Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Title page

Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CPR = Unique personal identification number

ICD = International Classification of Diseases

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

TOT = Trans-obturator vaginal tape

TVT = Tension-free vaginal tape

UI = Urinary Incontinence

Article Summary:

Article focus: Urinary incontinence is a prevalent disorder among women. This study focus on both surgical and medical treatment of urinary incontinence. We examined the effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Key messages: The majority of women with prior usage of antimuscarinic drugs or duloxetine cease medical treatment after surgery for urinary incontinence. Only a minority of preoperative non-users initiated usage of similar drugs after surgery. Compared to other included factors, preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest predictor of postoperative use.

Strengths and limitations of this study:

A population-based study.

2,151 included women.

High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on symptomatology.

Abstract

Objective To describe the use of symptom-relieving drugs (antimuscarinic drugs or duloxetine) before and after surgery for urinary incontinence (UI); and for those with use of antimuscarinic drugs or duloxetine before surgery, to estimate the risk of being postoperative user, relative to those without use before surgery.

Design A historical cohort study

Setting Denmark

Participants Women ≥ 18 years with a primary surgical procedure for UI from the county of Funen, Denmark between 1 January 1996 and 31 December 2006, extended to the Region of Southern Denmark from 1 January 2007 to end of 2010. For these women, data on redeemed prescriptions +/- 365 days of date of surgery were extracted.

Main outcome measures Effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Results Of 2,151 women with a primary surgical procedure for UI; 358 (16.6%) were preoperative users of antimuscarinic drugs or duloxetine and 1,793 were not (83.4%). Among preoperative users, 110 (30.7%) and 152 (42.5%) also redeemed prescriptions for these drugs within 0-60 and 61-365 days after surgery, respectively. Among preoperative non-users, 25 (1.4%) and 145 (8.1%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antimuscarinic drugs or duloxetine was a strong determinant of postoperative drug use, both within 0-60 days (adjusted OR=29.0, 95% confidence interval (CI) 18.0-46.9) and 61-365 days (OR=6.8, CI 5.1-9.0).

Conclusions

The majority of women with prior usage of antimuscarinic drugs or duloxetine cease medical treatment after surgery for urinary incontinence. Only a minority of preoperative non-users initiated

usage of similar drugs after surgery. Compared to other factors included in the regression model, preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest predictor of postoperative use.

Introduction

Urinary incontinence (UI) is a very prevalent disorder among women (1), and a wide array of options for clinical managements exists. Current best practice is a stepwise strategy moving from conservative treatments such as behavioural alteration, pelvic floor muscle training and weight loss to pharmacological treatment and in selected cases surgery (2).

There are several pharmacological options to relieve the symptoms of UI, i.e. antimuscarinic drugs, duloxetine, and oestrogens. Antimuscarinic drugs remain the main-stay in the treatment of urgency UI, mixed UI as well as the overactive bladder syndrome (3). Antimuscarinics reversibly block muscarinic receptors in the bladder wall, acting primarily by increasing bladder capacity rather than ablating detrusor overactivity. Although the site of action has been thought to be M2 and M3 receptors in detrusor smooth muscle during contraction, there is growing evidence that the therapeutic response might also be the result of antagonist effects on muscarinic receptors on afferent neurons (4) as well as central modulation. Duloxetine, a selective serotonin- and norepinephrine-reuptake inhibitor, is predominantly used as an antidepressant, but has also been licensed in some European countries for stress UI. Presumably duloxetine acts by central modulations, causing an increase in urethral sphincter tone (5).

During the last decades, the surgical treatments of UI in women have improved with the introduction of minimally-invasive sub-urethral sling procedures for stress UI (6–8), submucosal intraurethal injections of bulking agents (9) and intravesical injections of botulinum toxin (10); and the number of surgeries for UI have been increasing as well (11,12).

Metaanalyses have shown a statistically significant improvement in urinary symptoms for the antimuscarinic drugs (3). Vaginal oestrogen use has been proven to reduce irritative symptoms in postmenopausal women with urgency UI or overactive bladder syndrome and is widely used as adjunctive symptomatic therapy (13). In Denmark, oestrogen vaginal tablets or suppositories are

routinely offered to postmenopausal women before urogynecological surgery in order to relieve irritative symptoms and possibly improve surgical outcome through mucosal healing.

Two small studies by Segal et al. (n= 98), and Yoo et al. (n=84) (14,15) have shown, that nearly 60% of preoperative antimuscarinic drug users ceased the use after surgery for UI. Yoo et al also found that preoperatively use of antimuscarinic drugs as well as increasing age were significantly associated with postoperative use of antimuscarinics.

This topic is highly relevant in advising women who are candidates for surgical treatment for UI, if the results could be confirmed in larger studies.

The purpose of this study was to assess the use of symptom-relieving drugs before and after surgery for UI in a larger population and to examine possible determinants of postoperative drug use.

Materials and Methods

Study population and settings

Data on all primary surgical procedures for UI in women during the study period from 1 January 1996 to 31 December 2010 were retrieved from the Danish National Patient Registry (NPR) (16). The International Classification of Diseases (ICD) procedure codes for data extraction are listed in Appendix 1. The study population included women ≥ 18 years undergoing a primary surgical procedure for UI in a hospital in the county of Funen (4 hospitals), Denmark, between 1 January 1996 and 31 December 2006. For the period 2007 through 2010 the geographical area was extended to include all hospitals from the Region of Southern Denmark (including Funen, a total of 13 hospitals). The latter was due to a change in the structure of health care in Denmark from counties to regions in 2007. Women with concomitant or prior surgery for pelvic organ prolapse were not excluded.

Data sources

Data for this study were retrieved from three Danish registers: the NPR, the Odense University Pharmacoepidemiologic Database (OPED), and the Statistics Denmark.

The NPR was established in 1977, and contains data on discharges from public somatic hospitals in Denmark. The completeness of recordings has been estimated to be 99.4% (17). The registry contains information about the unique personal identification number (CPR) assigned for all Danish citizens, the dates of admission and discharge, the surgical procedures performed, and up to 10 diagnoses for every discharge, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (18,19) as well as codes from the Danish classification system of surgical procedures (20).

Information on relevant drugs (antimuscarinic drugs, duloxetine, and oestrogens) was retrieved within 1995-2011 for the entire study population from OPED by using CPR.

OPED contains person-identifiable data with complete coverage on all computerized prescription reimbursements from the County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and the prescription of drugs is very similar to the national average (21). The OPED is pharmacy-based and captures all reimbursed prescriptions.

Prescription reimbursements are offered as a part of the National Health Service to all legal inhabitants of Denmark; and given independently of patient income. Each record includes the CPR, the date of purchase, the pharmacy, a full account of what have been purchased, including brand name, Anatomical Therapeutic Chemical (ATC) classification code, defined daily dose, dose unit, and quantity. The database does not contain information on drugs sold over the counter or drugs not reimbursed by the county authority (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level and annual income were retrieved from the Danish Integrated Database for Labor Market Research at the Statistics of Denmark. This database contains annually updated socioeconomic data for each Danish citizen, mainly supplied by tax authorities, educational institutions, and employment services (22).

Study drugs

Included drugs were antimuscarinic drugs (tolterodine [ATC G04BD07], solifenacin [ATC G04BD08], trospium chloride [ATC G04BD09], darifenacin [ATC G04BD10], fesoterodine [ATC G04BD11], oxybutinin [ATC G04BD04], flavoxate [ATC G04BD02]), duloxetine [ATC N06AX21], and oestrogens [ATC G03C].

Exposed and unexposed cohorts

Exposed cohort: All women ≥ 18 years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and having redeemed one or more prescriptions for antimuscarinic drugs or duloxetine for UI within 365 days preceding the date of surgery (index date).

Unexposed cohort: All women ≥ 18 years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark without having redeemed similar prescriptions within the same time frame.

Outcome data

For both exposed and unexposed women, the primary outcome was the use of symptom-relieving drugs, defined as having redeemed at least one prescription for antimuscarinic drugs or duloxetine within 1) 60 days after the index date (short term postoperatively), and 2) 61 days to 365 days after index date (long term postoperatively). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively.

Covariates

The use of symptom-relieving drugs might be affected by age, highest attained educational level, annual income, comorbidity, calendar time and menopausal status; therefore these variables (or proxy measures) were included in the analysis as potential confounders.

Oestrogen: Having redeemed at least one redeemed prescription for oestrogens (ATC G03C) within 365 days prior to surgery was used as a proxy measurement for post menopause, because the menopausal status of the women was not available.

Socio economic status: To measure socio economic status, information on education and annual income for each woman was retrieved. Education was categorized according to the highest attained educational level as "Basic" (equals basic school/high school education: 7-12 years of primary, secondary and grammar-school education), "Secondary" (equals vocational education, 10-12 years of education), and "Higher" (equals a university degree or an examination in another higher institution requiring an average a total of 13 years or more) (23).

On the basis of quartiles of annual income for each women at the year of her surgery, we categorised women in low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile) recipients.

Comorbidity: The comorbidity was classified according to the Charlson comorbidity index (CCI) (24) – a well-known, validated and widely used quantitative measure of comorbid illness (25). It assigns different weights (1, 2, 3, and 6) to 19 different disease categories specified by medical condition and severity (for example, diabetes, cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). For each woman the CCI was computed based on her complete hospital discharge history from the NPR since 1977. A categorized version of the CCI with score values grouped were used: 0 (low), 1-2 (medium) and 3+ (high) (26).

Statistical analysis

We describe in a flowchart the use of symptom-relieving drugs within the first 365 days after surgery for the two groups of users and non-users of drugs prior to surgery.

We also constructed contingency tables for the main study variables, and computed the odds ratio (OR), with 95 % confidence intervals (CI).

To analyse the significance of preoperative symptom-relieving drug use as determinants of postoperative use (short- and long term), adjusted ORs were estimated by means of multivariate

logistic regression models. Adjustment was made for age (≥60 years as a reference, 18-39, 40-59), procedures (TOT/TVT-O as a reference, TVT, Bulking, others), education (basic as a reference, secondary, higher), annual income (low as a reference, middle, high), comorbidity (CCI 0 as a reference, CCI 1-2, CCI 3+), calendar year (2007-2008 as a reference, 1996-2006, 2009-2010), and local or systemic use of oestrogen within 365 days preceding surgery.

All analyses were performed using Stata Release 12.0.

Results

A total of 2,151 women had a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 (2,073 had solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse).

Of the 2,151 women, 358 (16.6%) were exposed to symptom-relieving drugs within 365 days before surgery, and 1,793 (83.4%) were not. The use of symptom-relieving drugs within 365 days after surgery is detailed in both these cohorts (Figure 1).

Women having redeemed prescriptions for symptom-relieving drugs before surgery (exposed)

Out of the 358 women with prior drug use of antimuscarinic drugs or duloxetine, 248 (69.3%) women did not redeem a prescription for symptom-relieving drugs within 0-60 days after surgery, and the majority of these women (192/358=53.6%) also abstained from symptom-relieving drugs during the time frame 61-365 days after surgery (Figure 1). On the other hand, 110 of the 358 women (30.7%) did redeem prescriptions for these drugs within 0-60 days after surgery, and 98 out of the 358 women (26.8%) even within 61-365 days after surgery (Figure 1).

Women with no usage of symptom-relieving drugs before surgery (unexposed)

Out of the 1,793 women who did not redeem prescription before surgery, 1,768 (98.6%) women remained non-users within 0-60 days after surgery, and the vast majority of these women (1,643/1,793=91.6%) continued as non-users also within 61-365 days after surgery (Figure 1). Only 25 women (1.4%) redeemed a first time prescription for symptom-relieving drugs within 0-60 days after surgery and these women typically continued their use within 61-365 days after surgery (20 women) (Figure 1).

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedures were mid-urethral slings with either retropubic trocar passage (TVT-type slings) or trans-obturator trocar passage (i.e. TVT-O or TOT-type slings). The exposed women were more likely to have had a trans-obturator mid-urethral sling or a billings agent injection compared to unexposed women, where retropubic mid-urethral sling was the preferred procedure. The most commonly prescribed drugs prior to surgery were solifenacin and tolterodine. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, to have more comorbidity, a lower educational level, and a lower annual income.

