1.1. Atomoxetine, methylphenidate and spontaneous ejaculation

Introduction
Attention-Deficit/Hyperactivity Disorder (ADHD) is a disorder with a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development. About 3-5% of the children are diagnosed with ADHD [1]. Methylphenidate (Ritalin®, Concerta®) and atomoxetine (Strattera®) are the most widely used drugs for the treatment of ADHD. In 2008, 103,730 patients used methylphenidate. Atomoxetine was used by 5686 patients [2]. Spontaneous ejaculation is the occurrence of ejaculation in male without any stimuli. There is no information available about the prevalence of this ejaculation disorder [3]. This report describes the occurrence of spontaneous ejaculation with the use of ADHD drugs atomoxetine and methylphenidate.

Reports
Up to February 10, 2010, Lareb received two well documented reports of spontaneous ejaculation with the use of atomoxetine and methylphenidate.

Report 1: atomoxetine
This report from a psychiatrist concerns a male aged 31 – 40 years who received atomoxetine (40 mg once daily) for ADHD. Three weeks after start, he developed spontaneous ejaculations following micturition urgency up to eight times a day. The patient did not experience sexual feelings. In the past, the patient used dexamphetamine, which also gave spontaneous ejaculations. The patient recovered after withdrawal of dexamphetamine and atomoxetine. Concomitant medication was not reported.

Report 2: methylphenidate
This report from a consumer concerns a male aged 21 – 30 years who experienced spontaneous ejaculation following testicular pain after micturition with the use of methylphenidate (15 mg three times daily). The patient did not have any sexual feelings when the spontaneous ejaculations occurred. The spontaneous ejaculations were mainly present in times of stress and fatigue. The use of concomitant medication was not reported. Past drug therapy included atomoxetine which gave also spontaneous ejaculations following micturition. At the time of reporting, the patient was still using methylphenidate and was still having testicular pain and spontaneous ejaculations.

Other sources of information
Literature
Spontaneous ejaculation is not mentioned in the SmPC of methylphenidate or atomoxetine [4,5]. In literature, we found no cases of this specific association. Atomoxetine and methylphenidate are both norepinephrine reuptake inhibitors. A Medline search of the published literature revealed a few case reports concerning spontaneous ejaculation with the use other norepinephrine reuptake inhibitors [6-8].

A case report of spontaneous ejaculation with the use of milnacipran was described. This serotonin and noradrenalin reuptake inhibitor is not registered in the Netherlands. A 31-year old man started with milnacipran for depression. Four weeks after the beginning of milnacipran, he
experienced ejaculation without orgasm after defaecation about once per 2 or 3 weeks. A positive dechallenge was found [6].

Another case report of spontaneous ejaculation was described with the use of zotepine. Zotepine is an inhibitor of dopamine, serotonin and norepinephrine and is not registered in the Netherlands. The patient used zotepine for the indication psychotic symptoms and experienced spontaneous ejaculation many times a day. Sexual stimulation was absent and the ejaculations were not associated with a pleasurable sensation. Concomitant medication was haloperidol for schizophrenia. After withdrawal of zotepine, the patient recovered from the spontaneous ejaculations [7].

Reboxetine is a norepinephrine reuptake inhibitor, and also not registered in the Netherlands. A 44 year old man with depression experienced seminal emission and ejaculation during defecation and micturition with the use of reboxetine. This patient had a pleasurable sensation with the ejaculations. After reboxetine was replaced by sertraline, his spontaneous ejaculation subsided in 2 weeks [8].

Databases
Ejaculation disorder is the nearest MedDRA term to describe spontaneous ejaculation. On February 3rd, 2010, the database of the World Health Organization (WHO), contained 74 reports of ejaculation disorders with the use of atomoxetine with an odds ratio of 9.6 (95% CI 7.7-12.1). Ejaculation disorder was mentioned six times in association with the use of methylphenidate, with an odds ratio of 3.0 (95% CI 1.3 - 6.6).

On February 3rd 2010, the Eudravigilance database contained no cases of atomoxetine associated spontaneous ejaculation in cases which were listed under the preferred term “ejaculation disorder”. For methylphenidate the Eudravigilance database contained two reports of ejaculation disorders. In one case this disorder was unspecified, in the other case, infertility was the primary medical condition.

Mechanism
Ejaculation is a complex mechanism with a central and peripheral pathway in the Central Nervous System (CNS). In humans, the peripheral pathway is adrenergic and mainly facilitated by norepinephrine. Adrenergic activity may decrease ejaculatory latency and induce spontaneous ejaculation [8]. In rats, ejaculation was induced by administration of p-chloroamphetamine, which releases catecholamines and serotonin [9].

Methylphenidate is structurally related to amphetamine, dexamphetamine is an amphetamine. Amphetamines act as reuptake inhibitors of norepinephrine, serotonin and dopamine. Atomoxetine is a norepinephrine reuptake inhibitor. Hypothetically, through the inhibition of the reuptake of norepinephrine, more noradrenalin becomes available. Because of this, ejaculatory latency time decreases and spontaneous ejaculation can occur.

Discussion
Lareb received one report of spontaneous ejaculation with the use of methylphenidate and one report of spontaneous ejaculation with the use of atomoxetine. This number of reports is not remarkably high but the threshold to mention spontaneous ejaculation is high for the most patients. Not all complaints of spontaneous ejaculation will be mentioned to health professionals. Additionally, because the low number of patients the awareness is very low and the underreporting of such associations might be high.
The reasons just mentioned can also explain the low number of case reports described in literature. However, a few cases of spontaneous ejaculation of pharmacologically related drugs were found. Probably, other factors could be associated with the use of spontaneous ejaculation, but we found no information about this in literature. Besides, the well documented reports and positive de- and rechallenge with other similar drugs suggests a causal relationship. The possible terms provided in the MedDRA terminology are insufficient to describe spontaneous ejaculation. Ejaculation disorder is the nearest MedDRA term to describe spontaneous ejaculation. It should be considered to look at the original description of the ADRs in Periodic Safety Update Reports if this signal is further investigated.

Conclusion
The two case reports illustrate a new possible adverse drug reaction of spontaneous ejaculations with the use of methylphenidate and atomoxetine which may be mediated by to the re-uptake inhibition of norepinephrine.

- Possible new signal of spontaneous ejaculation with the use of atomoxetine and methylphenidate

References
2. CVZ. GIPdatabase. (version date: 9-6-2009, access date: 10-2-2010) www.gipdatabank.nl.
5. Dutch SmPCs Ritalin®. (version date: 04-02-2010, access date: 15-02-2010. www.cbg-meb.nl.

This signal has been raised on June 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).