

of 0.1–1.0%.<sup>[1]</sup> Debate exists over the safety of switching to an angiotensin-II receptor blocker (ARB), due to case reports of angioedema.<sup>[2]</sup>

**Aim:** To systematically examine published case reports of ARB-associated angioedema using the DoTS classification system.<sup>[3]</sup>

**Methods:** Published case reports of ARB-induced angioedema from January 1966 to January 2009 were identified using MEDLINE. Bibliographies of all retrieved case reports were used to identify any additional cases.

Information on age, gender, ethnicity, ARB regimen, duration of ARB therapy, severity of angioedema, prior use of ACE-I, rechallenge, history of angioedema, known allergies, co-morbidities, and concomitant medication was abstracted from individual case reports. Dose data for different ARBs were normalised and expressed using multiples of the Defined Daily Dose (DDD) for each drug.<sup>[4]</sup>

**Results:** Thirty-six case reports were retrieved: candesartan (2), irbesartan (2), losartan (25), olmesartan (1), telmisartan (1), valsartan (5). ARB dose information was available for 31 case reports. Sixty-eight percent of cases occurred at the DDD. Five cases of angioedema occurred below the DDD; one case occurred at 4 times the DDD (table 1). ARB-induced angioedema occurred within hours of administration or up to a year (median onset 19 days).

Female patients accounted for 78% of the reports of angioedema. Age ranged from 27 to 81 years (median 59 years). In 81% of cases the ethnicity of the patient was unspecified. Prior use of an ACE-I was present in 12 cases, with eight cases having previous ACE-I-induced angioedema.

**Conclusions:** ARB-induced angioedema is a collateral time independent reaction. Gender and prior ACE-I-induced angioedema appear to be susceptibility factors for the development of ARB-induced angioedema. The DoTS classification system served as a useful template for the analysis of published case reports.

#### References

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**Table 1.** A dose-time susceptibility analysis of 36 case reports of ARB-induced angioedema

Multiple of Defined Daily Dose (N)	Time (N)	Susceptibility	
		Age (N)	Gender (N)
0.5 (5)	<24 h (7)	<30 (1)	Female (28)
1 (21)	<7 days (6)	30–44 (3)	Male (8)
2 (4)	7 days–1 month (8)	45–59 (14)	
3 (0)	1–6 month (7)	60–74 (17)	
4 (1)	6 month–1 y (5)	75–89 (1)	
	>1 y (3)	>90 (0)	

## 59. Spontaneous Ejaculation with the Use of ADHD Drugs

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**Background:** Methylphenidate and atomoxetine are indicated for treatment of attention deficit-hyperactivity disorder (ADHD). The Netherlands Pharmacovigilance Centre Lareb received two reports of spontaneous ejaculation associated with the use of these drugs.

**Objective:** To describe two case reports of spontaneous ejaculation associated with the use of methylphenidate and atomoxetine. In addition, a suggestion for a possible mechanism is provided.

**Methods:** A search of spontaneous reports received by the Netherlands Pharmacovigilance Centre Lareb between January 1996 and May 2009. Medline search of the published literature.

**Results:** Lareb received two reports of spontaneous ejaculation associated with the use of these drugs. The first report from a psychiatrist concerns a 40-year-old male who receives atomoxetine for ADHD. Three weeks after start, he develops spontaneous ejaculations following micturition urgency up to eight times a day. There were no sexual feelings. In the past, the patient used dexamphetamine, which gave also spontaneous ejaculations. The patient recovered after dexamphetamine and atomoxetine withdrawal. Concomitant medication is not reported. The second report from a consumer concerns a 25-year-old male who experiences spontaneous ejaculation following testicular cramps after micturition with the use of methylphenidate. Sexual feelings are not present. The spontaneous ejaculations are mainly present in times of stress and fatigue. Concomitant medication is not reported. Past drug therapy included atomoxetine which gave also spontaneous ejaculations following micturition. At the time of reporting, the patient is still using methylphenidate and is still having testicular cramps and spontaneous ejaculations.

**Discussion:** Atomoxetine is a norepinephrine reuptake inhibitor. Methylphenidate and dexamphetamine are amphetamines, who act as reuptake inhibitors of norepinephrine, serotonin and dopamine. The exact mechanism of these drugs on ADHD is not clear.<sup>[1]</sup> Ejaculation is a complex mechanism with a central and peripheral pathway. The peripheral pathway is adrenergic and mainly facilitated by norepinephrine. Also, adrenergic activity may decrease ejaculatory latency and induce spontaneous ejaculation.<sup>[2]</sup> Through the inhibition of the reuptake of noradrenalin spontaneous ejaculation can occur. In literature, a few cases are described concerning spontaneous ejaculation with the use of milnacipran,<sup>[3]</sup> reboxetine<sup>[2]</sup> and zotepine<sup>[4]</sup> due to a norepinephrine-reuptake effect.

**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 the re-uptake inhibition of norepinephrine. Physicians should be aware of the possibility of these drugs to cause spontaneous ejaculations.

#### References

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