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ORIGINAL REPORT

Selective serotonin reuptake inhibitor-induced urinary incontinence

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SUMMARY

Purpose Irrespective of its cause, urinary incontinence is a medical condition seriously affecting quality of life and is increasingly recognized. In this study, we examined the association between the use of selective serotonin reuptake inhibitors (SSRIs) and urinary incontinence.

Methods A retrospective follow-up study among starters with an SSRI was performed to estimate the relative and absolute risk for urinary incontinence associated with SSRI use. Data came from the PHARMO database, which includes information on drug dispensing for approximately 450 000 residents living in eight Dutch cities. All patients initially using an SSRI between 1994 and 1998 were selected. The frequency measures for urinary incontinence were estimated by using prescription sequence analysis, where initiation of spasmolytic drugs or absorbent products was used as a measure for urinary incontinence. Besides crude incidence density calculations, Andersen–Gill's model was used in order to control for possible confounding factors and time varying covariates.

Results A total of 13 531 were identified as first time users of an SSRI. Compared to non-exposure, the incidence density ratio for urinary incontinence during SSRI exposure was 1.75 (95% CI 1.56–1.97). Overall, compared to baseline, SSRI use caused 14 extra cases of urinary incontinence per 1000 patients treated per year; the elderly were more at risk resulting in 60 extra cases per 1000 patients per year. The adjusted relative risk for urinary incontinence due to SSRI use was 1.61 (95% CI 1.42–1.82); the risk for sertraline users was 2.76; 95% CI 1.47–5.21).

Conclusions Exposure to SSRIs is associated with an increased risk for developing urinary incontinence, which can be explaned pharmacologically. Approximately 15 out of 1000 patients treated per year with an SSRI developed urinary incontinence. The elderly and users of sertraline are at the highest risk. Copyright © 2002 John Wiley & Sons, Ltd.

KEY WORDS — SSRIs; antidepressants; urinary incontinence; prescription sequence analysis; Cox proportional hazards; Andersen–Gill model; pharmacoepidemiology; adverse drug effects

INTRODUCTION

Although tricyclic antidepressant drugs (TCAs) have been widely used for decades, in daily clinical practice they often have to compete with the selective serotonin reuptake inhibitors (SSRIs). In general, the various SSRIs appear to be equivalent in effectiveness in patients treated for depression or anxiety disorders.[1] Switching to SSRIs is often promoted because of the better tolerability of these agents and the undesirable suggested side-effects of the TCAs.[2] Anticholinergic and cardiovascular problems of TCAs are the most troublesome and have been well recognized.

SSRIs are suggested to have no or substantially less affinity for adrenergic, cholinergic, or histaminergic receptors and are therefore devoid of the adverse effects associated with their blockade.[3] Adverse effects

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of the SSRIs are attributed to the pharmacological action mediated via various serotonergic receptors. These adverse effects include nausea and vomiting, agitation, sexual dysfunction, and hyponatraemia.[4,5]

Recently, two case reports have been published, which described a possible association between the use of serotonergic drugs and the occurrence of urinary incontinence.[6,7] Urinary effects of SSRIs are expected to be different from TCAs, which through their anticholinergic and noradrenergic effects can reverse incontinence.[8]

Urinary incontinence is a common problem in the community, and is increasingly recognized as an important medical condition, which seriously affects quality of life.[9] It is estimated that it affects about 15% per lifetime of the Dutch population.[10]

Drug treatment can contribute to the onset of urinary incontinence by sedative effects or direct pharmacological action disrupting the normal physiological bladder function.[11] The major pharmacological action of SSRIs is considered to be inhibition of a specific neurotransmitter transport protein, which transports serotonin back into the presynaptic neuron.[12] Thus, serotonin reuptake inhibition by SSRIs can indirectly cause stimulation of all available subtypes of the serotonin receptor. There is evidence that serotonin can indirectly potentiate cholinergic neuromuscular transmission in isolated human detrusor muscle by activation of 5HT4 receptors.[13,14] It has been suggested that this pharmacological reaction can lead to minor urinary leakage or incontinence.[15]

The objective of the present study was to investigate a possible association between the use of SSRIs and the occurrence of urinary incontinence, and to establish the absolute risk of this adverse drug reaction.

