products. None of the psychiatric adverse event cases in this review report or deny concomitant psychiatric illness.

Four cases of skin adverse events, possibly immune-system mediated, were reported in this 1-year period with immediate-release MPH. These adverse events are anaphylactoid purpura, rash and purpura, Schamberg's purpura, and lupus erythematosus-like lesions. There were no similar adverse events reported with Concerta or other extended-release MPH products during the same year; however, as with psychiatric adverse events, we cannot conclude that this represents a true difference between MPH products. Methylin and Ritalin labeling include in the *Adverse Reactions* section "hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura)." Therefore, these skin adverse events may be adequately labeled.

Conclusion

This review encompasses 1 year's experience with methylphenidate products in children. The area of concern raised by the Concerta review, neuropsychiatric effects, is reinforced by this review. Cardiovascular and cerebrovascular effects are previously identified concerns. Small differences in the numbers of reports and the details they provide do not substantiate true differences between methylphenidate products. Observed differences in adverse event profiles may be artifacts of the 1-year limited scope of these reviews as well as differential adverse event reporting.

Because of the common and extended use of these drugs, additional study of their effects in children is warranted. AERS reviews of these issues may help to illuminate and prioritize directions for study. AERS data are valuable in identifying possible drug risks, but will not answer with certainty whether a drug's association with an adverse event is causal.

Signed June 14, 2005
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Safety Evaluator

Concur:

Signed June 14, 2005
Cindy Kortepeter, Pharm. D.
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Limitations of the Adverse Event Reporting System (AERS)

AERS collects reports of adverse events from health care professionals and consumers submitted to the product manufacturers or directly to the FDA. The main utility of a spontaneous reporting system, such as AERS, is to identify potential drug safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

Attachments

1. Immediate-release methylphenidate (N=56)
2. Extended-release methylphenidate other than Concerta (N=40)
3. Case in which no adverse event was reported (N=1)

Attachment 1: Immediate-release methylphenidate (N=56)

Cases that are strongly confounded (N=4)

ISR#	Age (yrs)	Gender	Summary
4258306-5	15	F	Arthralgia after 3 weeks methylphenidate. Tested positive for acute parvovirus B19 infection. Arthralgia resolved, methylphenidate resumed without recurrence.
4316812-9	8	M	Drowsiness after taking methadone 5 mg dispensed in error on prescription for Methylin 5 mg.
4293858-0	14	M	Leg pain and weakness for 1 day while in bed with a viral illness during methylphenidate use. Methylphenidate continued, event resolved.
4477582-7	15	M	Amnestic episode after 3 weeks methylphenidate. Attributed to concussion following motor vehicle accident

Cases that do not report strongly confounding information (N=52)

ISR#	Age (yrs)	Gender	Summary
<i>Overdose/Abuse (N=2)</i>			
4366764-0	8	M	Ingested 25 methylphenidate “pills” of unknown strength for unknown reason. Effects and outcome unknown.
4296344-7	11	M	Ingested 20 tablets of 20 mg methylphenidate for unknown reason. Experienced hyperexcitability, decreased peripheral circulation, tachycardia. Hospitalized, treated with lavage, charcoal, laxative. Recovered.
<i>Lack of Effect (N=10)</i>			
4523236-8	7	M	Very poor behavior on generic methylphenidate.
4430593-X	7	F	Higher-than-recommended dose of generic methylphenidate needed to achieve same effect as lower dose Ritalin.
4512875-6	4	M	Generic methylphenidate was ineffective.
4356663-2	5	M	Generic methylphenidate was ineffective.
4358696-9	6	M	Generic methylphenidate was ineffective.

