1.1. Overview of reports on methylphenidate in adults

Introduction

Methylphenidate (Ritalin®) is indicated as part of a comprehensive treatment programme *for Attention Deficit Hyperactivity Disorder (ADHD) in children from the age of six years and older when remedial measures alone are insufficient.*
Furthermore methylphenidate (Ritalin®) it is indicated for the treatment of *narcolepsy*.
Methylphenidate is an indirect centrally acting sympathomimetic and has a stimulating effect on the central nervous system. The pharmacological properties resemble those of amphetamines. It is a racemic mixture consisting of d-methylphenidate and l-methylphenidate in the ratio 1:1, where it is assumed that the L-enantiomer is pharmacologically inactive.
Methylphenidate was granted marketing authorization in the Netherlands in 1982 (1).
Registration of methylphenidate for ADHD in adults was previously refused by the registration authorities, because of an uncertain risk-benefit balance and risks including cardiovascular and psychiatric effects (2).

The Dutch guideline for psychiatrists "ADHD in adults", indicate methylphenidate or dexamphetamine as *preference drug for adults with ADHD*, despite the fact that both methylphenidate and dexamphetamine are not registered for the indication ADHD in this age group of adults. An addendum as part of the guideline describes the indication being off label. In the guideline the described adverse events of methylphenidate include headache, irritability, decreased appetite, dry mouth, anxiety and problems sleeping. Concerning cardiovascular effects, the guideline describes an slight increase in blood pressure (mean of 1-5 mm Hg) and pulse rate (4-10 beats/minute). Furthermore, palpitations were described with a relative risk of 2.24 (with 95% confidence interval 1.38-3.65) based on 1416 patients in six studies, with an assessed low grade of evidence (3).

In 2015 Lareb published a report of the experiences of adult patients with medication used for ADHD (4). In addition to this report, this overview describes the reports received by Lareb for specifically methylphenidate in adult patients (that is patient of 18 years of older) concerning reports up until February 6, 2017.

Reports

On February 6, 2017 the Netherlands Pharmacovigilance Centre Lareb, had received 1178 reports with 2441 ADRs concerning patients of all ages. The remainder of this report, will focus on the reports concerning adult patients. Concerning adult patients, Lareb had received 542 reports with 1187 ADRs. Additional information is provided in table 1.

Table 1. Numbers of reports received by Lareb in the national reporting database for methylphenidate in adults

	Methylphenidate
Total number of reports	542
Number of serious reports	98 (18%)
Total number of ADRs*	1187
Reports with a fatal outcome#	3

* One report can contain multiple ADRs
# The causal relation between the death of a patient and the use of the drug in question is not always clear.

Cases with fatal outcome

The three cases with fatal outcome are described here in more detail. In all these cases the cause of death could not be established for certain.

Case 178219:
This serious (Death) spontaneous report from a general practitioner concerns a male aged 61 years, with sudden death following administration of methylphenidate for ADHD with a latency of one year after start. The cause of death was unknown.

Case 193282:
This serious (Death) spontaneous report from a physician concerns a male aged 56 years, with sudden death following administration for unknown indication with unknown latency. The autopsy (without skull autopsy) did not reveal a cause of death. It was unknown whether the patient used over-the-counter drugs and it was unknown what the compliance was.

Case 226532:
This serious (Death) spontaneous report from a general practitioner concerns a male aged 48 years, with sudden death with unknown cause (but a cardiac arrest is suspected) following administration of methylphenidate for ADHD with a latency of four years after start. The days before, he complained of fatigue. Concomitant medication was not reported. Patient used methylphenidate Concerta® (54 mg, later 36 mg and 10 mg shortacting) for three years and afterwards methylphenidate mga Mylan followed by methylphenidate Sandoz. Blood pressures over the last two years were in temporary sequence 104/90, 140/92, 122/74 and 130/84 mm Hg. The patient had a history of smoking. There were no cardiac diseases in family.