METHODS

Design

A retrospective follow-up study was conducted using Petri's classical concept of prescription sequence analysis (PSA) to quantify the risk for SSRI-induced urinary incontinence.[16,17] PSA is based on the observation that side-effects themselves may induce the prescription of another medication ('proxy-drug'). In such situations analysis of aggregated drug histories of individual patients can reveal an unusual frequency of a particular drug sequence.

Setting

Prescription data for this study were obtained from the PHARMO record linkage system affiliated with Utrecht University, the Netherlands. The system was designed in 1985 to provide relevant demographic and prescription data at individual level for five medium-sized cities in the Netherlands from 1985 up to 1989. Since 1990 it has been further updated, covering a total of six cities ($n = 300\,000$), and from 1993 up to 1998 covering eight cities ($n = 450\,000$). This database has been described in detail elsewhere.[18]

Computerized drug dispensing histories from Dutch pharmacies are virtually complete and include data concerning the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and the estimated duration of drug use. In the Netherlands there is a strong pharmacy–patient liaison for reimbursement of prescription drugs, a high degree of computerization, the use of standardized classification and coding systems, and a strong commitment by pharmacists to the surveillance of medication.

Study population and exposure definition

In this study all drug-dispensing histories were collected from patients who initially received a prescription for paroxetine, fluoxetine, fluvoxamine or sertraline from January 1994 to December 1998. The first prescription of an SSRI was defined as a prescription for an SSRI during the study period and no prescription for the same drug in the previous 4 months. In the Netherlands medicines are dispensed for a maximum of 3 months, with the exception of oral contraceptives. The theoretical duration of exposure was calculated using information on dispensing date, total supply, and dosage regimen. Patients were considered to be exposed to an SSRI for the theoretical duration of exposure plus 14 days; for fluoxetine 30 days were added to control for residual effects due to slow elimination of its metabolites. For all patients at least 90 days of follow-up before the first dispensing of the SSRI was required for inclusion in the study.

Non-exposure time *before* starting with an SSRI was defined as the period between cohort entry and SSRI initiation. Non-exposure time *after* SSRI use was defined as the period after SSRI exposure until the last date a patient filled a prescription. All drug use was coded according to the Anatomical Therapeutic Chemical (ATC) classification index of the World Health Organization.

Endpoint definition

Incident cases of urinary incontinence or leakage were identified by two proxys: (a) by initial use of a

spasmolytic agent (oxybutinine, tolterodine, or flavoxate) and, (b) initial use of 30 or more units of incontinence materials (incontinence-pads, protective sheets, or other incontinence wear) in a 3-month period, which ever came first. The incidence of urinary incontinence was defined as the number of endpoints per 1000 patients treated per year.

Potential confounders

In order to adjust for factors that may confound the association between the use of SSRIs and the occurrence of urinary incontinence, additional information on concomitant medication[†] with a possible effect on the continence status of a patient was collected. To define concomitant drug use the same definition was used as for the SSRIs. Indicators for co-morbidity of prostatic nature (benign prostatic hyperplasia (BPH) or prostate cancer surgery) were use of the selective alpha-adrenoreceptor antagonists (alfuzosin, finasteride, terazozin, and tamsulosin) or use of the (anti)-hormones, like flutamide or nilutamide.

Statistical analysis

The data were analysed in two ways; firstly, incidence density rates and ratios were crudely calculated in the total study population and secondly, a multiple time-dependent model was used to calculate more secure estimations of the risk for urinary incontinence during SSRI use and to control for potential confounding factors.

Incidence densities during the exposed and non-exposed periods were calculated by dividing the number of endpoints by the total follow-up time of the corresponding period. The incidence of an endpoint during SSRI use (Id) was compared to the incidence in the period before (Ib) and after SSRI (Ia) use. The relative risk (RR) was expressed as the incidence density ratio (IDR), in which the unexposed period (Ia + Ib) was taken as a baseline risk.