Among women with prior drug use, the unadjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 31.1, CI 19.9-49.4, and 8.4, CI 6.4-11.0, respectively. The adjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 33.0, CI 20.0-54.7, and 7.2, CI 5.4-9.6, respectively. The details from logistic regression models are presented in Table 2 showing the impact of each prognostic factor included. Preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest predictor of postoperative use (both short and long term); i.e. compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative user.

Discussion

Among 2,151 women undergoing surgery for UI, more than 80% did not redeem a prescription for antimuscarinic drugs or duloxetine within 365 days before surgery. Among the women without drug use before surgery, the vast majority continued being non-users after surgery, with less than 9% redeeming a first time prescription of the drugs. Less than 20% of the women had redeemed prescriptions before surgery, and of these nearly 70% ceased drug use within 2 months after surgery while those who continued using the drugs typically staid long term users.

Our study has several strengths: 1) it is a population-based study in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) The source of procedure has high coverage and validity. The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a moderate-to-high quality of the data with positive predictive values of 94-100% (27–29), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (21), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in the follow up period for all included women, 6) outcome data on postoperative drug prescriptions were obtained independently of exposure assessment preventing differential misclassification of the outcome, and finally 7) the drugs and the surgical procedures included in our study do not have other indications than UI, which strongly limits the number of alternative interpretations of our findings.

Our study also has limitations. Data on redeemed prescription are only a surrogate for drug intake. However, antimuscarinic drugs and especially duloxetine are expensive drugs with significant patient co-payment, and we find it unlikely that these drugs to any major extent would be bought and not consumed. We had no data on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome were predominant, or on urodynamic study. We were not

able to control for potential confounders such as body mass index or menopausal status (although we have used preoperative oestrogen use as a proxy), but the importance of these factors is not clear.

Currently available drugs for UI are expensive, have many side effects (30), and the long term persistence of the use of antimuscarinic drugs as well as duloxetine is low (without regarding surgery) (31–33). All the latter may contribute to the cessation of the drugs; and thus a reduction in the drug usage may not be explained entirely by the surgery. The reasons for cessation of drug use after surgery can be influenced by other factors as well. For example, misinterpretation of symptoms/investigations may lead to treatment of stress UI with symptom-relieving drugs.

The risk of initiating medical treatment after surgery for UI (based on de-novo surgery) is small, but well-known (34).

There was a low rate of concomitant pelvic reconstructive surgery, as was expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (35).

To our knowledge, this is the largest study addressing the changes in use of symptom-relieving drugs in relation to surgery for UI, and with a large number of possible determinants of postoperative use. Our results in this larger population are consistent with the previous smaller studies (14,15).

In conclusion, we found that for the majority of women with prior usage of antimuscarinic drugs or duloxetine ceased the medical treatment within 365 days after surgery, although there was an increased risk of continuing redemption of prescriptions after surgery. A small minority (8.1%) of preoperative non-users initiated usage of antimuscarinic drugs or duloxetine within 365 days after surgery. Compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative drug user.

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Competing interests "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Ethical approval The study was approved by the Danish Data Protection Agency (no. 2009-41-3564). According to Danish law, ethical review board approval or patient consent are not required for register-based studies.

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Data sharing According to the Danish Data Detection Agency, we are not allowed to share our data from the Danish National Patient Registry. This would require a special approval from both the Danish Data Detection Agency and the Statens Serum Institut who delivers the data from the Danish National Patient Registry.

Table 1 Baseline characteristics of all included women (N=2,151) having a primary surgical procedure for UI in Denmark, 1996-2010.

	Exposed n= 358 (16.6%)	Unexposed n=1,793 (83.4%)
Mean age (±SD), years (At time of first UI surgery)	60.9 (±12.7)	54.5 (±12.6)
Age groups n (%)		
18-39	13 (3.6)	199 (11.1)
40-59	151 (42.2)	956 (53.3)
60-	194 (54.2)	638 (35.6)
Procedures n (%)		
TVT	73 (20.4)	602 (33.6)
TOT/TVT-O	172 (48.0)	800 (44.6)
Bulking	101 (28.2)	259 (14.4)
Others	12 (3.4)	132 (7.4)
Concomitant prolapse surgery n (%)	11 (3.1)	67 (3.7)
Symptom-relieving medications n (%)*		
Solifenacin	176 (49.2)	-
Tolterodine	84 (23.5)	-
Fesoterodine	63 (17.6)	-
Trospium chloride	32 (8.9)	-
Obybutynin	29 (8.1)	-
Darifenacin	14 (3.9)	-
Emepronium	6 (1.7)	-
Duloxetine	6 (1.7)	-
Oestrogen users n (%)**	223 (62.3)	720 (40.2)
Comorbidity (CCI) n (%)		
0	214 (59.8)	1,298 (72.3)
1-2	107 (29.9)	413 (23.0)
3+	37 (10.3)	82 (4.6)
Educational level n (%)***		
Basic	178 (51.7)	739 (41.8)
Secondary	125 (36.3)	645 (36.5)
Higher	41 (11.9)	383 (21.7)
Annual income n (%)		
Low (1st quartile)	100 (27.9)	437 (24.4)
Middle (2nd-3rd quartile)	206 (57.6)	871 (48.6)
High (4th quartile)	52 (14.5)	485 (27.0)
Year of surgery n (%)		
1996-2006	50 (14.0)	409 (22.8)
2007-2008	118 (33.0)	673 (37.5)
2009-2010	190 (53.0)	711 (39.7)

*Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.
**Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
***Unknown highest attained educational level: 40 women
Abbreviations: SD = standard deviation, TVT = Tension-free vaginal tape, TOT/TVT-O = Trans-obturator vaginal tape, CCI = Charlson comorbidity index

Table 2 Determinants of postoperative use of antimuscarinic drugs/duloxetine. Multivariate logistic regression models on both i) a short term basis (0-60 days after surgery) and ii), and on a long term basis (61-356 days after surgery)

	Post op non-use	**Post op short term use**		Post op non-use	**Post op long term use**	
	Number	Number	OR (CI)	Number	Number	OR (CI)
Preoperative use						
No	1,768	25	reference	1,648	145	reference
Yes	248	110	33.0 (20.0-54.7)	145	152	7.2 (5.4-9.6)
Age group						
18-39	209	3	0.3 (0.1-1.4)	204	8	0.3 (0.1-0.7)
40-59	1,063	44	0.6 (0.3-0.9)	999	108	0.6 (0.4-0.8)
60-	744	88	reference	651	181	reference
Procedure						
TVT	659	16	0.6 (0.3-1.2)	612	63	0.6 (0.4-0.9)
TOT/TVT-O	894	78	reference	842	130	reference
Bulking	322	38	1.2 (0.7-2.0)	262	98	0.5 (0.3-0.7)
Others	141	3	0.5 (0.1-2.6)	138	6	0.3 (0.1-1.0)
Preoperative use of oestrogen*						
No	1,159	49	reference	1,090	118	reference
Yes	857	86	0.8 (0.5-1.4)	764	179	1.0 (0.7-1.4)
Comorbidity (CCI)						
0	1,442	70	reference	1,352	160	reference
1-2	467	53	1.5 (0.9-2.4)	419	101	1.5 (1.1-2.0)
3+	107	12	0.9 (0.4-1.9)	83	36	1.9 (1.2-3.2)
Educational level**						
Basic	846	71	reference	761	156	reference
Secondary	727	43	0.9 (0.6-1.5)	674	96	0.9 (0.6-1.2)
Higher	407	17	1.1 (0.6-2.3)	385	39	0.8 (0.5-1.3)
Annual income						
Low	489	48	reference	442	95	reference
Middle	1,010	67	0.7 (0.4-1.2)	929	148	0.9 (0.6-1.2)
High	517	20	0.9 (0.4-1.8)	483	54	1.1 (0.7-1.9)
Year of surgery						
1996-2006	448	11	0.7 (0.3-1.7)	427	32	0.5 (0.3-0.9)
2007-2008	739	52	reference	675	116	reference
2009-2010	829	72	0.9 (0.6-1.4)	752	149	1.0 (0.7-1.4)

* Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
** Unknown highest attained educational level: 40 womenAbbreviations: OR = odds ratio, CI = confidence interval , TVT = Tension-free vaginal tape, TOT/TVT-O = Trans-obturator vaginal tape, CCI = Charlson comorbidity index

Figure 1 Women with a primary surgical procedure for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. N=2,151
Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.
Unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.

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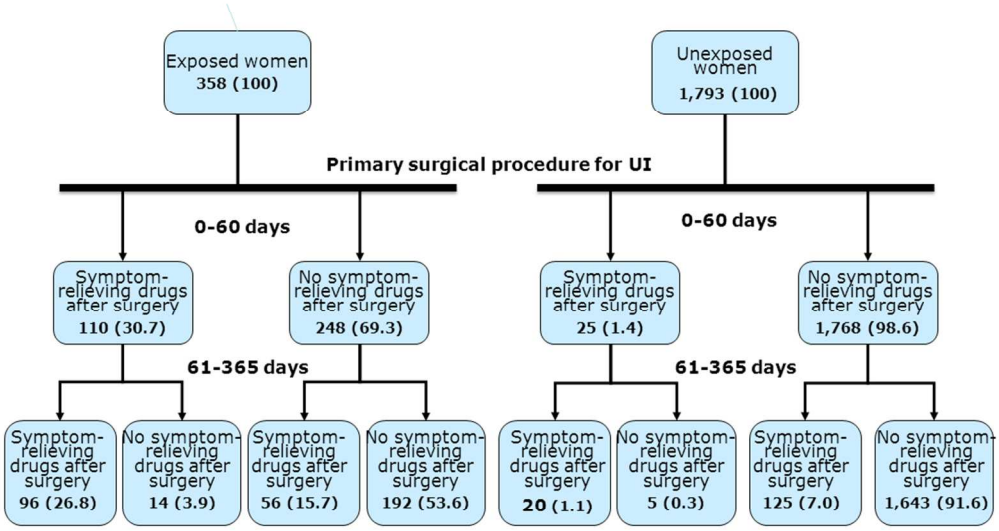

Women with a primary surgical procedure for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. N=2,151
Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.
Unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery

286x199mm (96 x 96 DPI)

Appendix 1 Surgical procedures according to the Danish Nordic Medico-Statistical Committee

KDG00 = Retropubic suspension of urethra
KDG01 = Percutaneous endoscopic retropubic suspension of urethra
KDG10 = Abdominovaginal suspension of bladder neck
KDG30 = Suprapubic sling urethrocystopexy
KDG31 = Percutaneous endoscopic suprapubic sling
KDG40 = Suprapubic urethrocystopexy
KDG50 = Transabdominal plastic repair of pelvic floor for urinary incontinence
KDG96 = Other operation on urethra or bladder neck for incontinence
KDG97 = Other percutaneous endoscopic operation on urethra or bladder neck for incontinence
KDV20 = Submucous urethral injection
KDV22 = Transluminal endoscopic submucous urethral injection
LEG00 = Vaginal urethrocystorrhaphy
LEG10 = Vaginal urethrocystopexy with use of sling
LEG10A = Vaginal urethrocystopexy with use of sling through foramen obturatum
LEG20 = Plastic repair of female pelvic floor with levator division
LEG96 = Other vaginal operation for incontinence

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 – Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5+6
Objectives	3	State specific objectives, including any prespecified hypotheses	5+6
Methods			
Study design	4	Present key elements of study design early in the paper	3+7,8,9,10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3+7,8,9,10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7+8
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9+10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10+11
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13 + Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13 +Table 2
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14+15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14+15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Title page

Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CPN = Unique personal identification number

DDD = total Defined Daily Dose

ICD = International Classification of Diseases

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

Abstract

Objective To describe the use of symptom-relieving drugs (antimuscarinic drugs or duloxetine) before and after surgery for urinary incontinence (UI); and for those with use of antimuscarinic drugs or duloxetine before surgery, to estimate the risk of being postoperative user, relative to those without use before surgery.

Design A historical population-based cohort study

Setting Denmark

Participants Women ≥ 18 years with a primary surgical procedure for UI from the county of Funen, Denmark between 1 January 1996 and 31 December 2006, extended to the Region of Southern Denmark from 1 January 2007 to end of 2010. For these women, data on redeemed prescriptions +/- 365 days of date of surgery were extracted.

