

## Mirtazapine and urinary retention

### Introduction

Mirtazapine is an antidepressant that has been approved for the Dutch market since March 1994. It is indicated for the treatment of *episodes of major depression* [1]. By blocking the presynaptic  $\alpha_2$  receptors, mirtazapine increases the noradrenergic and serotonergic (5-HT) neurotransmission. The enhancement of 5-HT neurotransmission is specifically mediated via 5-HT<sub>1</sub> receptors, since 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors are blocked by mirtazapine. The sedative effect of mirtazapine is explained by the strong blockage of the histamine H<sub>1</sub> receptor. According to the SmPC of mirtazapine, the drug has practically no anticholinergic activity [1].

The current observation describes the possible association between mirtazapine and urinary retention. Urinary retention is a condition in which impaired emptying of the bladder results in the retention of residual urine. It can be categorized into 'chronic' or 'acute'. Chronic urinary retention develops over a long period with development of a painless, palpable bladder. Risk factors are detrusor hypocontractility, chronic bladder outlet obstruction or neurological bladder dysfunction. In acute urinary retention, the symptoms develop acute and the retention itself is often painful and requires treatment by urinary catheterization. It occurs most frequently in men over age 60 and is often the result of BPH [10,19].

### Reports

Until October 10<sup>th</sup> 2013, the Netherlands Pharmacovigilance Centre Lareb had received 6 reports concerning urinary retention associated with the use of mirtazapine, see Table 1. Additionally, Lareb received 2 reports of "micturition disorder" associated with the use of mirtazapine, see Table 2. One patient had a dropwise micturition (G) and the other H had the urgency to urinate but there was no micturition (H).

All reports were made by healthcare professionals. The age of the patients varied from 24 to 90 years with a median of 56 years. A positive dechallenge was reported 4 times (A, B, D, F). With the exception of patient C, the time to onset varied from 8 hours till 7 days after start of mirtazapine with a median of 1 day. In two patients (C, E) besides mirtazapine, another suspected drug was reported: for patient C venlafaxine and patient E carbidopa/levodopa. For both of these drugs urinary retention is mentioned in the SmPC [3,4].

Table 1. Reports of urinary retention associated with the use of mirtazapine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 30234 M, 51-60 years General Practitioner	mirtazapine tablet 30mg	acetylsalicylic acid, diltiazem	urinary retention	not reported discontinued recovering
B 38053 M, 41-50 years Specialist	mirtazapine tablet 30mg depressive episode		urinary retention	2 days discontinued recovered

doctor				
C 48575 M, 70 years and older Specialist doctor	mirtazapine tablet 30mg depression, venlafaxine tablet 75mg neurotic depression	oxazepam, flurazepam	urinary retention	mirtazapine: 1 year no change  venlafaxine: 1 day discontinued recovered
D 108030 M, 51-60 years Specialist doctor	mirtazapine tablet 15mg depression	clemastine, venlafaxine , bisoprolol , simvastatin, gabapentin, paracetamol/codeine	urinary retention	8 hours after increase of the dosage discontinued recovered
E 142843 M, 70 years and older Specialist doctor	carbidopa/levodopa tablet 100/25mg parkinson's disease, mirtazapine tablet 15mg mood swings	tamsulosine	bladder retention	mirtazapine: 7 days no change  carbidopa/ levodopa: 6 years no change unknown
F 154911 M, 70 years and older General Practitioner	Mirtazapine tablet 15 mg depression		urinary retention	1 day discontinued recovered

Patient A used paroxetine in the past and developed urinary retention. For this drug this is a known ADR [18]. Mirtazapine was prescribed because urinary retention was not a known ADR for this drug.

Patients B is known with micturition difficulties and patient D and E are known with BPH. For patient D it was reported that he never experienced urinary retention until increase of the dosage of mirtazapine of 7,5 mg to 15 mg once a day. In patient E the urinary retention is treated with catheterization. For the other reports no information about treatment was given.

For patient C the urinary retention started 1 day after start of venlafaxine and recovered after withdrawal of venlafaxine. In patient D venlafaxine is reported as concomitant medication. In this patient the urinary retention started 8 hours after increase of the dosage of mirtazapine and recovered after withdrawal of mirtazapine.

Table 2. Reports of micturition disorder associated with the use of mirtazapine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
G 15706 F, 21-30 years General Practitioner	mirtazapine tablet 15 mg depression	ethinylestradiol/ desogestrel, clobetason	micturition disorder	12 hours dose reduced unknown
H 38053 M, 41-50 years General practitioner	mirtazapine tablet 30mg		micturition disorder, leg pain	1 day no change unknown

## Other sources of information

### SmPC

Urinary retention is not mentioned in section 4.8 of the SmPC of mirtazapine. In section 4.4 (special warnings and precautions before use) of the SmPC is mentioned that mirtazapine should be used with caution in patients with micturition disorders (although there is little chance of problems with mirtazapine because of the very weak anticholinergic activity) [1].

### Literature

Oulis et al. described a 85-year-old male who experienced urinary retention within 24 hours of initiating treatment with mirtazapine 15 mg/day for depression. Within 24 hours of starting mirtazapine he developed acute urinary retention requiring catheterization. Mirtazapine was discontinued and within 24 hours his urinary retention subsided. One week later, a rechallenge demonstrated the same pattern of urinary retention [5].