ISR#	Age (yrs)	Gender	Summary
4414277-X	7	M	Methylphenidate from one manufacturer was ineffective; another manufacturer's product was effective.
4504361-4	9	M	Generic methylphenidate was less effective than Ritalin.
4318475-5	13	M	Generic methylphenidate was ineffective.
4462023-6	13	M	Generic methylphenidate was less effective than Ritalin.
4335301-9	14	M	Duration of action of immediate release methylphenidate insufficient.
<i>Psychiatric Adverse Events (N=9)</i>			
4498015-0	4	F	Increased "whiney" behavior, no improvement in ADHD behavior during about 6 months methylphenidate treatment. Outcome unknown.
4601314-2	6	M	Violent behavior, "psychotic" per mother, after 3 days methylphenidate. Methylphenidate discontinued and patient had severe headache all day. Events resolved.
4276318-2	6	M	Increased school problems, refusal to do any work after switch to generic methylphenidate. Outcome unknown.
4393027-X	9	M	Acute psychosis (agitation, anxiety, social withdrawal, sweating, hyperventilation, confusion, quivering) same day methylphenidate was added to ongoing fluticasone propionate/salmeterol xinafoate inhaler treatment. Hospitalized, methylphenidate discontinued, events resolved.
4305792-8	10	M	Irritability, stomach burning, and nausea during 1 month use of methylphenidate. Methylphenidate discontinued, events resolved.
4420654-3	13	M	Hallucinations and mood swings during methylphenidate and paroxetine use. Onset, treatment, outcome unknown. Report source: consumer speaking on TV show.
4288789-6	13	M	Manic symptoms during methylphenidate use. Hospitalized. Onset, treatment, outcome unknown.
4288742-2	16	M	Mania with methylphenidate and Adderall. Onset, treatment, outcome unknown. Unknown whether these drugs were used concurrently.
4358726-4	12	M	Violent behavior during concurrent immediate-release methylphenidate and Concerta use. Drugs discontinued, event resolved.

ISR#	Age (yrs)	Gender	Summary
<i>Neurological Adverse Events (N=7)</i>			
4300540-X	5	M	Difficulty controlling eye movement, confusion, anxiety 1 day after starting methylphenidate. Events continued with dosage adjustments, resolved with methylphenidate discontinuation.
4436699-3	4	F	Generic methylphenidate causes drowsiness.
4362495-1	10	F	Syncope and bilateral delta waves on EEG after 1 year methylphenidate. Treatment and outcome unknown.
4601412-3	13	M	Seizure during methylphenidate use. Treatment and outcome unknown.
4359306-7	12	M	Seizure after 2 years extended-release methylphenidate and concomitant immediate-release methylphenidate of unknown duration. All methylphenidate discontinued, event resolved.
4510046-0	8	M	Loss of consciousness and hypertonia of limbs after about 2 months methylphenidate. Methylphenidate ongoing.
4451998-7	13	F	Headache and vomiting during methylphenidate use. Methylphenidate discontinued, event resolved.
<i>Cardiovascular Adverse Events (N=2)</i>			
4257507-X	13	M	Sinus tachycardia after 1.5 years methylphenidate. Methylphenidate dosage decreased, event ongoing.
4288752-5	14	M	Chest pain after 1 month concurrent immediate-release and long-acting methylphenidate use. Drugs discontinued, event resolved.
<i>Cerebrovascular Adverse Events (N=2)</i>			
4497285-2	9	M	Three cerebral ischemic episodes with headache and paresthesia and weakness of left arm during methylphenidate use. Methylphenidate ongoing.
4529701-1	12	M	Cerebral ischemic infarction with evidence of inflammatory arteritis after about 7 years methylphenidate. Methylphenidate discontinued. Event resolved with sequelae. No evidence of active vasculitis in the subsequent 6 years. (Trugman JM)