Main outcome measures Effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Results Of 2,151 women with a primary surgical procedure for UI; 358 (16.6%) were preoperative users of antimuscarinic drugs or duloxetine and 1,793 were not (83.4%). A total of 110 (30.7%) of the preoperative users also redeemed prescriptions for these drugs within 0-60 days after surgery, and 152 (42.5%) of the preoperative users redeemed prescriptions for these drugs within 61-365 days after surgery. Among preoperative non-users, 25 (1.4%) and 145 (8.1%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antimuscarinic drugs or duloxetine was a strong risk factor of postoperative drug use, both within 0-60 days (adjusted OR=33.0, 95% confidence interval (CI) 20.0-54.7) and 61-365 days (OR=7.2, 95% CI 5.4-9.6).

Conclusions

A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other factors included in the regression model, preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor for postoperative use.

Introduction

Urinary incontinence (UI) is a very prevalent disorder among women (1), and a wide array of options for clinical managements exists. Current best practice is a stepwise strategy moving from conservative treatments such as behavioural alteration, pelvic floor muscle training and weight loss to pharmacological treatment and in selected cases surgery (2).

There are different pharmacological options to relieve the symptoms of UI, including antimuscarinic drugs, and duloxetine. Antimuscarinic drugs remain the main-stay in the treatment of urgency UI, mixed UI as well as the overactive bladder syndrome (3). Antimuscarinics reversibly block muscarinic receptors in the bladder wall, acting primarily by increasing bladder capacity rather than ablating detrusor overactivity. Although the site of action has been thought to be M2 and M3 receptors in detrusor smooth muscle during contraction, there is growing evidence that the therapeutic response might also be the result of antagonist effects on muscarinic receptors on afferent neurons (4) as well as central modulation. Duloxetine, a selective serotonin- and norepinephrine-reuptake inhibitor, is predominantly used as an antidepressant, but has also been licensed in some European countries for stress UI. Presumably duloxetine acts by central modulations, causing an increase in urethral sphincter tone (5).

During the last decades, the surgical treatments of UI in women have improved with the introduction of minimally-invasive sub-urethral sling procedures for UI (6–8), submucosal intraurethal injections of bulking agents (9) and intravesical injections of botulinum toxin (10); and the number of surgeries for UI has been increasing as well (11,12).

Three small studies by Segal et al. (n= 98), Yoo et al. (n=84), and Barber et al. (n=162) (13–15) have shown, that nearly 40% of preoperative antimuscarinic drug users continued the use after surgery for UI.

This topic is highly relevant in advising women who are candidates for surgical treatment for UI, if the results could be confirmed in larger studies.

The purpose of this study was to assess the use of symptom-relieving drugs before and after surgery for UI in a larger population and to examine possible risk factors of postoperative drug use.

Materials and Methods

Study population and settings

Data on all primary surgical procedures for UI in women during the study period from 1 January 1996 to 31 December 2010 were retrieved from the Danish National Patient Registry (NPR) (16). The International Classification of Diseases (ICD) procedure codes for data extraction are listed in Appendix 1. The study population included women ≥ 18 years undergoing a primary surgical procedure for UI in a hospital in the county of Funen (4 hospitals), Denmark, between 1 January 1996 and 31 December 2006. For the period 2007 through 2010 the geographical area was extended to include all hospitals from the Region of Southern Denmark (including Funen, a total of 13 hospitals). The latter was due to a change in the structure of health care in Denmark from counties to regions in 2007. Women with concomitant or prior surgery for pelvic organ prolapse were not excluded.

Data sources

Data for this study were retrieved from three Danish registers: the NPR, the Odense University Pharmacoepidemiologic Database (OPED), and the Statistics Denmark.

The NPR was established in 1977, and contains data on discharges from public hospitals in Denmark. The completeness of recordings has been estimated to be 99.4% (17). The registry contains information about the unique personal identification number (CPN) assigned for all Danish citizens, the dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses for every discharge, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (18,19) as well as codes from the Danish classification system of surgical procedures (20).

Information on relevant drugs (antimuscarinic drugs, duloxetine, and oestrogens) was retrieved within 1995-2011 for the entire study population from OPED by using CPN.

OPED contains person-identifiable data with complete coverage on all computerized prescription reimbursements from the County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and the prescription of drugs is very similar to the national average (21). The OPED is pharmacy-based and captures all reimbursed prescriptions.

Prescription reimbursements are offered as a part of the National Health Service to all legal inhabitants of Denmark; and given independently of patient income. Each record includes the CPN, the date of purchase, the pharmacy, a full account of what have been purchased, including brand name, Anatomical Therapeutic Chemical (ATC) classification code, total defined daily dose (DDD), dose unit, and quantity. The database does not contain information on drugs sold over the counter or drugs not reimbursed by the county authority (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level and annual income were retrieved from the Danish Integrated Database for Labor Market Research at the Statistics of Denmark. This database contains annually updated socioeconomic data for each Danish citizen, mainly supplied by tax authorities, educational institutions, and employment services (22).

Study drugs

Included drugs were antimuscarinic drugs (tolterodine [ATC G04BD07], solifenacin [ATC G04BD08], trospium chloride [ATC G04BD09], darifenacin [ATC G04BD10], fesoterodine [ATC G04BD11], oxybutinin [ATC G04BD04], flavoxate [ATC G04BD02]), duloxetine [ATC

N06AX21], and oestrogens [ATC G03C]. Propiverine [ATC G04BD6] has not been licensed in Denmark.

Exposed and unexposed cohorts

Exposed cohort: All women ≥ 18 years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and having redeemed one or more prescriptions for antimuscarinic drugs or duloxetine for UI within 365 days preceding the date of surgery (index date).

Unexposed cohort: All women ≥ 18 years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark without having redeemed similar prescriptions within the same time frame.

Outcome data

For both exposed and unexposed women, the primary outcome was the use of symptom-relieving drugs, defined as having redeemed at least one prescription for antimuscarinic drugs or duloxetine within 1) 60 days after the index date (short term postoperatively), and 2) 61 days to 365 days after index date (long term postoperatively). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively.

Covariates

The use of symptom-relieving drugs might be affected by age, type of procedure, use of oestrogen, comorbidity, educational level, annual income, and calendar time; therefore these variables were included in the analysis as potential confounders.

Type of procedures: The types of UI surgery were divided into four groups according to the surgical procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types of UI surgeries.

Oestrogen: To adjust for preoperative oestrogen use, women were divided into those who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and those who had no preoperative oestrogen use. Both systemic and local oestrogens were included.

Comorbidity: The comorbidity was classified according to the Charlson comorbidity index (CCI) (23) – a well-known, validated and widely used quantitative measure of comorbid illness (24,25). It assigns different weights (1, 2, 3, and 6) to 19 different disease categories specified by medical condition and severity (for example, diabetes, cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). For each woman the CCI was computed based on her complete hospital discharge history from the NPR since 1977. A categorised version of the CCI with score values grouped were used: 0 (low), 1-2 (medium) and 3+ (high) (26).

Socio economic status: To measure socio economic status, information on education and annual income for each woman was retrieved. Education was categorised according to the highest attained educational level as "Basic" (basic school/high school education: 7-12 years of primary, secondary and grammar-school education), "Secondary" (vocational education, 10-12 years of education), and "Higher" (a university degree or an examination in another higher institution requiring an average a total of 13 years or more) (27).

On the basis of quartiles of annual income for each women at the year of her surgery, we categorised women in low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile) recipients.

Statistical analysis

We describe in a flowchart the use of symptom-relieving drugs within the first 365 days after surgery for the two groups of users and non-users of drugs prior to surgery.

We also constructed contingency tables for the main study variables, and computed the odds ratio (OR), with 95% confidence intervals (CI).

To analyse the significance of preoperative symptom-relieving drug use as risk factor of postoperative use (short- and long term), adjusted ORs were estimated by means of multivariate logistic regression models. Adjustment was made for age (18-39, 40-59, ≥ 60 years (reference)), type of procedures (toMUS (reference), rpMUS, Bulking, others), education (basic (reference), secondary, higher), annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+), calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365 days preceding surgery (No (reference), Yes).

All analyses were performed using Stata Release 12.0.

Results

A total of 2,151 women had a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 (2,073 had solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse).

Of the 2,151 women, 358 (16.6%) were exposed to symptom-relieving drugs within 365 days before surgery, and 1,793 (83.4%) were not. The use of symptom-relieving drugs within 365 days after surgery is detailed in both these cohorts (Figure 1).

Women having redeemed prescriptions for symptom-relieving drugs before surgery (exposed)

Out of the 358 women with prior drug use of antimuscarinic drugs or duloxetine, 110 (30.7%) women redeemed prescriptions for these drugs within 0-60 days after surgery, and 98 out of the 358 women (26.8%) even within 61-365 days after surgery (Figure 1). On the other hand, 248 (69.3%) women did not redeem a prescription for symptom-relieving drugs within 0-60 days after surgery, and the majority of these women (192/358=53.6%) also abstained from symptom-relieving drugs during the time frame 61-365 days after surgery (Figure 1). For the exposed women, the number of redeemed prescriptions was 1,360 preoperatively (DDD 174.6 (SD ±202)), postoperatively 126 (DDD 32.3 (SD ±63.5)) within 0-60 days, and 984 (DDD 140.4 (SD ±234.3)) within 61-365 days.

Women with no usage of symptom-relieving drugs before surgery (unexposed)

Only 25 of the 1,793 (1.4%) women redeemed a first time prescription for symptom-relieving drugs within 0-60 days after surgery, and these women typically continued their use within 61-365 days after surgery (20 women) (Figure 1). Of the 1,793 women who did not redeem prescription before surgery, 1,768 (98.6%) women remained non-users within 0-60 days after surgery, and the vast majority of these women (1,643/1,793=91.6%) continued as non-users also within 61-365 days after surgery (Figure 1). For the unexposed women, the number of redeemed prescriptions postoperatively was 129 (DDD 0.8 (SD ±8.8)) within 0-60 days, and 403 (DDD 11.9 (SD ±54.8)) within 61-365 days.

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedures were rpMUS or toMUS. The exposed women were more likely to have had a trans-obturator mid-urethral sling or a bulking agent injection compared to unexposed women, where retropubic mid-urethral sling was the preferred procedure. The most commonly prescribed drugs prior to surgery were solifenacin and tolterodine. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, to have higher comorbidity, a lower educational level, and a lower annual income.

Among women with prior drug use, the unadjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 31.1 (95% CI 19.9-49.4), and 8.4 (95% CI 6.4-11.0), respectively. The adjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 33.0 (95% CI 20.0-54.7), and 7.2 (95% CI 5.4-9.6), respectively. The details from logistic regression models are presented in Table 2 showing the impact of each risk factor included. Preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor of

postoperative use (both short and long term); i.e. compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative user.

Discussion

Among 2,151 women undergoing surgery for UI less than 20% had redeemed prescriptions for antimuscarinic drugs or duloxetine prior to surgery, and nearly 30% of these continued using the drugs within 2 months after surgery and typically staid long term users. Among the women without drug use before surgery, the vast majority continued being non-users after surgery, with less than 9% redeeming a first time prescription of the drugs.

Our study has several strengths: 1) it is a population-based study in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) The source of procedure has high coverage and validity. The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a moderate-to-high quality of the data with positive predictive values of 94-100% (28–30), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (21), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in the follow up period for all included women, 6) outcome data on postoperative drug prescriptions were obtained independently of exposure assessment preventing differential misclassification of the outcome, and finally 7) the drugs and the surgical procedures included in our study do not have other indications than UI, which strongly limits the number of alternative interpretations of our findings.

