**Background** The serotonin/noradrenaline uptake inhibitor duloxetine has been shown to be effective in the medical treatment of stress urinary incontinence (SUI) in women.

**Aim** To review the safety and tolerability of duloxetine with SUI.

**Methods** A systematic Medline search for the key word ‘duloxetine’ was performed, and abstracts from recent international gynaecological and urological meetings were also considered.

**Results** Various unpleasant adverse effects exist, among which nausea is the most frequent, but is mild to moderate and transient in most cases. Dose escalation upon initiation of treatment improves the tolerability of duloxetine. The use of duloxetine appears safe as it lacks the cardiovascular adverse effects of older amine reuptake inhibitors.

**Conclusions** Duloxetine has an acceptable safety profile. Dose escalation combined with patient counselling on the intensity and transient nature of adverse effects may help to further improve the benefit/tolerability ratio of duloxetine in the treatment of SUI.

**Keywords** Adverse effect, duloxetine, stress urinary incontinence, nausea.

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**Introduction**

Stress urinary incontinence (SUI) is a frequent condition in women of all ages. The prevalence of SUI in community-dwelling Dutch women aged 45–70 years is 29% and that of mixed incontinence is 23%. The treatment of SUI has long been considered to be a domain of physical therapy and surgery. However, recently, the mixed serotonin/noradrenaline reuptake inhibitor duloxetine has been introduced, and in 2004, the European Medicines Agency has approved it for the treatment of women with moderate to severe SUI. It has also been approved for the treatment of major depression, and furthermore, it is effective in alleviating neuropathic pain. The efficacy of duloxetine relative to placebo in the treatment of moderate to severe SUI has consistently been demonstrated in various controlled studies either alone or in combination with pelvic floor muscle training. Only one study in women with SUI failed to demonstrate a statistically significant benefit of duloxetine relative to placebo; the results of this study are difficult to compare with those of the other studies because the degree of SUI was only mild to moderate, because urge-predominant mixed incontinence was not excluded and because a different primary endpoint, i.e. quality of life, was used. As with almost any other treatment, the benefits of duloxetine in the treatment of SUI can be accompanied by adverse events. The present manuscript summarises the tolerability and safety data regarding the use of duloxetine in SUI and compares them with data in other indications (depression, neuropathic pain). Subsequently, we propose strategies to minimise adverse effects to obtain an optimal risk/benefit ratio.

**Frequency and severity of adverse events in the treatment of SUI**

Treatment-emerging adverse events in the use of duloxetine in SUI have been described in the reported pivotal studies, which led to its registration by the European Medicines Evaluation Agency. Adverse events were elicited by non-probing inquiry at each visit and recorded regardless of perceived causality. An event was considered a treatment-emergent adverse event if it occurred for the first time or worsened during the double-blind treatment period. Serious adverse events were defined according to the recommendations of the International Conference on Harmonization and included serious adverse events resulting in hospitalisation, permanent disability, cancer, a threat to life, death, and those deemed serious for any other reason by the investigator. An integrated
safety analysis has been carried out by combining data from all these trials in one database as reported recently.\textsuperscript{15}

The incidence of adverse events associated with duloxetine 40 mg twice daily treatment within individual studies ranged between 73 and 81%, whereas corresponding incidences with placebo ranged between 50 and 64% ($P < 0.05$ within each study).\textsuperscript{7–10} Adverse events that occurred in at least 5% of women and more often than placebo in those studies are summarised in Table 1. Other adverse effects occurring in at least 1% of duloxetine-treated women with SUI and more often than with placebo included vomiting (4.8%), increased sweating (4.5%), anorexia (3.9%), dyspepsia (3.0%), tremor (2.7%), lethargy (2.6%), decreased appetite (2.3%), sleep disorder (2.2%), anxiety (1.9%), decreased libido (1.5%), anorgasmia (1.5%), pruritus (1.4%), weakness (1.3%), blurred vision (1.3%), nervousness (1.1%) and thirst (1.1%). This adverse event profile in the pivotal studies is largely consistent with that observed in later studies with duloxetine in women with SUI\textsuperscript{11,12,14} and with that seen in patients receiving duloxetine for the treatment of depression or diabetic neuropathic pain in doses ranging from 40 to 120 mg daily.\textsuperscript{6,16–21} Moreover, this adverse effect profile is also consistent with that of other amine reuptake inhibitors used in urological indications or in patients with depression.\textsuperscript{22} Therefore, it can be assumed that the adverse events associated with duloxetine treatment are largely related to its mechanism of action at the molecular level, i.e. a mixed inhibition of neuronal serotonin and noradrenaline reuptake.\textsuperscript{23,24}