Adjusted relative risks and 95% confidence intervals were calculated using a multiplicative intensity model, also known as the Andersen–Gill model.[19] A standard Cox proportional hazard model could not be applied because patients entered the study at different calender times. The Andersen–Gill model takes into account the fact that at time zero not every patient is as yet under observation and uses time-dependent covariates. The data were censored from both the left and the right. In this multiple model adjusted estimates were calculated and controlled for potential confounding effects such as concurrently used medication known to have a possible effect on the patient's continence status.

Next, we only considered the period in which SSRI medication was used. Survival analysis (Kaplan–Meier) was used to estimate the cumulative probability of urinary incontinence for the different serotonergic agents used. Cox proportional hazard analysis was used to estimate the hazard ratios for urinary incontinence associated with individual SSRIs and to establish important risk factors, which might predispose to this complication. Hazard ratios can be interpreted as relative risks in this analysis.

RESULTS

The final study population included 13 531 patients who met the criteria for starting an SSRI during the study period (Table 1). Patients were predominantly female (68%). The mean age of the study population was 48 years (SD 17 years); age did not differ between sexes. The majority of the study patients were treated with paroxetine (52%). The mean exposure and non-exposure time per patient was 354 days and 3.4 years, respectively.

Table 1. Baseline characteristics of the study population ($n = 13\,531$)

Characteristics	Number of patients (%)
Sex	
Male	4315 (32%)
Female	9216 (68%)
Age (years), mean 48 ± 17	
18–34	3404 (25%)
35–49	4590 (34%)
50–64	2830 (21%)
≥ 65	2707 (20%)
Number of SSRI drug users	
Paroxetine	7060 (52%)
Fluoxetine	3163 (23%)
Fluvoxamine	2966 (22%)
Sertraline	342 (3%)
Mean observation 'exposed period'	354 days/patient
Mean observation 'non-exposed period'*	3.4 years/patient

*Period before and after SSRI exposure.

[†]Anti-Parkinsonian drugs, antiepileptics, antipsychotics, hyponotics, benzodiazepine, laxatives, anti-hypertensive drugs, misoprostol, metoclopraminde, gynecological anti-infection drugs, muscle relaxants, cough- and coldmedication, cisapride, opioid analgesics.

Table 2. The incidence density (ID) for urinary incontinence while exposed/not exposed to SSRIs, and the relative risk (RR) expressed as incidence density ratio (IDR)

All patients	Endpoints urinary incontinence	Follow-up period (years)	ID/1000 years	IDR	95% CI
During versus before					
Before SSRI	499	24 334	21	Reference	
During SSRI	422	13 108	32	1.57	1.38–1.79
During versus after					
After SSRI	337	21 205	16	Reference	
During SSRI	422	13 108	32	2.03	1.76–2.34
During versus before + after					
Before + after SSRI*	836	45 539	18	Reference	
During SSRI	422	13 108	32	1.75	1.56–1.97

*Non-exposed period.

In total there were 1278 starts of a spasmolytic agent or urinary protective garment. Table 2 presents the number of patients with an incontinence period, the incidence density while exposed to SSRIs compared to before and after SSRI use, and the incidence density ratio for the exposed period compared to non-exposed. Overall, the period before and after SSRI use are merged into one period 'non-exposed' because there was no significant difference between the two periods.

The incidences of urinary incontinence during the exposure and non-exposure period were 32 cases and 18 cases per 1000 patient treated per year, respectively, which is in accordance with an IDR of 1.75 (95% CI 1.56–1.97). Overall, the absolute risk difference, which provides information about the absolute risk attributed to the exposure to SSRIs, was $32 - 18 = 14$ extra cases of urinary incontinence per 1000 patients treated with SSRIs per year compared to unexposed patients.

When stratified for age, there were no differences in relative risks for SSRI-induced urinary incontinence in the different age classes (Table 3). However, the absolute risk difference was strongly different between the groups and increased strongly with age (Figure 1). The absolute risk difference for patients over 65 years of age was over 60 extra cases of urinary incontinence per 1000 initial SSRI users compared to the non-exposure period.