Our study also has limitations. Data on redeemed prescription are only a surrogate for drug intake. However, antimuscarinic drugs and especially duloxetine are expensive drugs with significant patient co-payment, and we find it unlikely that these drugs to any major extent would be bought and not consumed. We had no data on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome were predominant, just as there was no available data on findings in urodynamic studies. The exposed cohort were receiving symptom-relieving drugs, and

thus these women most likely had predominantly mixed UI, whereas the unexposed women most likely had predominantly stress UI. We were not able to control for potential confounders such as body mass index, parity, grade of concomitant cystocele, severity of UI symptoms, intrinsic factor deficiency, or menopausal status, which are well-known risk factors for persistent UI after surgery for UI (31–35). One might speculate whether duration of time with UI symptoms and preoperative conservative treatment could impact our estimates of postoperative drug use, as women in the exposed cohort could have longer disease duration before surgery than women in the unexposed cohort. This could be due to a more extensive preoperative evaluations including urodynamic studies, as well as waiting time to evaluate the effect of drug treatment in the exposed cohort. However, to our knowledge no studies have indicated that disease duration or conservative treatment of UI is a risk factor for postoperative drug use, and therefore we do not believe our estimates of postoperative drug use are influenced by duration of time with UI symptoms.

Currently available drugs for UI are expensive, have many side effects (36), and the long term persistence of the use of antimuscarinic drugs as well as duloxetine is low (without regarding surgery) (37–39). All the latter may contribute to the cessation of the drugs; and thus a reduction in the drug usage may not be explained entirely by the surgery. The reasons for cessation of drug use after surgery can be influenced by other factors as well. For example, misinterpretation of symptoms/investigations may lead to treatment of stress UI with symptom-relieving drugs.

The risk of initiating medical treatment after surgery for UI (based on de-novo surgery) is small, but well-known (40).

There was a low rate of concomitant pelvic reconstructive surgery, as was expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (41).

To our knowledge, this is the largest study addressing the changes in use of symptom-relieving drugs in relation to surgery for UI, and with a large number of possible risk factors of postoperative use. Our results in this larger population are consistent with the previous smaller studies (13–15). Compared to the previous studies, our study included a larger number of women with UI surgery, estimated the risk of postoperatively symptom-relieving drug use with adjustment for a number of relevant covariates, and assessed the risk of both short term and long term use. Our study also showed that educational level, personal income, and type of procedure did not seem to influence the risk of postoperative drug use. High comorbidity was found to significantly increase the risk, but it did not influence the estimates as much as the preoperative drug use, which was the strongest risk factor of postoperative drug use.

In conclusion, we found that a substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority (8.1%) of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to preoperative drug use no other factors in the regression model contributed considerably to the OR of being short or long term postoperative user of symptom-relieving drugs.

Acknowledgement None

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Contributors All authors have drafted the article, revised it critically for important intellectual content, and approved the finale version to be published. All authors are responsible for the study concept and design, and participated in the interpretation of data. RG is the guarantor and has full access to all of the data in the study.

Competing interests "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Ethical approval The study was approved by the Danish Data Protection Agency (no. 2009-41-3564). According to Danish law, ethical review board approval or patient consent are not required for register-based studies.

languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.

Data sharing According to the Danish Data Detection Agency, we are not allowed to share our data from the Danish National Patient Registry. This would require a special approval from both the Danish Data Detection Agency and the Statens Serum Institut who delivers the data from the Danish National Patient Registry.

Article Summary:

Article focus: Urinary incontinence is a prevalent disorder among women. This study focus on both surgical and medical treatment of urinary incontinence. We examined the effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Key messages: A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other included factors, preoperative use of antimuscarinic drugs or duloxetine was the strongest risk factor of postoperative use.

Strengths and limitations of this study:

A population-based study.

2,151 included women.

High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, and personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on type of urinary incontinence or urodynamic studies

Table 1 Baseline characteristics of all included women (N=2,151) having primary surgery for urinary incontinence in Denmark, 1996-2010.

	Exposed n= 358 (16.6%)	Unexposed n=1,793 (83.4%)
Mean age (±SD), years (At time of first UI surgery)	60.9 (±12.7)	54.5 (±12.6)
Age groups n (%)	13 (3.6)	199 (11.1)
18-39	151 (42.2)	956 (53.3)
40-59	194 (54.2)	638 (35.6)
60-		
Procedures n (%)		
rpMUS	73 (20.4)	602 (33.6)
toMUS	172 (48.0)	800 (44.6)
Bulking	101 (28.2)	259 (14.4)
Others	12 (3.4)	132 (7.4)
Concomitant prolapse surgery n (%)	11 (3.1)	67 (3.7)
Symptom-relieving medications n (%)*		
Solifenacin	176 (49.2)	-
Tolterodine	84 (23.5)	-
Fesoterodine	63 (17.6)	-
Trospium chloride	32 (8.9)	-
Obybutynin	29 (8.1)	-
Darifenacin	14 (3.9)	-
Emepronium	6 (1.7)	-
Duloxetine	6 (1.7)	-
Oestrogen users n (%)**		
No	135 (37.7)	1,073 (59.8)
Yes	223 (62.3)	720 (40.2)
Comorbidity (CCI) n (%)		
0	214 (59.8)	1,298 (72.3)
1-2	107 (29.9)	413 (23.0)
3+	37 (10.3)	82 (4.6)
Educational level n (%)***		
Basic	178 (51.7)	739 (41.8)
Secondary	125 (36.3)	645 (36.5)
Higher	41 (11.9)	383 (21.7)
Annual income n (%)		
Low (1st quartile)	100 (27.9)	437 (24.4)
Middle (2nd-3rd quartile)	206 (57.6)	871 (48.6)
High (4th quartile)	52 (14.5)	485 (27.0)
Year of surgery n (%)		
1996-2006	50 (14.0)	409 (22.8)
2007-2008	118 (33.0)	673 (37.5)
2009-2010	190 (53.0)	711 (39.7)

*Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.
**Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
***Unknown highest attained educational level: 40 women
Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Table 2 Risk factors of postoperative use of antimuscarinic drugs/duloxetine. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii) on long term (61-356 days after surgery)

	Post op non-use Number	Post op short term use		Post op non-use Number	Post op long term use	
		Number	OR (95% CI)		Number	OR (95% CI)
Preoperative use						
No	1,768	25	reference	1,648	145	reference
Yes	248	110	33.0 (20.0-54.7)	145	152	7.2 (5.4-9.6)
Age group						
18-39	209	3	0.3 (0.1-1.4)	204	8	0.3 (0.1-0.7)
40-59	1,063	44	0.6 (0.3-0.9)	999	108	0.6 (0.4-0.8)
60-	744	88	reference	651	181	reference
Procedure						
rpMUS	659	16	0.6 (0.3-1.2)	612	63	0.6 (0.4-0.9)
toMUS	894	78	reference	842	130	reference
Bulking	322	38	1.2 (0.7-2.0)	262	98	0.5 (0.3-0.7)
Others	141	3	0.5 (0.1-2.6)	138	6	0.3 (0.1-1.0)
Preoperative use of oestrogen*						
No	1,159	49	reference	1,090	118	reference
Yes	857	86	0.8 (0.5-1.4)	764	179	1.0 (0.7-1.4)
Comorbidity (CCI)						
0	1,442	70	reference	1,352	160	reference
1-2	467	53	1.5 (0.9-2.4)	419	101	1.5 (1.1-2.0)
3+	107	12	0.9 (0.4-1.9)	83	36	1.9 (1.2-3.2)
Educational level**						
Basic	846	71	reference	761	156	reference
Secondary	727	43	0.9 (0.6-1.5)	674	96	0.9 (0.6-1.2)
Higher	407	17	1.1 (0.6-2.3)	385	39	0.8 (0.5-1.3)
Annual income						
Low	489	48	reference	442	95	reference
Middle	1,010	67	0.7 (0.4-1.2)	929	148	0.9 (0.6-1.2)
High	517	20	0.9 (0.4-1.8)	483	54	1.1 (0.7-1.9)
Year of surgery						
1996-2006	448	11	0.7 (0.3-1.7)	427	32	0.5 (0.3-0.9)
2007-2008	739	52	reference	675	116	reference
2009-2010	829	72	0.9 (0.6-1.4)	752	149	1.0 (0.7-1.4)

*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
**Unknown highest attained educational level: 40 women
Abbreviations: post op = postoperative, OR = odds ratio, CI = confidence interval, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Figure 1 Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.

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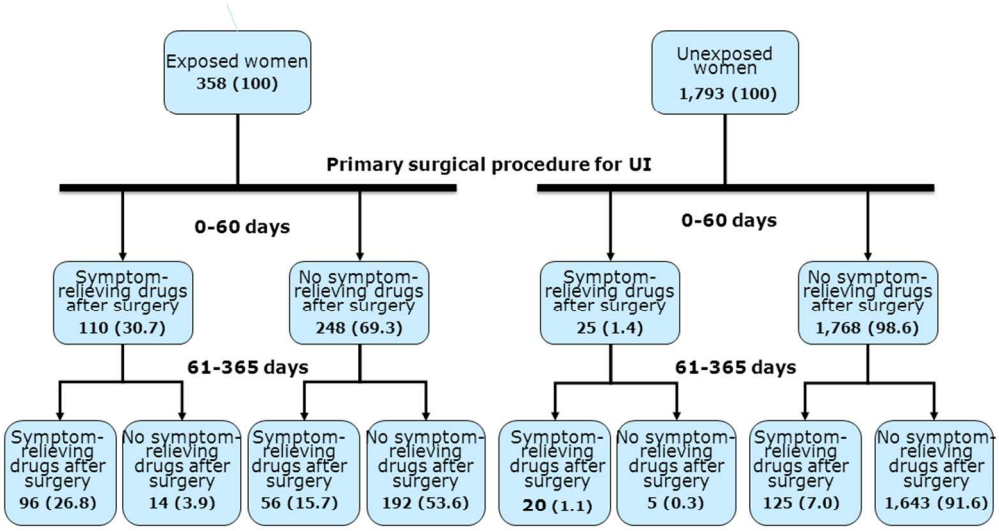

Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery

286x199mm (96 x 96 DPI)

Appendix 1 Surgical procedures according to the Danish Nordic Medico-Statistical Committee

KDG00 = Retropubic suspension of urethra
KDG01 = Percutaneous endoscopic retropubic suspension of urethra
KDG10 = Abdominovaginal suspension of bladder neck
KDG30 = Suprapubic sling urethrocystopexy
KDG31 = Percutaneous endoscopic suprapubic sling
KDG40 = Suprapubic urethrocystopexy
KDG50 = Transabdominal plastic repair of pelvic floor for urinary incontinence
KDG96 = Other operation on urethra or bladder neck for incontinence
KDG97 = Other percutaneous endoscopic operation on urethra or bladder neck for incontinence
KDV20 = Submucous urethral injection
KDV22 = Transluminal endoscopic submucous urethral injection
LEG00 = Vaginal urethrocystorrhaphy
LEG10 = Vaginal urethrocystopexy with use of sling
LEG10A = Vaginal urethrocystopexy with use of sling through foramen obturatum
LEG20 = Plastic repair of female pelvic floor with levator division
LEG96 = Other vaginal operation for incontinence

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 – Title page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5+6
Objectives	3	State specific objectives, including any prespecified hypotheses	5+6
Methods			
Study design	4	Present key elements of study design early in the paper	3+7,8,9,10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3+7,8,9,10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7-10
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7+8
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9+10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10+11
		(*b*) Describe any methods used to examine subgroups and interactions	-
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	13 + Table 1
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	9
Outcome data	15*	Report numbers of outcome events or summary measures over time	13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13 +Table 2
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14+15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14+15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Title page

Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Keywords: urinary incontinence, antimuscarinic drugs, surgery, clinical epidemiology, duloxetine

Word counts: 2,939

Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CPN = Unique personal identification number

DDD = total Defined Daily Dose

ICD = International Classification of Diseases

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

Abstract

Objective To describe the use of symptom-relieving drugs (antimuscarinic drugs or duloxetine) before and after surgery for urinary incontinence (UI); and for those with use of antimuscarinic drugs or duloxetine before surgery, to estimate the risk of being postoperative user, relative to those without use before surgery.

Design A historical population-based cohort study

Setting Denmark

Participants Women ≥ 18 years with a primary surgical procedure for UI from the county of Funen, Denmark between 1 January 1996 and 31 December 2006, extended to the Region of Southern Denmark from 1 January 2007 to end of 2010. For these women, data on redeemed prescriptions +/- 365 days of date of surgery were extracted.