Adverse events leading to study discontinuation were observed in 15–24% of duloxetine-treated women compared with 2–5% of women on placebo.\textsuperscript{7–10} Specific numbers for individual adverse effects are shown in Table 1. The overall incidence of serious adverse events did not differ significantly between duloxetine and placebo (Table 2); moreover, no serious adverse event resulted in chronic sequelae.\textsuperscript{25} A single death reported during these studies was not attributed to study medication (a 70-year-old woman randomised to duloxetine died from a multifocal cerebrovascular accident). Therefore, it can be concluded that adverse events associated with the use of duloxetine in women with SUI relate to tolerability rather than safety. This compares favourably with the adverse effect profile of many older inhibitors of serotonin and/or noradrenaline uptake such as the tricyclic antidepressants as studied in other urological or in psychiatric indications.\textsuperscript{22}

### Table 1. Treatment-emerging adverse events observed with duloxetine or with placebo in studies on women with SUI

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (%)</th>
<th>Duloxetine (%)</th>
<th>Study withdrawal in duloxetine group (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>3.7</td>
<td>23.2</td>
<td>3.1–6.4</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1.5</td>
<td>13.4</td>
<td>0.0–0.4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3.8</td>
<td>12.7</td>
<td>0.0–2.6</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.9</td>
<td>12.6</td>
<td>0.7–2.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>2.3</td>
<td>11.0</td>
<td>0.0–0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>6.6</td>
<td>9.7</td>
<td>0.3–1.4</td>
</tr>
<tr>
<td>Dizziness (except vertigo)</td>
<td>2.6</td>
<td>9.5</td>
<td>0.7–3.6</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0.1</td>
<td>6.8</td>
<td>0.0–2.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>2.7</td>
<td>5.1</td>
<td>0.0–0.4</td>
</tr>
</tbody>
</table>

Data represent % of women reporting a given adverse effect and are from the aggregate analysis of the pivotal studies for the use of duloxetine in SUI ($n = 958$ women on duloxetine 40 mg twice daily and $n = 955$ women on placebo). Study withdrawals due to a given adverse event while on duloxetine treatment are also % of women, but range of reported frequencies in the various studies rather than aggregate means are presented.

### Table 2. Serious adverse events observed with duloxetine or with placebo in studies on women with SUI

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (%)</th>
<th>Duloxetine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total serious adverse events</td>
<td>1.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Other</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Death</td>
<td>0.0</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Data represent % of women reporting a given adverse effect and are from the aggregate analysis of the pivotal studies for the use of duloxetine in SUI ($n = 958$ women on duloxetine 40 mg twice daily and $n = 955$ women on placebo).
Duloxetine is also used to treat patients with major depressive disorders. Therefore, it has been investigated whether duloxetine may alter mood in women with SUI. An analysis of the four double-blind, placebo-controlled duloxetine SUI studies (involving 1913 women) and their uncontrolled long-term follow up (involving 1877 women) did not provide any evidence for an induction of mania or hypomania. Thus, one case of euphoria has been observed in women with SUI treated with duloxetine, whereas one case each of euphoria and mania have been seen in corresponding women on placebo. Moreover, there was only a low incidence of mania, euphoria or elevated mood in long-term, open-label follow up. No case of study discontinuation due to mood elevation has been reported in women with SUI. This is in line with the general observation that monoamine uptake inhibitors improve mood in depressed but not in mentally healthy people.

**Suicide and suicidal behaviour**

Recent discussions have highlighted the possibility that serotonin uptake inhibitors used in the treatment of depression may induce suicidal behaviour, particularly in children. It should be pointed out that duloxetine is not licensed for the use in paediatric patients. Suicidal behaviour has not been reported in the published studies with duloxetine in the treatment of SUI. Since suicide fortunately is a rare event, the available data nevertheless have limited statistical power to firmly exclude such behaviour. Therefore, the duloxetine label states 'As with other drugs with similar pharmacological action (antidepressants), isolated cases of suicidal ideation and suicidal behaviours have been reported during duloxetine therapy or early after treatment discontinuation. Physicians should encourage patients to report any distressing thoughts or feelings at any time'. In the absence of specific data pointing to a risk for suicidal behaviour in women receiving duloxetine for the treatment of SUI, this label information should be considered a general note of caution.

**Urogenital adverse effects**

As the administration of duloxetine to women with SUI is intended to increase bladder outlet resistance, the possibility exists that this may lead to obstructive voiding symptoms or even acute urinary retention. However, only 3 (2 men and 1 woman) of 4719 duloxetine-treated patients discontinued treatment because of obstructive voiding symptoms in a meta-analysis of nine studies in patients with depression and four studies in patients with SUI; acute urinary retention requiring catheterisation was not observed in any patient. This is in line with the proposed mechanism of action, where duloxetine works mainly as an enhancer of endogenous glutamate effects and hence only during the storage phase of the micturition cycle.