In contrast to this case report, Lenze et al. described a case of reversal of SSRI-associated urinary retention with mirtazapine augmentation. This case concerns a 30-year-old female who developed urinary retention after administration of citalopram. After mirtazapine augmentation the urinary retention recovered. The authors state that because the variable affinity of mirtazapine for 5-HT receptors, it may reverse SSRI-associated urinary retention [6].

### Databases

On October 11<sup>th</sup> 2013, the database of Lareb, the WHO and Eudravigilance contained respectively 6, 118 and 88 reports of urinary retention associated with the use of mirtazapine. The reporting odd ratio (ROR) for all these databases is disproportional, see Table 3.

Table 3. Number of reported cases of urinary retention associated with the use of mirtazapine in the dataset of Lareb, the WHO and Eudravigilance

Drug	Number of reports	ROR (95% CI)
mirtazapine	Lareb: 6	3.6 (1.6-8.0)
	WHO: 118	4.9 (4.1-5.9)
	Eudravigilance: 88	4.3 (3.5- 5.3)

### Prescription data

The number of mirtazapine users in the Netherlands is shown in table 4.

Table 4. Number of patients using mirtazapine in the Netherlands between 2008 and 2012 [7]

	2008	2009	2010	2011	2012
Mirtazapine	92,152	93,596	98,289	102,940	105,890

### Mechanism

The act of micturition follows a very complex mechanism. There are two sphincters (the internal and external urethral sphincters) in the urethral wall that prevent urine loss as the bladder fills. The storage function of the bladder is controlled by the sympathetic nervous system including bladder relaxation by the binding of

noradrenaline to the  $\beta_3$ -adrenergic receptors on the detrusor smooth muscle cells and internal sphincter contraction by stimulating  $\alpha_1$  receptors on the internal sphincter. The external sphincter is under control of the Onuf's nucleus. Both  $\alpha$  and 5-HT<sub>2</sub> receptors are located in the Onuf's nucleus and they facilitate the storage reflex. The serotonergic activity facilitates urine storage by enhancing the sympathetic reflex pathway and inhibiting the parasympathetic voiding pathway. When the bladder volume reaches a certain capacity a trigger signal is sent to the cerebral cortex and the desire to micturate is perceived. With the decision to void, both the internal and the external sphincter relax and the bladder detrusor muscle contracts. Bladder contraction is a result of the binding of acetylcholine to muscarinic M<sub>3</sub> receptors on the detrusor smooth muscle cell [2].

By its noradrenergic activity mirtazapine can theoretically increase bladder relaxation by the binding of noradrenaline to the  $\beta_3$ -adrenergic receptors. Further, anticholinergic activity can reduce bladder contraction by preventing acetylcholine to bind to muscarinic M<sub>3</sub> receptors. The SmPC of mirtazapine describes that the drug has practically no anticholinergic activity. The database of the Psychoactive Drug Screening Program demonstrates some anticholinergic M<sub>3</sub> receptor activity [8].

Another possible mechanism involves glutamate. Glutamate functions as an excitatory transmitter in the micturition reflex pathway in the brain [10]. 5-HT receptors have an effect on the glutamate release: 5-HT<sub>2A</sub> receptors stimulate the glutamate release while 5-HT<sub>1A</sub> receptors inhibit the glutamate release [9]. Mirtazapine specifically acts on the 5-HT<sub>1</sub> receptors and blocks 5-HT<sub>2</sub> receptors. This would theoretically result in inhibition of glutamate release which may subsequently lead to loss of micturition reflex.

#### *Class effect*

Mirtazapine belongs to the group of 'other' antidepressants. Within this group, the drugs mianserin and trazodone have similar actions. Both drugs block  $\alpha_1$  and 5-HT<sub>2</sub> receptors. Urinary retention is not described in the SmPC of mianserin or trazodone [20,21]. The SmPC of mianserin describes micturition disorders [20]. Lareb received no reports of urinary retention associated with the use of mianserin or trazodone. The database of the WHO contains 29 reports of urinary retention associated with the use of mianserin and 50 associated with the use of trazodone resulting in a ROR of respectively 3.1 (95%CI 2.1-4.4) and 2.8 (95% CI 2.1-3.7). Furthermore, urinary retention is described associated with these drugs in literature [23]. A possible class effect cannot be excluded.

### **Discussion and conclusion**

Lareb received 6 reports of urinary retention and 2 reports of micturition disorder associated with the use of mirtazapine. One case (C) is strongly confounded by the use of venlafaxine. In another case (D) venlafaxine was reported as concomitant medication. In this patient the urinary retention started 8 hours after increase of the dosage of mirtazapine and recovered after withdrawal of mirtazapine. This makes a causal relationship with mirtazapine likely. Most reports concern older men in which you would expect urinary retention to occur more frequently. For three patients micturition difficulties or BPH was reported as a comorbidity. Although urinary retention may occur spontaneously in patients with micturition difficulties, a positive dechallenge for two of these patients points towards a causal relation with the use of mirtazapine. Overall, a positive

dechallenge was reported 4 times. With exception of patient C, the time to onset corresponds between the several reports.

This association is disproportionately present in the database of Lareb, the WHO and Eudravigilance. There are several possible mechanism of how mirtazapine could cause urinary retention. Mirtazapine its noradrenergic and anticholinergic activity as well as its possible effect on the glutamate release may all contribute to the occurrence of the urinary retention.

- Urinary retention should be mentioned in the SmPC of mirtazapine.

#### References

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*This signal has been raised on February 2014. 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).*