Main outcome measures Effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Results Of 2,151 women with a primary surgical procedure for UI; 358 (16.6%) were preoperative users of antimuscarinic drugs or duloxetine and 1,793 were not (83.4%). A total of 110 (30.7%) of the preoperative users also redeemed prescriptions for these drugs within 0-60 days after surgery, and 152 (42.5%) of the preoperative users redeemed prescriptions for these drugs within 61-365 days after surgery. Among preoperative non-users, 25 (1.4%) and 145 (8.1%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antimuscarinic drugs or duloxetine was a strong risk factor of postoperative drug use, both within 0-60 days (adjusted OR=33.0, 95% confidence interval (CI) 20.0-54.7) and 61-365 days (OR=7.2, 95% CI 5.4-9.6).

Conclusions

A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other factors included in the regression model, preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor for postoperative use.

Introduction

Urinary incontinence (UI) is a very prevalent disorder among women (1), and a wide array of options for clinical managements exists. Current best practice is a stepwise strategy moving from conservative treatments such as behavioural alteration, pelvic floor muscle training and weight loss to pharmacological treatment and in selected cases surgery (2).

There are different pharmacological options to relieve the symptoms of UI, including antimuscarinic drugs, and duloxetine. Antimuscarinic drugs remain the main-stay in the treatment of urgency UI, mixed UI as well as the overactive bladder syndrome (3). Antimuscarinics reversibly block muscarinic receptors in the bladder wall, acting primarily by increasing bladder capacity rather than ablating detrusor overactivity. Although the site of action has been thought to be M2 and M3 receptors in detrusor smooth muscle during contraction, there is growing evidence that the therapeutic response might also be the result of antagonist effects on muscarinic receptors on afferent neurons (4) as well as central modulation. Duloxetine, a selective serotonin- and norepinephrine-reuptake inhibitor, is predominantly used as an antidepressant, but has also been licensed in some European countries for stress UI. Presumably duloxetine acts by central modulations, causing an increase in urethral sphincter tone (5).

During the last decades, the surgical treatments of UI in women have improved with the introduction of minimally-invasive sub-urethral sling procedures for UI (6–8), submucosal intraurethal injections of bulking agents (9) and intravesical injections of botulinum toxin (10); and the number of surgeries for UI has been increasing as well (11,12).

Three small studies by Segal et al. (n= 98), Yoo et al. (n=84), and Barber et al. (n=162) (13–15) have shown, that nearly 40% of preoperative antimuscarinic drug users continued the use after surgery for UI.

This topic is highly relevant in advising women who are candidates for surgical treatment for UI, if the results could be confirmed in larger studies.

The purpose of this study was to assess the use of symptom-relieving drugs before and after surgery for UI in a larger population and to examine possible risk factors of postoperative drug use.

Materials and Methods

Study population and settings

Data on all primary surgical procedures for UI in women during the study period from 1 January 1996 to 31 December 2010 were retrieved from the Danish National Patient Registry (NPR) (16). The International Classification of Diseases (ICD) procedure codes for data extraction are listed in Appendix 1. The study population included women ≥ 18 years undergoing a primary surgical procedure for UI in a hospital in the county of Funen (4 hospitals), Denmark, between 1 January 1996 and 31 December 2006. For the period 2007 through 2010 the geographical area was extended to include all hospitals from the Region of Southern Denmark (including Funen, a total of 13 hospitals). The latter was due to a change in the structure of health care in Denmark from counties to regions in 2007. Women with concomitant or prior surgery for pelvic organ prolapse were not excluded.

Data sources

Data for this study were retrieved from three Danish registers: the NPR, the Odense University Pharmacoepidemiologic Database (OPED), and the Statistics Denmark.

The NPR was established in 1977, and contains data on discharges from public hospitals in Denmark. The completeness of recordings has been estimated to be 99.4% (17). The registry contains information about the unique personal identification number (CPN) assigned for all Danish citizens, the dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses for every discharge, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (18,19) as well as codes from the Danish classification system of surgical procedures (20).

Information on relevant drugs (antimuscarinic drugs, duloxetine, and oestrogens) was retrieved within 1995-2011 for the entire study population from OPED by using CPN.

OPED contains person-identifiable data with complete coverage on all computerized prescription reimbursements from the County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and the prescription of drugs is very similar to the national average (21). The OPED is pharmacy-based and captures all reimbursed prescriptions.

Prescription reimbursements are offered as a part of the National Health Service to all legal inhabitants of Denmark; and given independently of patient income. Each record includes the CPN, the date of purchase, the pharmacy, a full account of what have been purchased, including brand name, Anatomical Therapeutic Chemical (ATC) classification code, total defined daily dose (DDD), dose unit, and quantity. The database does not contain information on drugs sold over the counter or drugs not reimbursed by the county authority (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level and annual income were retrieved from the Danish Integrated Database for Labor Market Research at the Statistics of Denmark. This database contains annually updated socioeconomic data for each Danish citizen, mainly supplied by tax authorities, educational institutions, and employment services (22).

Study drugs

Included drugs were antimuscarinic drugs (tolterodine [ATC G04BD07], solifenacin [ATC G04BD08], trospium chloride [ATC G04BD09], darifenacin [ATC G04BD10], fesoterodine [ATC G04BD11], oxybutinin [ATC G04BD04], flavoxate [ATC G04BD02]), duloxetine [ATC

N06AX21], and oestrogens [ATC G03C]. Propiverine [ATC G04BD6] has not been licensed in Denmark.

Exposed and unexposed cohorts

Exposed cohort: All women ≥ 18 years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and having redeemed one or more prescriptions for antimuscarinic drugs or duloxetine for UI within 365 days preceding the date of surgery (index date).

Unexposed cohort: All women ≥ 18 years undergoing a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark without having redeemed similar prescriptions within the same time frame.

Outcome data

For both exposed and unexposed women, the primary outcome was the use of symptom-relieving drugs, defined as having redeemed at least one prescription for antimuscarinic drugs or duloxetine within 1) 60 days after the index date (short term postoperatively), and 2) 61 days to 365 days after index date (long term postoperatively). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively.

Covariates

The use of symptom-relieving drugs might be affected by age, type of procedure, use of oestrogen, comorbidity, educational level, annual income, and calendar time; therefore these variables were included in the analysis as potential confounders.

Type of procedures: The types of UI surgery were divided into four groups according to the surgical procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types of UI surgeries.

Oestrogen: To adjust for preoperative oestrogen use, women were divided into those who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and those who had no preoperative oestrogen use. Both systemic and local oestrogens were included.

Comorbidity: The comorbidity was classified according to the Charlson comorbidity index (CCI) (23) – a well-known, validated and widely used quantitative measure of comorbid illness (24,25). It assigns different weights (1, 2, 3, and 6) to 19 different disease categories specified by medical condition and severity (for example, diabetes, cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). For each woman the CCI was computed based on her complete hospital discharge history from the NPR since 1977. A categorised version of the CCI with score values grouped were used: 0 (low), 1-2 (medium) and 3+ (high) (26).

Socio economic status: To measure socio economic status, information on education and annual income for each woman was retrieved. Education was categorised according to the highest attained educational level as "Basic" (basic school/high school education: 7-12 years of primary, secondary and grammar-school education), "Secondary" (vocational education, 10-12 years of education), and "Higher" (a university degree or an examination in another higher institution requiring an average a total of 13 years or more) (27).

On the basis of quartiles of annual income for each women at the year of her surgery, we categorised women in low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile) recipients.

Statistical analysis

We describe in a flowchart the use of symptom-relieving drugs within the first 365 days after surgery for the two groups of users and non-users of drugs prior to surgery.

We also constructed contingency tables for the main study variables, and computed the odds ratio (OR), with 95% confidence intervals (CI).

To analyse the significance of preoperative symptom-relieving drug use as risk factor of postoperative use (short- and long term), adjusted ORs were estimated by means of multivariate logistic regression models. Adjustment was made for age (18-39, 40-59, ≥ 60 years (reference)), type of procedures (toMUS (reference), rpMUS, Bulking, others), education (basic (reference), secondary, higher), annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+), calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365 days preceding surgery (No (reference), Yes).

All analyses were performed using Stata Release 12.0.

Results

A total of 2,151 women had a primary surgical procedure for UI between 1 January 1996 and 31 December 2010 (2,073 had solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse).

Of the 2,151 women, 358 (16.6%) were exposed to symptom-relieving drugs within 365 days before surgery, and 1,793 (83.4%) were not. The use of symptom-relieving drugs within 365 days after surgery is detailed in both these cohorts (Figure 1).

Women having redeemed prescriptions for symptom-relieving drugs before surgery (exposed)

Out of the 358 women with prior drug use of antimuscarinic drugs or duloxetine, 110 (30.7%) women redeemed prescriptions for these drugs within 0-60 days after surgery, and 98 out of the 358 women (26.8%) even within 61-365 days after surgery (Figure 1). On the other hand, 248 (69.3%) women did not redeem a prescription for symptom-relieving drugs within 0-60 days after surgery, and the majority of these women (192/358=53.6%) also abstained from symptom-relieving drugs during the time frame 61-365 days after surgery (Figure 1). For the exposed women, the number of redeemed prescriptions was 1,360 preoperatively (DDD 174.6 (SD ±202)), postoperatively 126 (DDD 32.3 (SD ±63.5)) within 0-60 days, and 984 (DDD 140.4 (SD ±234.3)) within 61-365 days.

Women with no usage of symptom-relieving drugs before surgery (unexposed)

Only 25 of the 1,793 (1.4%) women redeemed a first time prescription for symptom-relieving drugs within 0-60 days after surgery, and these women typically continued their use within 61-365 days after surgery (20 women) (Figure 1). Of the 1,793 women who did not redeem prescription before surgery, 1,768 (98.6%) women remained non-users within 0-60 days after surgery, and the vast majority of these women (1,643/1,793=91.6%) continued as non-users also within 61-365 days after surgery (Figure 1). For the unexposed women, the number of redeemed prescriptions postoperatively was 129 (DDD 0.8 (SD ±8.8)) within 0-60 days, and 403 (DDD 11.9 (SD ±54.8)) within 61-365 days.

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedures were rpMUS or toMUS. The exposed women were more likely to have had a trans-obturator mid-urethral sling or a bulking agent injection compared to unexposed women, where retropubic mid-urethral sling was the preferred procedure. The most commonly prescribed drugs prior to surgery were solifenacin and tolterodine. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, to have higher comorbidity, a lower educational level, and a lower annual income.

Among women with prior drug use, the unadjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 31.1 (95% CI 19.9-49.4), and 8.4 (95% CI 6.4-11.0), respectively. The adjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 33.0 (95% CI 20.0-54.7), and 7.2 (95% CI 5.4-9.6), respectively. The details from logistic regression models are presented in Table 2 showing the impact of each risk factor included. Preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor of

postoperative use (both short and long term); i.e. compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative user.

Discussion

Among 2,151 women undergoing surgery for UI less than 20% had redeemed prescriptions for antimuscarinic drugs or duloxetine prior to surgery, and nearly 30% of these continued using the drugs within 2 months after surgery and typically staid long term users. Among the women without drug use before surgery, the vast majority continued being non-users after surgery, with less than 9% redeeming a first time prescription of the drugs.

Our study has several strengths: 1) it is a population-based study in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) The source of procedure has high coverage and validity. The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a moderate-to-high quality of the data with positive predictive values of 94-100% (28–30), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (21), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in the follow up period for all included women, 6) outcome data on postoperative drug prescriptions were obtained independently of exposure assessment preventing differential misclassification of the outcome, and finally 7) the drugs and the surgical procedures included in our study do not have other indications than UI, which strongly limits the number of alternative interpretations of our findings.