In Table 4 the results using the Andersen–Gill model are shown. Overall, during the exposed period compared to the non-exposure period, patients had a 61% higher risk for urinary incontinence (adjusted relative risk 1.61; 95% CI 1.42–1.82). Stratified analysis showed that users of sertraline were at the highest risk for developing urinary incontinence (RR_{adj} 2.76; 95% CI 1.47–5.21). Multiple analysis showed that use of SSRIs and potentially confounding factors were independent from each other.

Table 3. The incidence density (ID) for urinary incontinence while exposed/not exposed to SSRIs, and the relative risk (RR) expressed as incidence density ratio (IDR) stratified for age categories

Age (years)	Endpoints urinary incontinence	Follow-up period (years)	ID/1000 years	IDR	95% CI
<35					
Before + after	59	11 521	5	Reference	
During SSRI	29	3303	9	1.71	1.10–2.67
35–50					
Before + after	121	15 749	8	Reference	
During SSRI	73	5047	15	1.88	1.41–2.52
51–64					
Before + after	149	9918	15	Reference	
During SSRI	88	2836	31	2.07	1.59–2.69
⩾65					
Before + after	507	8351	61	Reference	
During SSRI	232	1920	121	1.99	1.70–2.33

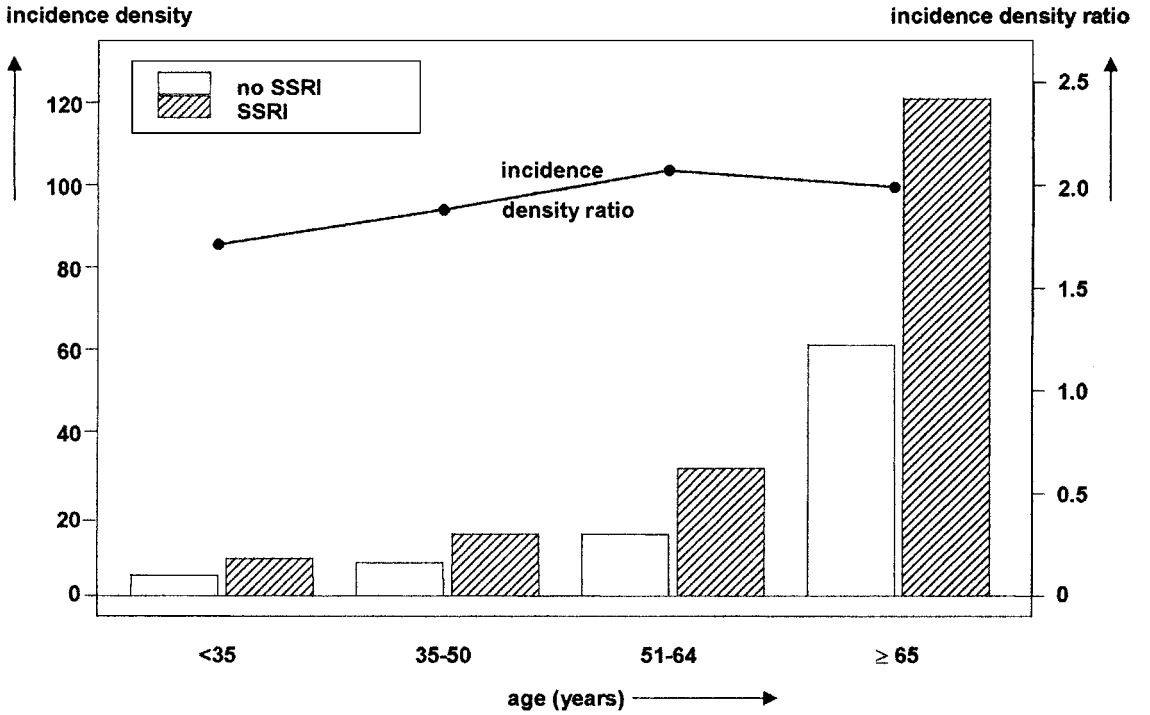

Figure 1. Absolute risk (incidence density) and relative risk (incidence density ratio) for SSRI-induced urinary incontinence compared to non-use calculated for different age categories. Bars represent absolute risk for urinary incontinence in numbers of extra cases per 1000 patients treated per year

