

## Trazodone and urinary incontinence

### Introduction

Trazodone (Trazolan<sup>®</sup>) is indicated for the treatment of *depression with or without anxiety*. The presence of vital symptoms in the depression increases the change on a therapeutic response. The effect usually starts to be noticed only after 1 – 2 weeks [1].

Trazodone is chemically not related to tricyclic, tetracyclic and other antidepressants. In low doses it has a serotonin-antagonizing effect, while in high doses the re-uptake of serotonin is inhibited. The antagonizing effects of trazodone on muscarinic- and histaminereceptors are small. The antagonizing effects on these receptors go together with different anticholinergic, cardiovascular and sedative adverse events. Somnolence and sedation related to trazodone could be the result of the alpha1-adrenergic blocking effect. It cannot be ruled out that the serotonin-mimetic effect of trazodone can be attributed to m-chlorophenylpiperazine, a metabolite of trazodone [1].

Trazolan<sup>®</sup> was granted marketing authorization in the Netherlands in 1983 [1].

Urinary incontinence often has an identifiable cause in younger persons. In older persons a multifactorial syndrome is more likely. Neuro-urinary pathology, age-related factors, comorbid conditions, medications, and functional and cognitive impairments may play a role in the older population [2].

The Dutch SmPC of trazodone mentions micturition problems as an adverse drug reaction, but does not mention urinary incontinence specifically [1]. This observation describes the association between urinary incontinence and the use of trazodone.

### Reports

On 22 March 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports concerning urinary incontinence associated with the use of trazodone.

#### Case A (report number 70148)

This non-serious spontaneous report from a pharmacist concerns a female aged over 71 years, with urinary incontinence following administration of trazodone 100 mg per day for depression and sleeplessness with a latency of 6 hours after start. Trazodone was withdrawn and the patient recovered. Concomitant medications were oxazepam, metoprolol / hydrochlorothiazide, dipyridamol, candesartan, carbasalate calcium, simvastatin.

#### Case B (report number 101999)

This non-serious spontaneous report from a specialist doctor concerns a female aged between 41 and 50 years, with urine incontinence during the day and night following administration of trazodone 100 mg per day with a latency of 31 days after start. Urine incontinence stopped abruptly 1 day after trazodone was withdrawn. Concomitant medication was not reported. The medical history indicates “surgery because of inflammation of the urinary duct 29 years ago”.

#### Case C (report number 131672)

This non-serious spontaneous report from a pharmacist concerns a female aged between 61 and 70 years, with urinary incontinence following administration of trazodone 50 mg before the night with a latency of within 10 days after start. The drug trazodone was withdrawn. The patient recovered. Concomitant medications were clemastine, lorazepam, calciumcarbonate, mometason, desloratadine, olopatadine, alendroninate. The patient has no known medical history.

## Other sources of information

### SmPC

In the Dutch SmPC of trazodone it is mentioned that careful dosing and a regular control is recommended in patients with micturition disturbances, like prostate hypertrophy, although problems are not to be expected because the anticholinergic action of trazodone is small. Disturbed micturition are mentioned in the SmPC text, with an unknown frequency, but urinary incontinence is not mentioned in the Dutch SmPC of trazodone specifically [1]. The US SmPC of the FDA mentions urinary incontinence as an infrequent (defined as occurring in less than 1/100 patients) occurring adverse drug reaction in the section "Clinical Studies Experience". The section "Postmarketing Experience" from spontaneous reports regarding trazodone hydrochloride also mentions urinary incontinence [3].

### Literature

An article by *Fisher et al* [4], describes adverse clinical events reported by outpatients being treated with either trazodone or fluoxetine. In this study three patients (aged 49, 74 and 80 years) in the trazodone group (N=815 patients; incidence estimate 0.37%) mentioned urinary incontinence and none in the fluoxetine group (N=2,487 patients; incidence estimate 0.00%). The authors mention that it is important to keep in mind that even if the differences are truly drug related, the effects could also be an unsuspected benefit associated with fluoxetine instead of an adverse drug reaction of trazodone.

### Databases

On 22 March 2013 the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of the MedDRA® Preferred Term (PT) urinary incontinence associated with the use of trazodone. The reporting odds ratio (ROR) was 20.5 (95% CI 6.4-65.5), which is disproportional.