Cardiovascular ADRs

The reported ADRs concerning cardiovascular events, are presented in table 2. Totally 109 ADRs concerning cardiovascular events in adults were reported, of which 38% was serious. In 61% of the reported ADRs the patients had recovered at the moment of reporting. It should be noted that the numbers reported in table 2 do not necessarily represent distinct reports, since one report can contain multiple ADRs.
The reactions indicated in **bold** are described in more detail below table 2. Furthermore the table reports whether the reactions are labelled as adverse drug reaction in the SmPC (1).

Table 2. Cardiovascular ADRs*

	Labelled in SmPC	Number of reports	Number of serious reports (%)	Recovered/ recovering (%)	Not recovered (%)	Outcome unknown (%)
Palpitations	Often	30	10	19	6	5
Heart rate increased	Often	10	4	6	4	0
Hypertension	Often	10	5	7	1	2
Tachycardia	Often	9	1	6	3	0
Chest pain	Sometimes	8	2	3	3	2
Myocardial infarction	Very rare	6	5	4	0	2
Raynaud's phenomenon	Very rare	6	1	4	1	1
Peripheral coldness	Often	5	1	4	1	0
Blood pressure increased	Hypertension often	4	1	2	1	1
Arrhythmia	Often	4	3	1	2	1
Chest discomfort	Sometimes	4	1	2	0	2
Blood pressure diastolic increased	Hypertension often	2	1	1	0	1
Reversible ischaemic neurological deficit	Very rare	2	0	2	0	0
Cardiac failure	No	1	1	0	1	0
Acute coronary syndrome	Myocardial infarction very rare	1	1	1	0	0
Arterial stenosis	No	1	1	1	0	0
Atrial fibrillation	No	1	0	1	0	0

Flushing	Only in overdose	1	0	0	1	0
Supraventricular tachycardia	Yes, frequency unknown	1	1	1	0	0
Vasoconstriction	No, but Raynaud and cold extremities are	1	0	1	0	0
Vasospasm	No, but Raynaud and cold extremities are	1	1	0	0	1
Ventricular tachycardia	Ventricular extrasystoles with unknown frequency	1	1	0	0	1
Total		*109*	*41 (38%)*	*66 (61%)*	*24 (22%)*	*19 (17%)*

* Several ADRs can originate from a single report

Myocardial infarction / acute coronary syndrome
The reports of myocardial infarction (with case numbers 202918, 62680, 190404, 222881, 91489, 110778) and acute coronary syndrome (case number 62680) concern five males and one female, with ages between 58 and 63 in five patient, and 29 and 31 years in the other two patients. Latencies were two days, two years, eight years, ten years or unknown (in two reports). In four reports risk factors were specifically described: smoking in one patient; known atherosclerosis in one patient; in the 31-year-old patient smoking, hypercholesterolaemia and family history for cardiac problems; in the 29-year-old patient cocaine abuse, hypercholesterolemia and father with myocardial infarction at young age. In one patient the acute coronary syndrome was preceded by severe tachycardia. There were no risk factors described in one patient, a 63-year old male.

Heart rate increased / tachycardia
Of the reports of heart rate increased and tachycardia (with case numbers 222248, 135377, 226402, 228840, 233300, 61911, 77923, 140186, 182850, 213363, 112050, 182851, 230308, 37729, 60955, 194652, 204510, 99024, 222881), in most patients the heart rate was not reported. In only five patients, all concerning young patients with ages between 21 and 32 years, pulse rates were reported of 83, 92, 120, between 160 and 180 and 180 beats/minute. Four of five patient had recovered or were recovering at the moment of reporting (except for the patient with the rate of 92 beats per minute). Furthermore there was one report with very limited information of a 58-year old female with tachycardia of more than 200 beats per minute following substitution.

Arterial stenosis
Lareb received one report (case number 193084) concerning a male aged 55 years, with arterial stenosis in the superficial femoral artery and embolism in the foot with a latency of about 14 years after start. a described risk factor was thirty pack years of smoking.