Table 4. Relative risk (expressed as hazard ratio (HR)) for urinary incontinence during use of selective serotonine reuptake inhibitors compared to non-exposure period

Item	RR	95% CI	RR*	95% CI
SSRI use				
During versus before	1.74	1.46–2.06	1.91	1.61–2.26
During versus after	1.39	1.20–1.61	1.45	1.25–1.68
Overall	1.55	1.37–1.76	1.61	1.42–1.82
Separate SSRIs				
Paroxetine	1.50	1.28–1.76	1.80	1.53–2.13
Fluvoxamine	1.30	1.06–1.70	1.80	1.36–2.39
Fluoxetine	1.68	1.37–2.06	2.03	1.58–2.61
Sertraline	2.68	1.82–4.63	2.76	1.47–5.21

*Adjusted for potential confounding factors.

Table 5. Risk determinants for urinary incontinence among starters with SSRIs

Item	RR*	95% CI
Gender		
Male	1	Reference
Female	1.36	1.05–1.77
Age (years)		
<35	1	Reference
35–50	1.60	1.04–2.47
51–64	3.21	2.09–4.92
⩾ 65	8.94	5.95–13.43
SSRI		
Paroxetine	1	Reference
Fluvoxamine	0.89	0.69–1.15
Fluoxetine	1.15	0.91–1.46
Sertraline	1.74	1.07–2.83
Sertraline versus other SSRIs	1.72	1.10–2.78

*Adjusted for potential confounding factors.

In Table 5 risk determinants for urinary incontinence among starters with SSRIs are presented. Stratified analysis was performed for those characteristics that were most likely to demonstrate an increased risk for urinary incontinence. Female patients more frequently developed urinary incontinence compared to male patients (RR_{adj} 1.36; 95% CI 1.05–1.77). Compared to other SSRIs, first time users of setraline were more likely to develop urinary incontinence (RR_{adj} 1.72; 95% CI 1.10–2.78) (Figure 2), and compared to younger patients the elderly had an increased probability of developing urinary incontinence (RR_{adj} 8.94; 95% CI 5.95–13.43).