The WHO database of the Uppsala Monitoring contained 89 reports of Urinary incontinence and two reports of Incontinence associated with the use of trazodone. These were disproportionally with a combined ROR (95% CI) of 4.5 (95% CI 3.7 – 5.5) (see table 1).

Table 1. Reports of urinary incontinence associated with trazodone in the WHO database

Drug	MedDRA PT	Number of reports	ROR (95% CI)
Trazodone	Urinary incontinence	89	5.1 (4.1 - 6.2)
	Incontinence	2	-
	Combined	91	4.5 (3.7 - 5.5)

The reports of urinary incontinence for trazodone in the Eudravigilance database are given in table 2.

Table 2. Reports of urinary incontinence associated with trazodone in the Eudravigilance database

Drug	MedDRA PT	Number of reports	ROR (95% CI)
Trazodone	Urinary incontinence	15	2.3 (1.4 – 3.9)
	Incontinence	4	2.0 (0.8 – 5.5)
	Combined	19	2.0 (0.8 – 5.5)
	Combined	19	2.3 (1.4 – 3.6)

### Prescription data

The number of patients using trazodone in The Netherlands is shown in Table 3.

Table 3. Number of patients using selective trazodone in the Netherlands between 2007 and 2011 [5].

Drug	2007	2008	2009	2010	2011
trazodone	9,579	10,132	10,986	11,965	12,857

### Mechanism

A possible explanation of urinary incontinence while using trazodone could be an agonistic effect on the 5HT<sub>4</sub> receptors in the bladder dome. This activation causes contraction of the bladder [6,7]. Anticholinergic effects and inhibition of the serotonin reuptake in the central nervous system could lead to urinary retention [8,9]. Somnolence and sedation related to trazodone [1] might further contribute to urinary incontinence.

### Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received three reports of urinary incontinence associated with the use of trazodone. In the WHO database there are 91 cases present of (urinary) incontinence associated with trazodone. In the Lareb-, WHO- and Eudravigilance databases the association is disproportionally present. The FDA SmPC also mentions urinary incontinence as an infrequent occurring adverse event in the section "Clinical Studies Experience" and urinary incontinence is mentioned in the section "Postmarketing Experience" [3].

In all the three cases from Lareb there were clear positive dechallenges, after the trazodone was withdrawn, the patients recovered.

Weak aspects of the associations were the differences in latencies of 6 hours, 31 days and within 10 days. There were also different dosages of 100 mg per day, 100 mg per day and 50 mg before the night. All cases were women. There was a great variety in ages 88, 48 and 62 years.

In case A the indication was mentioned, which was depression and sleeplessness. There is a strong association between urinary incontinence and depression [10] so confounding by indication might have been present. The concomitant medication of this patient, dipyridamol and carbasalate calcium might imply that the patient had a history of cerebrovascular disease / stroke which are linked to detrusor overactivity with urge urinary incontinence from decreased central control of urgency and bladder sensation and to impaired function and cognition [10]. These factors might have played a role in the urinary incontinence, but this does not explain the positive dechallenge. The patient also used oxazepam. Sedative hypnotics are linked to sedation, delirium and immobility [11]. These factors might also have played a role in the urinary incontinence in this patient.

The medical history of the patient in case B indicated "surgery because of inflammation of urinary duct 29 years ago". It was not mentioned whether the patient experienced any urinary complaints since then. Indication and co-medication were not mentioned.

The patient in case C also used lorazepam, what might have played a role in the urinary incontinence [11]. The indication and medical history were not mentioned.

Furthermore urinary incontinence is frequently occurring [2,12] and in older persons a multifactorial syndrome is more likely instead of a single identifiable cause [2].

Although confounding by indication, by concomitant medication and by medical history could not be ruled out, and although there was a great variety in latencies, the association was disproportionally present in both the Lareb- and WHO database and supported by the FDA SmPC text and there were positive dechallenges in all cases. For this reason, it is suggested that trazodone might have a causative role in the occurrence of urinary incontinence.

- Further investigation of the information of the marketing authorization holders is advisable.

## References

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*This signal has been raised on July 2013. 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](http://www.cbgmeb.nl/cbg/en/default.htm) or the responsible marketing authorization holder(s).*