Hypertension / blood pressure increased / blood pressure diastolic increased
Concerning the reports of hypertension, blood pressure increased or blood pressure diastolic increased (report numbers 120393, 140186, 155040, 172727, 182865, 186166, 213363, 216071, 69980, 206184, 202916, 60955, 59482, 48844, 88683, 88830), in three reports (excluding a report with very limited information and a report concerning substitution) values were described. These values were: increase in diastolic pressure from 85 to 110 mmHg in an 48-year-old-male with unknown latency, and the same change in a 60-year-old male with a latency of days; and blood pressures which were sometimes low (110/55 mmHg) but sometimes high (175/100 mmHg) in 42-year-old male, who also experienced palpitations, cluster headaches and anxiety.
Furthermore there was one report based on a published scientific article concerning an increase of urinary metanephrine with an increased blood pressure of 201/103 mmHg (5).

Cardiac failure
Lareb received one report (case number 56976) with limited information of a 46-year old male who experienced ventricular tachycardia and heart failure with unknown latency after start of methylphenidate. Other possible causes were a possible infection, alcohol abuse and smoking.

Psychiatric ADRs

The ADRs concerning psychiatric events that were reported ten times or more or concerned ADRs under special attention, are presented in table 3. It should be noted that the numbers reported in table 3 do not necessarily represent distinct reports, since one report can contain multiple ADRs.
The reactions indicated in **bold** are described in more detail below table 3. Furthermore the table reports whether the reactions are labelled as adverse drug reaction in the SmPC (1).

Table 3. Psychiatric ADRs*

	Labelled in SmPC	Number of reports	Number of serious reports (%)	Recovered/ recovering (%)	Not recovered (%)	Outcome unknown (%)
Depressed mood	Depression often	28	3 (11%)	20	5	3
Restlessness	Often	16	2 (13%)	10	2	4
Depression	Often	13	6 (46%)	7	3	3
Suicidal ideation	Sometimes	13	9 (69%)	10	1	2
Agitation	Often	12	0 (0%)	9	3	0
Insomnia	Very often	12	2 (17%)	6	5	1
Anxiety	Often	10	3 (30%)	5	5	0
Suicide attempt	Very rare	2	2	1	0	1
Agression	Often	8	3	4	1	3

* Several ADRs can originate from a single report

Depression
The reports of depression concerned eight females and five males. Ages varied between twenty and 83 years, mean 34 years, median 28 years. Latencies were hours in two reports, days to weeks in five reports, one year, seven years and fifteen years in three reports, and unknown in three reports.

Suicidal ideation or attempts
The sixteen reports of suicidal ideation or attempts concerned seven females and six males, with ages between twenty and 52 years. Latencies were between one hour and seventeen days in eight reports, in the other reports longer (up till fifteen years) and unknown in three reports. In seven reports other causes for the reaction were specifically described and three reports concerned reactions after substitution.

Aggression
The eight reports of aggression (case numbers 84857, 139561, 156269, 33566, 122518, 165563, 185795, 225356), concerned four males and four females with ages between 28 and 42 years. Latencies were hours to days in three reports, five months in one report and unknown in four reports. In four reports other causes for the reaction were specifically described that is other suspect drugs including cocaine and cannabis, abuse of methylphenidate, tapering of paroxetine or stress. In one report the reaction occurred after substitution.

Most frequently reported other ADRs exclusive cardiovascular and psychiatric events

The most frequently reported ADRs (ten received reports or more) exclusive cardiovascular and psychiatric events, are presented in table 4. It should be noted that the numbers reported in table 4 do not necessarily represent distinct reports, since one report can contain multiple ADRs.
The reactions indicated in **bold** are described in more detail below table 4. The table reports whether the reactions are labelled as adverse drug reaction in the SmPC and the frequency of occurrence described in the SmPC (1).

Table 4. Most frequently reported ADRs (10 or more)*

	Labelled in SmPC	Number of reports	Number of serious reports (%)	Recovered/ recovering (%)	Not recovered (%)	Outcome unknown (%)
Therapeutic response unexpected (substitution)	Not applicable (NA)	70	5 (7%)	41	17	12
Headache	Very often	32	4 (13%)	18	5	9
Hyperhidrosis	Only in overdose	30	3 (10%	13	12	5
Drug interaction	Variable reports	23	2 (9%)	10	4	9
Decreased appetite	Anorexia often	21	2 (10%)	9	10	2
Drug ineffective	NA	20	3 (15%)	11	2	7
Nausea	Very often	20	0 (0%)	15	3	2
Dry mouth	Very often	19	1 (5%)	6	10	3
Alopecia	Often	18	0 (0%)	4	4	10
Fatigue	Often	18	1 (6%)	8	4	6
Product quality issue	NA	16	0 (0%)	10	0	6
Therapeutic response decreased	NA	14	2 (14%)	8	2	4
Dizziness	Often	14	4 (29%)	11	1	2
Weight decreased	Mild decrease of weight often	13	2 (15%)	6	5	2
Paraesthesia	Not as isolated symptom	12	1 (8%)	5	3	4
Muscle spasms	Very rare	11	4 (36%)	5	5	1
Trismus	Dyskinesia often	11	3 (27%)	6	3	2