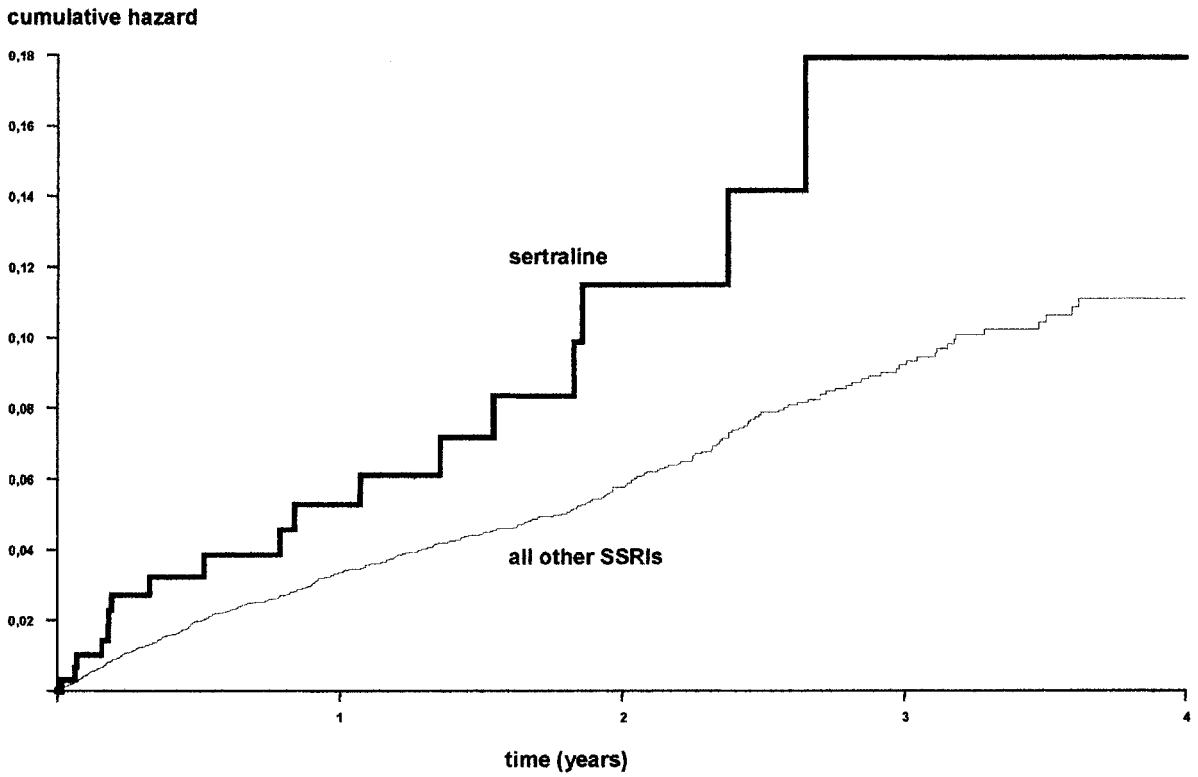

Figure 2. Kaplan–Meier curve for urinary incontinence during SSRI drug therapy

DISCUSSION

In this retrospective follow-up study we found that patients using SSRIs had an almost two-fold increased risk for developing urinary incontinence compared with non-use of these agents. The elderly and patients receiving sertraline were at the highest risk for urinary incontinence compared to the other SSRIs.

In this study, two data analytic approaches were used. Both showed a consistent association between serotonergic drug use and urinary incontinence. In the first analysis, conducted according to Petri's original PSA concept, we found that the risk for urinary incontinence during SSRI use was 1.75 times higher compared to non-exposure and occurred with an overall absolute incidence of 14 new cases of urinary incontinence per 1000 patients treated per year. This absolute risk was highest in elderly patients (≥ 65 years) with 60 new cases per 1000 treated patients per year; however, there was no difference in relative risk between the age categories.

In addition to the PSA analysis, a model according to Andersen–Gill was used in order to control for potential confouding. After adjustment a strong significant association was found between SSRI use and urinary incontinence compared to non-use of these antidepressive agents. Patients using sertraline more frequently developed urinary incontinence when compared to users of fluvoxamine, fluoxetine, or paroxetine.

The association of SSRI use and urinary incontinence is biologically plausible. In general, it is accepted that the effectiveness of antidepressants is attributed to their interaction with certain key receptors in serotonergic, noradrenergic and/or dopaminergic neurotransmission systems.[12] Activation of the 5-HT4 receptor located on the enteric cholinergic fibre is thought to be the main mechanism underlying the gastrointestinal prokinetic activity.[20] From this pharmacological point of view there is evidence that serotonin, as well as e.g. 5-HT4 receptor agonists, such as cisapride, can potentiate cholinergic neuromuscular transmission in isolated detrusor muscle strips from human bladder. Stimulating the 5-HT4 receptors with cisapride increases bladder voiding efficiency, and increase the frequency of micturation in patients

treated for gastrointestinal motor disturbances.[14,21] Based on this pharmacological evidence it was proposed that urinary incontinence is mediated by activation of neuronal 5-HT4 receptors in the M. detrusor.[15]

Urinary incontinence is a well-known problem in Parkinson patients.[22] Morbus Parkinson is attributed to the degeneration of dopaminergic neurons resulting in relative dopamine deficiency in the CNS. From animal studies it has been suggested that dopamine receptors play a role in controlling the bladder function; stimulation of centrally located dopamine-2 receptors stimulates urine micturation.[23] From experimental research it is known that sertraline is a relatively strong and potent inhibitor of the dopamine reuptake in the CNS compared to the other SSRIs.[24] As a result, sertraline may act as an indirect dopamine agonist. These pharmacological facts support our finding that patients using sertraline, with a mixed serotoneric *and* dopaminergic property, were at the highest risk for developing urinary incontinence.