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With regard to other genitourological adverse effects, it is well established that serotonin reuptake inhibitors can have adverse effects on sexual function; some of them are even recommended for the off-label treatment of premature ejaculation. Therefore, it is not surprising that duloxetine was associated with decreased libido, loss of libido or anorgasmia in a small number of patients but more often than with placebo (see above). Similar findings have been obtained in patients with depression treated with duloxetine, whereas direct comparative studies indicate that it may occur less frequently than with other serotonin uptake inhibitors such as paroxetine.

**Cardiovascular effects**

Based upon the role of noradrenaline and serotonin in the control of cardiovascular function, possible adverse effects of inhibiting their uptake on the cardiovascular system should be considered. These could be related to blood pressure control and/or cardiac rhythm. In small clinical pharmacology studies in healthy volunteers, minor and inconsistent elevations of blood pressure and/or heart rate have been reported. A small (i.e. less than 3 bpm) but statistically significant increase in heart rate upon duloxetine compared with placebo treatment was also reported in two studies in patients with SUI. Duloxetine-associated blood pressure elevations in the treatment of SUI were reported as ‘clinically insignificant’ or absent. A small but statistically significant increase in heart rate (1.6 versus –0.6 bpm) and in systolic blood pressure (1.0 versus –1.2 mmHg) was found in a meta-analysis of duloxetine studies in patients with depression. However, patients with elevated blood pressure prior to duloxetine treatment, if anything, had lowered values upon duloxetine exposure. Older uptake inhibitors, particularly the tricyclic antidepressants, have been associated with arrhythmias, which in some cases are life threatening. On the other hand, no arrhythmogenic potential has been observed with duloxetine. Specifically, no increases of heart-rate-corrected QT intervals were observed in patients with SUI, patients with depression or healthy people. Even at clearly supratherapeutic doses of 200 mg twice daily, QT prolongation was not observed. These data demonstrate that duloxetine has little effect on the cardiovascular system and specifically lacks the arrhythmogenic potential of older amine uptake inhibitors.

**Other adverse effects and drug–drug interactions**

Significant increases in several hepatic enzymes such as alkaline phosphatase, alanine aminotransferase and aspartate aminotransferase were reported upon duloxetine treatment, but all increases were within the normal range. As with any drug, allergic reactions are possible towards duloxetine or any of the excipients contained in the drug. Based upon the present data, however, such reactions appear rare.

Finally, it should be considered that adverse events can occur due to comediations. Such drug–drug interactions can be pharmacodynamic, i.e. due to overlapping functional effects of the two drugs, or pharmacokinetic, i.e. due to alterations of the available concentrations of drug A by concomitantly administered drug B. A classic pharmacodynamic drug–drug interaction of all serotonin uptake inhibitors is the induction of a serotonin syndrome upon concomitant use of an irreversible, non-selective monoamine oxidase inhibitor such as tranylcypromine. Since serotonin uptake and metabolism by monoamine oxidase are the two main physiological mechanisms for its clearance from the synaptic cleft, concomitant inhibition of both mechanisms can yield excessive local serotonin concentrations, which can potentially be lethal. Fortunately, such monoamine oxidase inhibitors are used only rarely as back-up drugs in psychiatry; hence, such interactions are not likely to occur. However, doctors prescribing duloxetine should be aware that this combination is a contraindication.

With regard to pharmacokinetic drug–drug interactions, it should be considered that CYP 1A2 is a main pathway of duloxetine metabolism. The concomitant use of drugs that inhibit CYP 1A2, such as the antidepressant fluvoxamine or the antibiotics enoxacine and ciprofloxacin, can markedly increase duloxetine concentrations in the body. Therefore, such combinations are also considered contraindications for the use of duloxetine. Among these potentially interacting drugs, ciprofloxacin, which is often used in the treatment of urinary tract infections, is probably most likely to be an issue for women with SUI. If a woman is on a current acute course of ciprofloxacin, it appears prudent to finish this course and only start duloxetine treatment of SUI thereafter. If a woman requires ciprofloxacin chronically or if a woman currently receiving duloxetine needs treatment of an acute urinary tract infection, alternative forms of antibiotic treatment should be considered.

**Summary**

The available data show that the adverse effect profile of duloxetine in the treatment of SUI is typical of serotonin/noradrenaline uptake inhibitors used in other urological or in psychiatric indications. However, in contrast to older uptake inhibitors, serious adverse events, particularly those related to the cardiovascular system such as arrhythmias, are rare with duloxetine. Unpleasant adverse effects such as nausea and dizziness may be minimised if a dose-escalation regimen is used at the beginning of treatment. Moreover, overexposure to duloxetine can be avoided if contra-indications regarding concomitant treatment with drugs inhibiting CYP 1A2 are respected. Finally, we propose that the patient compliance can be enhanced if they are adequately counselled.
regarding the mild to moderate and transient nature of adverse effects such as nausea upon initiation of treatment.

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References