* Several ADRs can originate from a single report

Therapeutic response unexpected (substitution) and drug ineffective

In 2014 and 2015 Lareb received several reports of lack of drug effect after substitution from Concerta® to generics, or from one to another generic from different manufacturers. This matter was also analysed by the Danish Health and Medicines Authority (DHMA), who wrote a report on their analyses in 2015. The DHMA performed a number of tests to measure the active substances in the original and generic product, but did not discover any defects in quality (6).

Product quality issue

In 2015 several patients experienced falling apart of methylphenidate HCL 36 mg Retard tablets from Mylan. In 2015 a DHPC (Dear Healthcare Professional Letter) was distributed to optimize storing conditions to prevent this problem for the estimated small amount of existing tablets, and the coating of newly produced tablet were changed (7). No reports of product quality issue were received concerning tablets with the new coating.

Drug interaction

The reports concerning drug interactions concerned a wide range of drugs and reactions and did not give rise to a signal at this moment.

Other sources of information

Prescription data

The number of patients using methylphenidate in the Netherlands is shown in table 5. For 2015 the number of patient using methylphenidate in several age groups are available in the GIP database, the Dutch database of number of users of drugs in the Netherlands, and therefore separately described in table 6.

Table 5. Number of patients of all ages using methylphenidate in the Netherlands between 2011 and 2014 (8).

Drug	2011	2012	2013	2014
Methylphenidate	157,310	170,460	180,200	188,230

Table 6. Number of patients of according to years of age (and % of total number of users) using methylphenidate in the Netherlands in 2015 (7).

Drug	0-14 years	15-24 years	25+years	Total
Methylphenidate	76,086 (39%)	59,777 (31%)	57,417 (30%)	193,280 (100%)

Discussion and conclusion

This overview describes the reports received by Lareb of ADRs associated with the use of the methylphenidate in adults, with special focus on cardiovascular and psychiatric events. It is noticeable though that methylphenidate is widely prescribed for adult patients with 30% of patients using methylphenidate being 25 years of age or older in 2015, and the large number of 542 reports concerning adults received by Lareb (46% of the reports received in all age groups), despite the previous refusal of registration by the registration authorities based on an uncertain risk-benefit analysis including cardiovascular and psychiatric risks (2). Therefore, Lareb advises to monitor the effects and ADRs of the use of ADHD medications in adults in daily practice, for example by monitoring through a register.

Reference List

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(3) Dutch guideline for psychiatrists [ADHD in adults] Richtlijn ADHD bij volwassenen, fase 1 diagnostiek en medicamenteuze behandeling (2015). http://www nvvp net/website/richtlijnen/overzicht-richtlijnen 2015 July 8 [cited 2017 Feb 6];
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(5) Man WH, Hagen C, Wielders J, Malingre M. Increased urinary levels of metanephrines with methylphenidate use can lead to suspicion of a pheochromocytoma. Nederlands Tijdschrift voor Klinische Chemie 2014 Jan;39(1):34-6.
(6) ADR reports of substitution problems and lack of efficacy of Methylphenidate "Sandoz". Danish pharmacovigilance update 2015;5(6):10-1.
(7) Website CBG. DHPC methylfenidaat HCL Mylan Retard. https://www cbg-meb nl/documenten/brieven/2015/07/16/dhpc-methylfenidaat-hcl-mylan-retard 2015 July 17 [cited 2017 Feb 8];
(8) GIP databank. Zorginstituut Nederland. www gipdatabank nl/ 2017 [cited 2017 Feb 6].