The study design used may have overcome difficulties of selecting an appropriate control group. PSA has been used in pharmacoepidemiological research to identify associations between drug exposure and acute effects.[17,25,26] However, interpretation of an association can be problematic because of possible biases, confounding or other limitations, which should be considered. The key feature of our design was that each possible case also served as a control patient. For a case–control study the ideal control would be some other group of patients who had never received an SSRI, but were alike in all other respects. A consequence of these criteria for this study would be to include control patients using a tricyclic antidepressant drug to treat a depressive episode. However, we chose not to use this classical case–control design because TCAs are often used to treat urinary incontinence.[8] Considering this aspect, SSRI users themselves were chosen as controls. Due to this methodology every patient was their own control, so selection bias was not likely to occur.

Information bias reflecting exposure to concomitantly used drugs was unlikely because a database of patients' pharmacy files was used. In the Netherlands, pharmacy files are used for reimbursement purposes at the time the prescription is filled, and contain complete information on all prescriptions dispensed.[18] However, no direct information on the diagnoses was available. In this study patients were considered incontinent if they had used a minimum of 30 units of incontinence material (absorbent products) in a 3-month period, or started with a spasmolytic drug. It is plausable to believe that these people suffered from urinary incontinence, however, there was no information about the exact time the problem started. It is unlikely that misclassification occurred because spasmolytics or incontinence pads would then have been prescribed for reasons other than urinary problems. Due to a possible non-differential misclassification bias the risk estimates will decrease towards null.

Underestimation of the absolute risk for urinary incontinence is likely because it is to be expected that patients will not usually volunteer to report this kind of information spontaneously. Despite the relatively high prevalence of urinary incontinence in the general population, care seeking for this complication is low. Fewer than 50% of persons with urinary incontinence seek care or tell their general practitioner (GP) about problems with (urinary) incontinence.[27,28] As with the lack of reporting sexual side-effects of SSRIs, there may also be various reasons for the lack of reporting and therefore detection of urinary problems during SSRI drug therapy:[29] embarrassment of the patient; unfamiliarity with the serotonergic-mediated mechanism of the bladder by the GP or urologist; or multiple drug use masking the effects, such as drug regimens containing antimuscarinic or noradrenergic agents.[30] The multivariate analysis allowed us to control for these possible correlations and determined which variables were independent risk factors for urinary incontinence.

Another important reason for underestimation of the risk might be the fact that urinary incontinence is primarily treated with self-care treatment, such as pelvic muscle exercises.[31] So, from this point of view our estimate might be just a small fraction of the true incidence because both proxys we used required a physician's prescription.

Most published data on urinary incontinence is based on inpatients or patients older than age 65 years; by contrast, this study also represents data of patients during normal daily practice and includes younger patients. Our findings suggest that these younger patients taking SSRIs are also at an increased risk for urinary incontinence; but it is not unlikely that this SSRI effect is only of importance in predisposed patients, such as the elderly, young mothers, or patients suffering from prostate (cancer) problems.

Taking stock of the biological serotonin mechanism and the methodological issues, this study strongly suggests a causal association between the use of SSRIs and urinary incontinence. In absolute numbers particularly elderly patients and those using sertraline are at an increased risk for developing urinary incontinence.

Based on the above hypotheses and the finding that SSRIs can induce urinary incontinence, this may be

KEY POINTS

- SSRIs are associated with an increased risk for urinary incontinence
- SSRI use leads to three extra cases of urinary incontinence per 200 people treated per year
- In particular, elderly patients and users of sertraline are at the highest risk
- Prescription sequence analysis, a Cox model, and an Andersen–Gill application, gave comparable risk estimates for urinary incontinence

indicative of an important role of endogenous serotonin in physiological bladder tone. So, from a urological point of view, future studies should focus on whether (selective) agonists at 5-HT4 receptors are valuable for the pharmacological treatment of micturition problems associated with decreased detrusor activity.

In general, SSRIs should not be prescribed and used without clinical monitoring, in view of their well known side-effects, as well as their lesser known but potentially clinically and socially important side-effects such as urinary incontinence.

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