Our study also has limitations. Data on redeemed prescription are only a surrogate for drug intake. However, antimuscarinic drugs and especially duloxetine are expensive drugs with significant patient co-payment, and we find it unlikely that these drugs to any major extent would be bought and not consumed. We had no data on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome were predominant, just as there was no available data on findings in urodynamic studies. The exposed cohort were receiving symptom-relieving drugs, and

thus these women most likely had predominantly mixed UI, whereas the unexposed women most likely had predominantly stress UI. We were not able to control for potential confounders such as body mass index, parity, grade of concomitant cystocele, severity of UI symptoms, intrinsic factor deficiency, or menopausal status, which are well-known risk factors for persistent UI after surgery for UI (31–35). One might speculate whether duration of time with UI symptoms and preoperative conservative treatment could impact our estimates of postoperative drug use, as women in the exposed cohort could have longer disease duration before surgery than women in the unexposed cohort. This could be due to a more extensive preoperative evaluations including urodynamic studies, as well as waiting time to evaluate the effect of drug treatment in the exposed cohort. However, to our knowledge no studies have indicated that disease duration or conservative treatment of UI is a risk factor for postoperative drug use, and therefore we do not believe our estimates of postoperative drug use are influenced by duration of time with UI symptoms.

Currently available drugs for UI are expensive, have many side effects (36), and the long term persistence of the use of antimuscarinic drugs as well as duloxetine is low (without regarding surgery) (37–39). All the latter may contribute to the cessation of the drugs; and thus a reduction in the drug usage may not be explained entirely by the surgery. The reasons for cessation of drug use after surgery can be influenced by other factors as well. For example, misinterpretation of symptoms/investigations may lead to treatment of stress UI with symptom-relieving drugs.

The risk of initiating medical treatment after surgery for UI (based on de-novo surgery) is small, but well-known (40).

There was a low rate of concomitant pelvic reconstructive surgery, as was expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (41).

To our knowledge, this is the largest study addressing the changes in use of symptom-relieving drugs in relation to surgery for UI, and with a large number of possible risk factors of postoperative use. Our results in this larger population are consistent with the previous smaller studies (13–15). Compared to the previous studies, our study included a larger number of women with UI surgery, estimated the risk of postoperatively symptom-relieving drug use with adjustment for a number of relevant covariates, and assessed the risk of both short term and long term use. Our study also showed that educational level, personal income, and type of procedure did not seem to influence the risk of postoperative drug use. High comorbidity was found to significantly increase the risk, but it did not influence the estimates as much as the preoperative drug use, which was the strongest risk factor of postoperative drug use.

In conclusion, we found that a substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority (8.1%) of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to preoperative drug use no other factors in the regression model contributed considerably to the OR of being short or long term postoperative user of symptom-relieving drugs.

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Competing interests "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Ethical approval The study was approved by the Danish Data Protection Agency (no. 2009-41-3564). According to Danish law, ethical review board approval or patient consent are not required for register-based studies.

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Data sharing According to the Danish Data Detection Agency, we are not allowed to share our data from the Danish National Patient Registry. This would require a special approval from both the Danish Data Detection Agency and the Statens Serum Institut who delivers the data from the Danish National Patient Registry.

Article Summary:

Article focus: Urinary incontinence is a prevalent disorder among women. This study focus on both surgical and medical treatment of urinary incontinence. We examined the effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Key messages: A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other included factors, preoperative use of antimuscarinic drugs or duloxetine was the strongest risk factor of postoperative use.

Strengths and limitations of this study:

A population-based study.

2,151 included women.

High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, and personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on type of urinary incontinence or urodynamic studies

Table 1 Baseline characteristics of all included women (N=2,151) having primary surgery for urinary incontinence in Denmark, 1996-2010.

	Exposed n= 358 (16.6%)	Unexposed n=1,793 (83.4%)
Mean age (±SD), years (At time of first UI surgery)	60.9 (±12.7)	54.5 (±12.6)
Age groups n (%)	13 (3.6)	199 (11.1)
18-39	151 (42.2)	956 (53.3)
40-59	194 (54.2)	638 (35.6)
60-		
Procedures n (%)		
rpMUS	73 (20.4)	602 (33.6)
toMUS	172 (48.0)	800 (44.6)
Bulking	101 (28.2)	259 (14.4)
Others	12 (3.4)	132 (7.4)
Concomitant prolapse surgery n (%)	11 (3.1)	67 (3.7)
Symptom-relieving medications n (%)*		
Solifenacin	176 (49.2)	-
Tolterodine	84 (23.5)	-
Fesoterodine	63 (17.6)	-
Trospium chloride	32 (8.9)	-
Obybutynin	29 (8.1)	-
Darifenacin	14 (3.9)	-
Emepronium	6 (1.7)	-
Duloxetine	6 (1.7)	-
Oestrogen users n (%)**		
No	135 (37.7)	1,073 (59.8)
Yes	223 (62.3)	720 (40.2)
Comorbidity (CCI) n (%)		
0	214 (59.8)	1,298 (72.3)
1-2	107 (29.9)	413 (23.0)
3+	37 (10.3)	82 (4.6)
Educational level n (%)***		
Basic	178 (51.7)	739 (41.8)
Secondary	125 (36.3)	645 (36.5)
Higher	41 (11.9)	383 (21.7)
Annual income n (%)		
Low (1st quartile)	100 (27.9)	437 (24.4)
Middle (2nd-3rd quartile)	206 (57.6)	871 (48.6)
High (4th quartile)	52 (14.5)	485 (27.0)
Year of surgery n (%)		
1996-2006	50 (14.0)	409 (22.8)
2007-2008	118 (33.0)	673 (37.5)
2009-2010	190 (53.0)	711 (39.7)

*Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.
**Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
***Unknown highest attained educational level: 40 women
Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Table 2 Risk factors of postoperative use of antimuscarinic drugs/duloxetine. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii) on long term (61-356 days after surgery)

	Post op non-use Number	Post op short term use		Post op non-use Number	Post op long term use	
		Number	OR (95% CI)		Number	OR (95% CI)
Preoperative use						
No	1,768	25	reference	1,648	145	reference
Yes	248	110	33.0 (20.0-54.7)	145	152	7.2 (5.4-9.6)
Age group						
18-39	209	3	0.3 (0.1-1.4)	204	8	0.3 (0.1-0.7)
40-59	1,063	44	0.6 (0.3-0.9)	999	108	0.6 (0.4-0.8)
60-	744	88	reference	651	181	reference
Procedure						
rpMUS	659	16	0.6 (0.3-1.2)	612	63	0.6 (0.4-0.9)
toMUS	894	78	reference	842	130	reference
Bulking	322	38	1.2 (0.7-2.0)	262	98	0.5 (0.3-0.7)
Others	141	3	0.5 (0.1-2.6)	138	6	0.3 (0.1-1.0)
Preoperative use of oestrogen*						
No	1,159	49	reference	1,090	118	reference
Yes	857	86	0.8 (0.5-1.4)	764	179	1.0 (0.7-1.4)
Comorbidity (CCI)						
0	1,442	70	reference	1,352	160	reference
1-2	467	53	1.5 (0.9-2.4)	419	101	1.5 (1.1-2.0)
3+	107	12	0.9 (0.4-1.9)	83	36	1.9 (1.2-3.2)
Educational level**						
Basic	846	71	reference	761	156	reference
Secondary	727	43	0.9 (0.6-1.5)	674	96	0.9 (0.6-1.2)
Higher	407	17	1.1 (0.6-2.3)	385	39	0.8 (0.5-1.3)
Annual income						
Low	489	48	reference	442	95	reference
Middle	1,010	67	0.7 (0.4-1.2)	929	148	0.9 (0.6-1.2)
High	517	20	0.9 (0.4-1.8)	483	54	1.1 (0.7-1.9)
Year of surgery						
1996-2006	448	11	0.7 (0.3-1.7)	427	32	0.5 (0.3-0.9)
2007-2008	739	52	reference	675	116	reference
2009-2010	829	72	0.9 (0.6-1.4)	752	149	1.0 (0.7-1.4)

*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
**Unknown highest attained educational level: 40 women
Abbreviations: post op = postoperative, OR = odds ratio, CI = confidence interval, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Figure 1 Women (N=2,151) with primary surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.

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Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Title page

Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CPN = Unique personal identification number

DDD = total Defined Daily Dose

ICD = International Classification of Diseases

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

Abstract

Objective To describe the use of symptom-relieving drugs (antimuscarinic drugs or duloxetine) before and after surgery for urinary incontinence (UI); and for those with use of antimuscarinic drugs or duloxetine before surgery, to estimate the risk of being postoperative user, relative to those without use before surgery.

Design A historical population-based cohort study

Setting Denmark

Participants Women ≥ 18 years with a first-time surgical procedure for UI from the county of Funen, Denmark between 1 January 1996 and 31 December 2006, extended to the Region of Southern Denmark from 1 January 2007 to end of 2010. For these women, data on redeemed prescriptions +/- 365 days of date of surgery were extracted.

Main outcome measures Effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Results Of 2,151 women with a first-time surgical procedure for UI; 358 (16.6%) were preoperative users of antimuscarinic drugs or duloxetine and 1,793 were not (83.4%). A total of 110 (30.7%) of the preoperative users also redeemed prescriptions for these drugs within 0-60 days after surgery, and 152 (42.5%) of the preoperative users redeemed prescriptions for these drugs within 61-365 days after surgery. Among preoperative non-users, 25 (1.4%) and 145 (8.1%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antimuscarinic drugs or duloxetine was a strong risk factor of postoperative drug use, both within 0-60 days (adjusted OR=33.0, 95% confidence interval (CI) 20.0-54.7) and 61-365 days (OR=7.2, 95% CI 5.4-9.6).

Conclusions

A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other factors included in the regression model, preoperative use of antimuscarinic drugs or duloxetine was the strongest risk factor for postoperative use.

Article Summary:

Article focus: Urinary incontinence is a prevalent disorder among women. This study focus on both surgical and medical treatment of urinary incontinence. We examined the effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Key messages: A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other included factors, preoperative use of antimuscarinic drugs or duloxetine was the strongest risk factor of postoperative use.

Strengths and limitations of this study:

A population-based study.

2,151 included women.

High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, and personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on type of urinary incontinence or urodynamic studies

Introduction

Urinary incontinence (UI) is a very prevalent disorder among women (1), and a wide array of options for clinical managements exists. Current best practice is a stepwise strategy moving from conservative treatments such as behavioural alteration, pelvic floor muscle training and weight loss to pharmacological treatment and in selected cases surgery (2).

There are different pharmacological options to relieve the symptoms of UI, including antimuscarinic drugs, and duloxetine. Antimuscarinic drugs remain the main-stay in the treatment of urgency UI, mixed UI as well as the overactive bladder syndrome (3). Antimuscarinics reversibly block muscarinic receptors in the bladder wall, acting primarily by increasing bladder capacity rather than ablating detrusor overactivity. Although the site of action has been thought to be M2 and M3 receptors in detrusor smooth muscle during contraction, there is growing evidence that the therapeutic response might also be the result of antagonist effects on muscarinic receptors on afferent neurons (4) as well as central modulation. Duloxetine, a selective serotonin- and norepinephrine-reuptake inhibitor, is predominantly used as an antidepressant, but has also been licensed in some European countries for stress UI. Presumably duloxetine acts by central modulations, causing an increase in urethral sphincter tone (5).

During the last decades, the surgical treatments of UI in women have improved with the introduction of minimally-invasive sub-urethral sling procedures for UI (6–8), submucosal intraurethal injections of bulking agents (9) and intravesical injections of botulinum toxin (10); and the number of surgeries for UI has been increasing as well (11,12).

Three small studies by Segal et al. (n= 98), Yoo et al. (n=84), and Barber et al. (n=162) (13–15) have shown, that nearly 40% of preoperative antimuscarinic drug users continued the use after surgery for UI.

This topic is highly relevant in advising women who are candidates for surgical treatment for UI, if the results could be confirmed in larger studies. Women being counselled for incontinence surgery would be better served with information on the likelihood of both having to remain on drug use or having to start the use for other lower urinary tract symptoms following their procedure, therefore the purpose of this study was to assess the use of symptom-relieving drugs before and after surgery for UI in a larger population and to examine possible risk factors of postoperative drug use.