ISR#	Age (yrs)	Gender	Summary
<i>Hematologic Adverse Events (N=4)</i>			
4511190-4	11	F	Pancytopenia after 1 month methylphenidate. Aplastic anemia diagnosed by bone marrow biopsy. Methylphenidate discontinued, event ongoing with immunosuppressant therapy.
4314090-8	15	F	Immune thrombocytopenic purpura diagnosed by bone marrow biopsy after 10 years methylphenidate. Methylphenidate discontinued, event ongoing.
4541013-9	5	M	Neutropenia after 1 month methylphenidate. Baseline, treatment, and outcome unknown.
4473096-9	12	M	Neutropenia after about 6.5 years methylphenidate. Methylphenidate discontinued, event resolved.
<i>Gastrointestinal Adverse Events (N=5)</i>			
4353380-X	8	F	Hepatic failure after almost 3 years immediate-release methylphenidate and 1.5 years extended-release methylphenidate used concurrently. Hospitalized, awaiting transplant. Methylphenidate discontinued. Medical history includes morbid obesity and mental retardation.
4533553-3	4	M	Severely elevated transaminases, normal bilirubin, vomiting, and decreased weight after 4 weeks methylphenidate to treat hyperkinetic syndrome that developed during chemotherapy for acute lymphocytic leukemia. Methylphenidate discontinued, events improving.
4273163-9	10	M	Nausea and loss of appetite 1.5 hours after each methylphenidate dose. Aggravation of pre-existing chronic juvenile arthritis during methylphenidate not attributed to drug. Treatment and outcome unknown.
4372116-X	13	F	Decreased appetite and weight loss during 2 months methylphenidate use. Methylphenidate immediate release switched to Concerta. Weight loss continued.
4441083-2	11	M	Gall stones and abdominal pain after 3 years methylphenidate. Methylphenidate continued for 1 more year. Treatment and outcome unknown.

ISR#	Age (yrs)	Gender	Summary
<i>Skin Adverse Events (N=4)</i>			
4358356-4	6	F	Anaphylactoid purpura after 6 weeks methylphenidate. Methylphenidate discontinued, rash improved. Methylphenidate resumed, rash worsened. Methylphenidate discontinued, rash resolved.
4340039-8	10	F	Rash and purpura during generic methylphenidate use. Methylphenidate discontinued, rash resolved.
4516467-4	13	M	Zosteriform pigmented purpura of Schamberg with petechiae diagnosed by histopathological exam beginning after about 1 year methylphenidate and worsening over 3 years methylphenidate use. Methylphenidate discontinued, events improved within 4 weeks.
4527213-2	11	M	Discoid lupus erythematosus-like lesions on cheeks and positive antinuclear antibody after 2 years methylphenidate. Methylphenidate discontinued, lesions resolved, positive ANA ongoing.
<i>Thyroid Adverse Events (N=3, all from same reporter)</i>			
4432533-6	10	M	Hypothyroidism after 4 months methylphenidate. Methylphenidate continued, event resolved in 4 weeks. Treatment unspecified.
4405226-9	9	M	Hypothyroidism during methylphenidate use. Methylphenidate continued. Event being treated with levothyroxine 50 mcg/day.
4405225-7	12	M	Hypothyroidism during methylphenidate use. Resolved without treatment during ongoing methylphenidate.
<i>Respiratory Adverse Events (N=2)</i>			
4453577-4	6	M	Worsened asthma during methylphenidate use. Treatment and outcome unknown.
4367303-0	12	M	Worsened asthma after about 2 years methylphenidate. Methylphenidate and event ongoing.

ISR#	Age (yrs)	Gender	Summary
<i>Miscellaneous Adverse Events (N=2)</i>			
4348366-5	7	M	Growth retardation and developmental delay, vomiting, agitation, headache, insomnia, body odor during 1 year methylphenidate. Methylphenidate discontinued, body odor improve, outcome of other events unknown.
4438437-7	7	M	Increased creatine phosphokinase after 11 days methylphenidate. Baseline, treatment, and outcome unknown.

Reference:

Trugman JM. Cerebral arteritis and oral methylphenidate [letter]. Lancet 1988 Mar 12; 1(8585):584-5.

