

## Spontaneous ejaculation with the use of noradrenergic reuptake inhibitors

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The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous adverse drug reaction (ADR) reporting system in the Netherlands. The primary aim of this system is to detect ADRs that were not identified prior to drug marketing [1]. Physicians, pharmacists, and patients can report suspected ADRs to the pharmacovigilance centre. We describe three case reports of spontaneous ejaculation, without sexual arousal, after micturition associated with the use of the noradrenergic reuptake inhibitors methylphenidate, atomoxetine, and venlafaxine reported by Lareb between January 1996 and December 2011.

The first report, from a psychiatrist, concerns a 40-year-old man who received atomoxetine. After 3 weeks, the patient developed spontaneous ejaculations following micturition urgency up to eight times a day without sexual arousal. The patient recovered after withdrawal of atomoxetine. The patient previously used dexamphetamine, which also gave spontaneous ejaculations. He recovered upon cessation of dexamphetamine. Concomitant medication is not reported.

The second report, from a consumer, concerns a 25-year-old man who experienced spontaneous ejaculation without sexual arousal following testicular pain after micturition with the use of methylphenidate. The use of concomitant medication was not reported. Past drug therapy included atomoxetine, which also gave spontaneous ejaculations following micturition. After 2 years, the patient uses mainly the

long-acting variant of methylphenidate (Concerta®) and sometimes the shorter-acting variant of methylphenidate (Ritalin®). Although spontaneous ejaculations are still present, they are less frequent with this drug regimen.

The third report, from a psychiatrist, concerns a 60-year-old man who experienced spontaneous ejaculations without sexual arousal one to two times a week within a day after commencing venlafaxine for depression. The ADR worsened after a dose increase from 225 to 375 mg. The outcome of this report is unknown.

In the literature, there are two case reports of spontaneous ejaculation with sexual arousal with the use of reboxetine. Both patients recovered within 2 weeks of reboxetine withdrawal [2, 3]. Case reports concerning spontaneous ejaculation without sexual arousal with the use of other noradrenergic reuptake inhibitors were described with the use of milnacipran [4], zotepine [5], and nefazodone [6]. Spontaneous ejaculation occurred after micturition [6] and defecation [4], with a frequency varying from once per 2 or 3 weeks [4] to several [5] to seven times daily [6]. All patients recovered after drug withdrawal [4–6].

The exact mechanism of spontaneous ejaculation is unknown. Ejaculation is controlled by both the sympathetic and parasympathic system and consists of an emission and expulsion phase [3]. Ejaculation latency time is regulated by the sympathetic system. Hypothetically, by reducing ejaculatory latency time, spontaneous ejaculation can occur [3]. Adrenergic drugs are sometimes used as treatment for delayed ejaculation [3]. In rats, ejaculation was induced by systemic administration of amphetamine [7]. Also, stimulation of noradrenaline (reboxetine [2], milnacipran [4]), and 5-hydroxytryptamine (5-HT2) antagonists (nefazodone) [6] could lead to decreased ejaculation latency time. On the other hand, selective serotonin reuptake inhibitors (SSRIs) [3, 4] and 5-HT1a antagonists could lead to increased ejaculation latency time [2, 3].

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In the case reports presented here, atomoxetine and venlafaxine (noradrenaline reuptake inhibitors) and methylphenidate and amphetamine (adrenaline agonists) were used, through which more adrenaline or noradrenaline is made available, ejaculatory latency time decreases, and spontaneous ejaculation can occur. These three reports illustrate a new possible ADR of spontaneous ejaculations with the use of noradrenergic reuptake inhibitors that may be mediated by the reuptake inhibition of norepinephrine. The number of spontaneous reports is not remarkably high, but the threshold for mentioning spontaneous ejaculation to healthcare professionals will be high [4]. Although other contributing factors, such as depression, could not completely be excluded in these reports, the patients recovered after drug withdrawal, suggesting a causal relationship. Physicians should be aware of the possibility of these drugs to cause spontaneous ejaculations.

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The cases described in this study have been reported to The Netherlands Pharmacovigilance Centre Lareb (atomoxetine NL-LRB-83557; methylphenidate NL-LRB-94935; venlafaxine NL-LRB-115751)