Materials and Methods

Study population and settings

Data on all first-time surgical procedures for UI in women during the study period from 1 January 1996 to 31 December 2010 were retrieved from the Danish National Patient Registry (NPR) (16). The International Classification of Diseases (ICD) procedure codes for data extraction are listed in Appendix 1. The study population included women ≥ 18 years undergoing a first-time surgical procedure for UI in a hospital in the county of Funen (4 hospitals), Denmark, between 1 January 1996 and 31 December 2006. For the period 2007 through 2010 the geographical area was extended to include all hospitals from the Region of Southern Denmark (including Funen, a total of 13 hospitals). The latter was due to a change in the structure of health care in Denmark from counties to regions in 2007. Women with concomitant or prior surgery for pelvic organ prolapse were not excluded. In women with more than one procedure code for UI in the study period, the first code was chosen as the included procedure.

Data sources

Data for this study were retrieved from three Danish registers: the NPR, the Odense University Pharmacoepidemiologic Database (OPED), and the Statistics Denmark.

The NPR was established in 1977, and contains data on discharges from public hospitals in Denmark. The completeness of recordings has been estimated to be 99.4% (17). The registry contains information about the unique personal identification number (CPN) assigned for all Danish citizens, the dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses for every discharge, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (18,19) as well as codes from the Danish classification system of surgical procedures (20).

Information on relevant drugs (antimuscarinic drugs, duloxetine, and oestrogens) was retrieved within 1995-2011 for the entire study population from OPED by using CPN.

OPED contains person-identifiable data with complete coverage on all computerized prescription reimbursements from the County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and the prescription of drugs is very similar to the national average (21). The OPED is pharmacy-based and captures all reimbursed prescriptions.

Prescription reimbursements are offered as a part of the National Health Service to all legal inhabitants of Denmark; and given independently of patient income. Each record includes the CPN, the date of purchase, the pharmacy, a full account of what have been purchased, including brand name, Anatomical Therapeutic Chemical (ATC) classification code, total defined daily dose (DDD), dose unit, and quantity. The database does not contain information on indicative diagnoses, drugs sold over the counter or drugs not reimbursed by the county authority (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level and annual income were retrieved from the Danish Integrated Database for Labor Market Research at the Statistics of Denmark. This database contains annually updated socioeconomic data for each Danish citizen, mainly supplied by tax authorities, educational institutions, and employment services (22).

Study drugs

Included drugs were antimuscarinic drugs (tolterodine [ATC G04BD07], solifenacin [ATC G04BD08], trospium chloride [ATC G04BD09], darifenacin [ATC G04BD10], fesoterodine [ATC G04BD11], oxybutinin [ATC G04BD04], flavoxate [ATC G04BD02]), duloxetine [ATC

N06AX21] (only brand name Yentreve®), and oestrogens [ATC G03C]. Propiverine [ATC G04BD6] has not been licensed in Denmark.

Exposed and unexposed cohorts

Exposed cohort: All women ≥ 18 years undergoing a first-time surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and having redeemed one or more prescriptions for antimuscarinic drugs or duloxetine for UI within 365 days preceding the date of surgery (index date).

Unexposed cohort: All women ≥ 18 years undergoing a first-time surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark without having redeemed similar prescriptions within the same time frame.

Outcome data

For both exposed and unexposed women, the first-time outcome was the use of symptom-relieving drugs, defined as having redeemed at least one prescription for antimuscarinic drugs or duloxetine within 1) 60 days after the index date (short term postoperatively), and 2) 61 days to 365 days after index date (long term postoperatively). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively.

Covariates

The use of symptom-relieving drugs might be affected by age, type of procedure, use of oestrogen, comorbidity, educational level, annual income, and calendar time; therefore these variables were included in the analysis as potential confounders.

Type of procedures: The types of UI surgery were divided into four groups according to the surgical procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types of UI surgeries.

Oestrogen: To adjust for preoperative oestrogen use, women were divided into those who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and those who had no preoperative oestrogen use. Both systemic and local oestrogens were included.

Comorbidity: The comorbidity was classified according to the Charlson comorbidity index (CCI) (23) – a well-known, validated and widely used quantitative measure of comorbid illness (24,25). It assigns different weights (1, 2, 3, and 6) to 19 different disease categories specified by medical condition and severity (for example, diabetes, cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). For each woman the CCI was computed based on her complete hospital discharge history from the NPR since 1977. A categorised version of the CCI with score values grouped were used: 0 (low), 1-2 (medium) and 3+ (high) (26).

Socio economic status: To measure socio economic status, information on education and annual income for each woman was retrieved. Education was categorised according to the highest attained educational level as "Basic" (basic school/high school education: 7-12 years of first-time, secondary and grammar-school education), "Secondary" (vocational education, 10-12 years of education), and "Higher" (a university degree or an examination in another higher institution requiring an average a total of 13 years or more) (27).

On the basis of quartiles of annual income for each women at the year of her surgery, we categorised women in low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile) recipients.

Statistical analysis

We describe in a flowchart the use of symptom-relieving drugs within the first 365 days after surgery for the two groups of users and non-users of drugs prior to surgery.

We also constructed contingency tables for the main study variables, and computed the odds ratio (OR), with 95% confidence intervals (CI).

To analyse the significance of preoperative symptom-relieving drug use as risk factor of postoperative use (short- and long term), adjusted ORs were estimated by means of multivariate logistic regression models. Adjustment was made for age (18-39, 40-59, ≥ 60 years (reference)), type of procedures (toMUS (reference), rpMUS, Bulking, others), education (basic (reference), secondary, higher), annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+), calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365 days preceding surgery (No (reference), Yes).

All analyses were performed using Stata Release 12.0.

Results

A total of 2,151 women had a first-time surgical procedure for UI between 1 January 1996 and 31 December 2010 (2,073 had solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse).

Of the 2,151 women, 358 (16.6%) were exposed to symptom-relieving drugs within 365 days before surgery, and 1,793 (83.4%) were not. The use of symptom-relieving drugs within 365 days after surgery is detailed in both these cohorts (Figure 1).

Women having redeemed prescriptions for symptom-relieving drugs before surgery (exposed)

Out of the 358 women with prior drug use of antimuscarinic drugs or duloxetine, 110 (30.7%) women redeemed prescriptions for these drugs within 0-60 days after surgery, and 98 out of the 358 women (26.8%) even within 61-365 days after surgery (Figure 1). On the other hand, 248 (69.3%) women did not redeem a prescription for symptom-relieving drugs within 0-60 days after surgery, and the majority of these women (192/358=53.6%) also abstained from symptom-relieving drugs during the time frame 61-365 days after surgery (Figure 1). For the exposed women, the number of redeemed prescriptions was 1,360 preoperatively (DDD 174.6 (SD ±202)), postoperatively 126 (DDD 32.3 (SD ±63.5)) within 0-60 days, and 984 (DDD 140.4 (SD ±234.3)) within 61-365 days.

Women with no usage of symptom-relieving drugs before surgery (unexposed)

Only 25 of the 1,793 (1.4%) women redeemed a first time prescription for symptom-relieving drugs within 0-60 days after surgery, and these women typically continued their use within 61-365 days after surgery (20 women) (Figure 1). Of the 1,793 women who did not redeem prescription before surgery, 1,768 (98.6%) women remained non-users within 0-60 days after surgery, and the vast majority of these women (1,643/1,793=91.6%) continued as non-users also within 61-365 days after surgery (Figure 1). For the unexposed women, the number of redeemed prescriptions postoperatively was 129 (DDD 0.8 (SD ±8.8)) within 0-60 days, and 403 (DDD 11.9 (SD ±54.8)) within 61-365 days.

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedures were rpMUS or toMUS. The exposed women were more likely to have had a trans-obturator mid-urethral sling or a bulking agent injection compared to unexposed women, where retropubic mid-urethral sling was the preferred procedure. The most commonly prescribed drugs prior to surgery were solifenacin and tolterodine. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, to have higher comorbidity, a lower educational level, and a lower annual income.

Among women with prior drug use, the unadjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 31.1 (95% CI 19.9-49.4), and 8.4 (95% CI 6.4-11.0), respectively. The adjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 33.0 (95% CI 20.0-54.7), and 7.2 (95% CI 5.4-9.6), respectively. The details from logistic regression models are presented in Table 2 showing the impact of each risk factor included. Preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor of

postoperative use (both short and long term); i.e. compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative user.

Discussion

Among 2,151 women undergoing first-time surgery for UI less than 20% had redeemed prescriptions for antimuscarinic drugs or duloxetine prior to surgery, and nearly 30% of these continued using the drugs within 2 months after surgery and typically stayed long term users. Among the women without drug use before surgery, the vast majority continued being non-users after surgery, with fewer than 9% redeeming a first time prescription of the drugs.

Our study has several strengths: 1) it is a population-based study in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) The source of procedure has high coverage and validity. The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a moderate-to-high quality of the data with positive predictive values of 94-100% (28–30), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (21), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in the follow up period for all included women, 6) outcome data on postoperative drug prescriptions were obtained independently of exposure assessment preventing differential misclassification of the outcome, and finally 7) the drugs and the surgical procedures included in our study do not have other indications than UI, which strongly limits the number of alternative interpretations of our findings.

Our study also has limitations. Data on redeemed prescription are only a surrogate for drug intake. However, antimuscarinic drugs and especially duloxetine are expensive drugs with significant patient co-payment, and we find it unlikely that these drugs to any major extent would be bought and not consumed. We had no data on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome were predominant, just as there was no available data on findings in urodynamic studies. The exposed cohort were receiving symptom-relieving drugs, and

thus these women most likely had predominantly mixed UI, whereas the unexposed women most likely had predominantly stress UI. We were not able to control for potential confounders such as body mass index, parity, grade of concomitant cystocele, severity of UI symptoms, intrinsic sphincter deficiency, or menopausal status, which are well-known risk factors for persistent UI after surgery for UI (31–35). One might speculate whether duration of time with UI symptoms and preoperative conservative treatment could impact our estimates of postoperative drug use, as women in the exposed cohort could have longer disease duration before surgery than women in the unexposed cohort. This could be due to a more extensive preoperative evaluations including urodynamic studies, as well as waiting time to evaluate the effect of drug treatment in the exposed cohort. However, to our knowledge no studies have indicated that disease duration or conservative treatment of UI is a risk factor for postoperative drug use, and therefore we do not believe our estimates of postoperative drug use are influenced by duration of time with UI symptoms.

Currently available drugs for UI are expensive, have many side effects (36), and the long term persistence of the use of antimuscarinic drugs as well as duloxetine is low (without regarding surgery) (37–39). All the latter may contribute to the cessation of the drugs; and thus a reduction in the drug usage may not be explained entirely by the surgery. The reasons for cessation of drug use after surgery can be influenced by other factors as well. For example, misinterpretation of symptoms/investigations may lead to treatment of stress UI with symptom-relieving drugs.

The risk of initiating medical treatment after surgery for UI (based on de-novo surgery) is small, but well-known (40).

There was a low rate of concomitant pelvic reconstructive surgery, as was expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (41). Age was higher among exposed than among unexposed, and therefore expectedly, we found a higher proportion of women

with high comorbidity in the exposed group – and furthermore not surprisingly a higher proportion of Bulking procedures among exposed as this procedure often is preferred in women with high comorbidity.

To our knowledge, this is the largest study addressing the changes in use of symptom-relieving drugs in relation to surgery for UI, and with a large number of possible risk factors of postoperative use. Our results in this larger population are consistent with the previous smaller studies (13–15). Compared to the previous studies, our study included a larger number of women with UI surgery, estimated the risk of postoperatively symptom-relieving drug use with adjustment for a number of relevant covariates, and assessed the risk of both short term and long term use. Our study also showed that educational level, personal income, and type of procedure did not seem to influence the risk of postoperative drug use. High comorbidity was found to significantly increase the risk, but it did not influence the estimates as much as the preoperative drug use, which was the strongest risk factor of postoperative drug use.

More studies are needed to examine the possible impact of body mass index, menopausal status, the predominant type of incontinence, and the relationship between time from diagnosis of UI to performed surgery and the following probability of receiving symptom-relieving drugs.

In conclusion, we found that a substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority (8.1%) of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to preoperative drug use no other factors in the regression model contributed considerably to the OR of being short or long term postoperative user of symptom-relieving drugs. Counselling women prior to UI surgery should therefore include information on a high risk of continuing use after surgery for preoperative users of symptom-relieving drugs, and preoperative non-users have a risk – although it is low – of becoming a user

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Competing interests "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Ethical approval The study was approved by the Danish Data Protection Agency (no. 2009-41-3564). According to Danish law, ethical review board approval or patient consent are not required for register-based studies.