Attachment 2: Extended-release methylphenidate other than Concerta (N=40)

Cases that are strongly confounded (N=3)

ISR#	Age (yrs)	Gender	Summary
4311745-6	10	F	Trichotillomania during use of methylphenidate and atomoxetine. Methylphenidate discontinued, event continued. Atomoxetine discontinued, event resolved.
4299470-1	13	M	Hallucinations, twitching, diagnosis of schizophrenia 2.5 months after methylphenidate and paroxetine were discontinued. Drugs were discontinued for eye twitching and sleep disturbance. Methylphenidate duration 1 year, paroxetine duration unknown.
4490443-2	15	F	Tested positive for hepatitis C during methylphenidate use. Onset, treatment, outcome unknown.

Cases that do not report strongly confounding information (N=37)

ISR#	Age (yrs)	Gender	Summary
<i>Lack of Effect (N=3)</i>			
4516244-4	16	M	Generic methylphenidate was not effective.
4449751-3	14	M	Generic methylphenidate was not effective.
4519745-8	15	M	Generic methylphenidate was not effective.
<i>Psychiatric Adverse Events (N=7)</i>			
4443828-4	12	Male	Hallucinations during methylphenidate. Methylphenidate discontinued, event resolved. Methylphenidate rechallenged and event returned. Methylphenidate discontinued, event resolved.
4443829-6	7	Male	Hallucinations during methylphenidate. Methylphenidate discontinued, event resolved.
4443812-0	7	Male	Hallucinations after about 1 year methylphenidate. Placebo substituted for methylphenidate and event resolved.
4459444-4	4	Male	Depression, crying, headache, stomach pain after 4 months methylphenidate. Hospitalized for meningitis during methylphenidate use. Methylphenidate continued, headache and stomach pain continue. Outcome of depression and crying unknown.

ISR#	Age (yrs)	Gender	Summary
4554624-1	8	F	Psychotic episode during use of methylphenidate. Symptoms, onset, treatment, outcome unknown.
4343669-2	13	M	Psychotic episode during methylphenidate use. Onset unknown. Methylphenidate discontinued, event resolved. Reporter's nurse later said event not due to methylphenidate.
4299018-1	13	M	Psychotic episodes during methylphenidate, sertraline, and salmeterol concomitant use and during methylphenidate, sertraline, and atomoxetine concomitant use. One episode resolved with salmeterol discontinuation, before atomoxetine initiated. Psychiatric drugs continued, event outcome unknown.
<i>Neurological Adverse Events (N=11)</i>			
4288796-3	2	?	Dyskinesia, psychomotor hyperactivity, tachycardia, vomiting after accidental ingestion of 40 mg methylphenidate. Treated in ER with lorazepam. Outcome unknown.
4366761-5	7	M	Paresis of left leg after 15 days methylphenidate. Methylphenidate discontinued, event ongoing.
4331504-8	11	M	Facial paresis during use of methylphenidate. Onset, treatment, outcome unknown.
4508976-9	7	M	Seizures, agitation, altered mental status same day methylphenidate dosage increased. Hospitalized. Treatment and outcome unknown.
4404706-X	8	M	Seizure after 1 year methylphenidate and 1 month after dosage increase. Dosage decreased, event resolved.
4554629-0	11	M	Increased seizure frequency after less than 1 month methylphenidate. Methylphenidate discontinued, event ongoing. Seizure history.
4347965-4	6	M	Tic after 2 months methylphenidate. Methylphenidate discontinued, tic treated with clonidine and risperidone. Tic subsided.
4394099-9	7	M	Tic after 2 months methylphenidate. Methylphenidate discontinued, event ongoing.
4352177-4	14	M	Tic exacerbated, "paradoxical effect", and insomnia after 1 month extended-release methylphenidate (Metadate CD). Switched to immediate-release methylphenidate (Ritalin), events resolved.

ISR#	Age (yrs)	Gender	Summary
4252008-7	9	M	Coma lasting 4 days and generalized slowed rhythm on EEG after 2-3 years methylphenidate. Hospitalized, methylphenidate discontinued, event slowly resolved. Previous similar incident while taking methylphenidate.
4554626-5	7	M	“Sleep problem” after 1 year methylphenidate. Withdrawal syndrome after “all ADHD medications” discontinued. Symptoms, outcome unknown.
<i>Special Senses Adverse Events (N=2)</i>			
4455545-5	6	M	Optic nerve neuropathy, peripheral vision loss, headaches, and mydriasis after about 1 month methylphenidate, 1 month desmopressin, 4 months fluvoxamine, and 6 months atomoxetine. All drugs except desmopressin discontinued, event ongoing.
4470846-2	11	F	Strabismus after less than 1 month methylphenidate (Ritalin). Methylphenidate discontinued, event resolved. Event recurred with generic methylphenidate. Outcome unknown.
<i>Cardiovascular Adverse Events (N=2)</i>			
4482688-2	13	M	Tachycardia few hours after dose of acetaminophen (APAP). Methylphenidate of several years switched to extended-release methylphenidate a few weeks before event. Tachycardia recurred with second dose of APAP next day. Drug interaction was suspected because of previous uneventful APAP use.
4340628-0	16	F	Palpitation, chest pain, left arm numb, stiff arms and jaw, headache, and abdominal pain 75 minutes after first dose methylphenidate. No previous methylphenidate exposure. Hospitalized, methylphenidate discontinued, events resolved over 2 days.

ISR#	Age (yrs)	Gender	Summary
<i>Cerebrovascular Adverse Events (N=2)</i>			
4539362-3	8	Male	Cerebral vasculitis with three episodes of paresthesia after 1 ½ years Concerta. Concerta discontinued, no further episodes but sequelae present
4364357-2	6	Male	Cerebral infarction after 6 weeks Concerta. Concerta discontinued, anticoagulation and physiotherapy treatment, event resolved with sequelae
<i>Thyroid Adverse Events (N=1)</i>			
4453581-6	10	M	Hyperthyroidism “shortly” after methylphenidate initiated. Methylphenidate continued, event treated with thiamazole and resolved. Event recurred and was again treated with thiamazole. Family history of hyperthyroidism.
<i>Respiratory Adverse Events (N=3)</i>			
4288543-5	0	M	Neonatal apnea after mother took methylphenidate, paroxetine, alprazolam, and flunitrazepam daily throughout pregnancy.
4519667-2	8	M	Hives and wheezing hours after first dose of methylphenidate. Methylphenidate discontinued, event treated with antihistamine and steroid. Event resolved.
4294170-6	10	M	Asthma attack and tachycardia on second day of methylphenidate use. Treated in ER with beta agonist. Asthma attack resolved, tachycardia improved. Asthma history.

ISR#	Age (yrs)	Gender	Summary
<i>Miscellaneous Adverse Events (N=6)</i>			
4284879-2	12	M	Sudden death after 15 months methylphenidate and 6 weeks after Ritalin SR changed to Ritalin LA and fluticasone started for allergic rhinitis. Asthma history. Autopsy found brain edema and slight lung inflammation.
4411155-7	7	M	Increased creatine kinase during methylphenidate use. Onset, treatment, outcome unknown.
4307089-9	6	M	Profuse nose bleeds same day extended-release methylphenidate replaced immediate-release methylphenidate. Switched back next day. Event resolved.
4537196-7	7	?	Loss of consciousness after “standing still too long”. Methylphenidate continued, event resolved.
4301926-X	10	M	Increased transaminases, lactate dehydrogenase and creatine kinase after about 3 years methylphenidate. Hospitalized, methylphenidate discontinued, event continued.
4402017-X	14	M	Raynaud’s-like phenomenon 3 weeks after immediate-release methylphenidate of unknown duration switched to extended-release methylphenidate. Event improving with warmer weather. Methylphenidate (formulation unknown) continued.

Attachment 3: Case in which no adverse event was reported (N=1)

ISR#	Age (yrs)	Gender	Summary
4458826-4	9	M	Wrong medication dispensed, not ingested.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kathleen Phelan
6/15/05 04:47:43 PM
DRUG SAFETY OFFICE REVIEWER

Mark Avigan
6/15/05 05:06:32 PM
DRUG SAFETY OFFICE REVIEWER