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Data sharing According to the Danish Data Detection Agency, we are not allowed to share our data from the Danish National Patient Registry. This would require a special approval from both the Danish Data Detection Agency and the Statens Serum Institut who delivers the data from the Danish National Patient Registry.

Table 1 Baseline characteristics of all included women (N=2,151) having first-time surgery for urinary incontinence in Denmark, 1996-2010.

	Exposed n= 358 (16.6%)	Unexposed n=1,793 (83.4%)
Mean age (±SD), years (At time of first UI surgery)	60.9 (±12.7)	54.5 (±12.6)
Age groups n (%)	13 (3.6)	199 (11.1)
18-39	151 (42.2)	956 (53.3)
40-59	194 (54.2)	638 (35.6)
60-		
Procedures n (%)		
rpMUS	73 (20.4)	602 (33.6)
toMUS	172 (48.0)	800 (44.6)
Bulking	101 (28.2)	259 (14.4)
Others	12 (3.4)	132 (7.4)
Concomitant prolapse surgery n (%)	11 (3.1)	67 (3.7)
Symptom-relieving medications n (%)*		
Solifenacin	176 (49.2)	-
Tolterodine	84 (23.5)	-
Fesoterodine	63 (17.6)	-
Trospium chloride	32 (8.9)	-
Obybutynin	29 (8.1)	-
Darifenacin	14 (3.9)	-
Emepronium	6 (1.7)	-
Duloxetine	6 (1.7)	-
Oestrogen users n (%)**		
No	135 (37.7)	1,073 (59.8)
Yes	223 (62.3)	720 (40.2)
Comorbidity (CCI) n (%)		
0	214 (59.8)	1,298 (72.3)
1-2	107 (29.9)	413 (23.0)
3+	37 (10.3)	82 (4.6)
Educational level n (%)***		
Basic	178 (51.7)	739 (41.8)
Secondary	125 (36.3)	645 (36.5)
Higher	41 (11.9)	383 (21.7)
Annual income n (%)		
Low (1st quartile)	100 (27.9)	437 (24.4)
Middle (2nd-3rd quartile)	206 (57.6)	871 (48.6)
High (4th quartile)	52 (14.5)	485 (27.0)
Year of surgery n (%)		
1996-2006	50 (14.0)	409 (22.8)
2007-2008	118 (33.0)	673 (37.5)
2009-2010	190 (53.0)	711 (39.7)

*Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.
**Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
***Unknown highest attained educational level: 40 women
Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Table 2 Risk factors of postoperative use of antimuscarinic drugs/duloxetine. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii) on long term (61-356 days after surgery)

	Post op non-use Number	Post op short term use		Post op non-use Number	Post op long term use	
		Number	OR (95% CI)		Number	OR (95% CI)
Preoperative use						
No	1,768	25	reference	1,648	145	reference
Yes	248	110	33.0 (20.0-54.7)	145	152	7.2 (5.4-9.6)
Age group						
18-39	209	3	0.3 (0.1-1.4)	204	8	0.3 (0.1-0.7)
40-59	1,063	44	0.6 (0.3-0.9)	999	108	0.6 (0.4-0.8)
60-	744	88	reference	651	181	reference
Procedure						
rpMUS	659	16	0.6 (0.3-1.2)	612	63	0.6 (0.4-0.9)
toMUS	894	78	reference	842	130	reference
Bulking	322	38	1.2 (0.7-2.0)	262	98	0.5 (0.3-0.7)
Others	141	3	0.5 (0.1-2.6)	138	6	0.3 (0.1-1.0)
Preoperative use of oestrogen*						
No	1,159	49	reference	1,090	118	reference
Yes	857	86	0.8 (0.5-1.4)	764	179	1.0 (0.7-1.4)
Comorbidity (CCI)						
0	1,442	70	reference	1,352	160	reference
1-2	467	53	1.5 (0.9-2.4)	419	101	1.5 (1.1-2.0)
3+	107	12	0.9 (0.4-1.9)	83	36	1.9 (1.2-3.2)
Educational level**						
Basic	846	71	reference	761	156	reference
Secondary	727	43	0.9 (0.6-1.5)	674	96	0.9 (0.6-1.2)
Higher	407	17	1.1 (0.6-2.3)	385	39	0.8 (0.5-1.3)
Annual income						
Low	489	48	reference	442	95	reference
Middle	1,010	67	0.7 (0.4-1.2)	929	148	0.9 (0.6-1.2)
High	517	20	0.9 (0.4-1.8)	483	54	1.1 (0.7-1.9)
Year of surgery						
1996-2006	448	11	0.7 (0.3-1.7)	427	32	0.5 (0.3-0.9)
2007-2008	739	52	reference	675	116	reference
2009-2010	829	72	0.9 (0.6-1.4)	752	149	1.0 (0.7-1.4)

*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
**Unknown highest attained educational level: 40 women
Abbreviations: post op = postoperative, OR = odds ratio, CI = confidence interval, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Figure 1 Women (N=2,151) with first-time surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.

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Title page

Use of symptom-relieving drugs before and after surgery for urinary incontinence in women – A cohort study

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Abbreviations

ATC = The Anatomical, Therapeutic and Chemical classification system

CCI = Charlson comorbidity index

CI = Confidence Interval

CPN = Unique personal identification number

DDD = total Defined Daily Dose

ICD = International Classification of Diseases

NPR = Danish National Patient Register

OPED = Odense University Pharmacoepidemiologic Database

OR = Odds ratio

rpMUS= retropubic mid-urethral sling

toMUS= Trans-obturator mid-urethral sling

UI = Urinary Incontinence

Abstract

Objective To describe the use of symptom-relieving drugs (antimuscarinic drugs or duloxetine) before and after surgery for urinary incontinence (UI); and for those with use of antimuscarinic drugs or duloxetine before surgery, to estimate the risk of being postoperative user, relative to those without use before surgery.

Design A historical population-based cohort study

Setting Denmark

Participants Women ≥ 18 years with a ~~primary~~first-time surgical procedure for UI from the county of Funen, Denmark between 1 January 1996 and 31 December 2006, extended to the Region of Southern Denmark from 1 January 2007 to end of 2010. For these women, data on redeemed prescriptions +/- 365 days of date of surgery were extracted.

Main outcome measures Effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Results Of 2,151 women with a ~~primary~~first-time surgical procedure for UI; 358 (16.6%) were preoperative users of antimuscarinic drugs or duloxetine and 1,793 were not (83.4%). A total of 110 (30.7%) of the preoperative users also redeemed prescriptions for these drugs within 0-60 days after surgery, and 152 (42.5%) of the preoperative users redeemed prescriptions for these drugs within 61-365 days after surgery. Among preoperative non-users, 25 (1.4%) and 145 (8.1%) redeemed prescriptions within 0-60 and 61-365 days after surgery, respectively.

Pre-surgery exposure to antimuscarinic drugs or duloxetine was a strong risk factor of postoperative drug use, both within 0-60 days (adjusted OR=33.0, 95% confidence interval (CI) 20.0-54.7) and 61-365 days (OR=7.2, 95% CI 5.4-9.6).

Conclusions

A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other factors included in the regression model, preoperative use of antimuscarinic drugs or duloxetine was the ~~absolutely~~ strongest risk factor for postoperative use.

Introduction

Urinary incontinence (UI) is a very prevalent disorder among women (1), and a wide array of options for clinical managements exists. Current best practice is a stepwise strategy moving from conservative treatments such as behavioural alteration, pelvic floor muscle training and weight loss to pharmacological treatment and in selected cases surgery (2).

There are different pharmacological options to relieve the symptoms of UI, including antimuscarinic drugs, and duloxetine. Antimuscarinic drugs remain the main-stay in the treatment of urgency UI, mixed UI as well as the overactive bladder syndrome (3). Antimuscarinics reversibly block muscarinic receptors in the bladder wall, acting primarily by increasing bladder capacity rather than ablating detrusor overactivity. Although the site of action has been thought to be M2 and M3 receptors in detrusor smooth muscle during contraction, there is growing evidence that the therapeutic response might also be the result of antagonist effects on muscarinic receptors on afferent neurons (4) as well as central modulation. Duloxetine, a selective serotonin- and norepinephrine-reuptake inhibitor, is predominantly used as an antidepressant, but has also been licensed in some European countries for stress UI. Presumably duloxetine acts by central modulations, causing an increase in urethral sphincter tone (5).

During the last decades, the surgical treatments of UI in women have improved with the introduction of minimally-invasive sub-urethral sling procedures for UI (6–8), submucosal intraurethal injections of bulking agents (9) and intravesical injections of botulinum toxin (10); and the number of surgeries for UI has been increasing as well (11,12).

Three small studies by Segal et al. (n= 98), Yoo et al. (n=84), and Barber et al. (n=162) (13–15) have shown, that nearly 40% of preoperative antimuscarinic drug users continued the use after surgery for UI.

This topic is highly relevant in advising women who are candidates for surgical treatment for UI, if the results could be confirmed in larger studies. Women being counselled for incontinence surgery would be better served with information on the likelihood of both having to remain on drug use or having to start the use for other lower urinary tract symptoms following their procedure, therefore t~~T~~he purpose of this study was to assess the use of symptom-relieving drugs before and after surgery for UI in a larger population and to examine possible risk factors of postoperative drug use.

Materials and Methods

Study population and settings

Data on all ~~primary~~first-time surgical procedures for UI in women during the study period from 1 January 1996 to 31 December 2010 were retrieved from the Danish National Patient Registry (NPR) (16). The International Classification of Diseases (ICD) procedure codes for data extraction are listed in Appendix 1. The study population included women ≥ 18 years undergoing a ~~primary~~first-time surgical procedure for UI in a hospital in the county of Funen (4 hospitals), Denmark, between 1 January 1996 and 31 December 2006. For the period 2007 through 2010 the geographical area was extended to include all hospitals from the Region of Southern Denmark (including Funen, a total of 13 hospitals). The latter was due to a change in the structure of health care in Denmark from counties to regions in 2007. Women with concomitant or prior surgery for pelvic organ prolapse were not excluded. In women with more than one procedure code for UI in the study period, the first code was chosen as the included procedure.

Data sources

Data for this study were retrieved from three Danish registers: the NPR, the Odense University Pharmacoepidemiologic Database (OPED), and the Statistics Denmark.

The NPR was established in 1977, and contains data on discharges from public hospitals in Denmark. The completeness of recordings has been estimated to be 99.4% (17). The registry contains information about the unique personal identification number (CPN) assigned for all Danish citizens, the dates of admission and discharge, the surgical procedures performed, and up to 20 diagnoses for every discharge, classified according to the ICD-8 (1977-1993) and ICD-10 (1994 and onward) (18,19) as well as codes from the Danish classification system of surgical procedures (20).

Information on relevant drugs (antimuscarinic drugs, duloxetine, and oestrogens) was retrieved within 1995-2011 for the entire study population from OPED by using CPN.

OPED contains person-identifiable data with complete coverage on all computerized prescription reimbursements from the County of Funen (population 2006: 479 000) from 1990 and from January 2007 onwards extended to the whole Region of Southern Denmark (population 1.2 million). The age and gender distribution of this population is very similar to that of the Danish population as a whole (2006: 5.4 mio.), and the prescription of drugs is very similar to the national average (21). The OPED is pharmacy-based and captures all reimbursed prescriptions.

Prescription reimbursements are offered as a part of the National Health Service to all legal inhabitants of Denmark; and given independently of patient income. Each record includes the CPN, the date of purchase, the pharmacy, a full account of what have been purchased, including brand name, Anatomical Therapeutic Chemical (ATC) classification code, total defined daily dose (DDD), dose unit, and quantity. The database does not contain information on indicative diagnoses, drugs sold over the counter or drugs not reimbursed by the county authority (mainly oral contraceptives, sedatives and hypnotics). Data on highest attained educational level and annual income were retrieved from the Danish Integrated Database for Labor Market Research at the Statistics of Denmark. This database contains annually updated socioeconomic data for each Danish citizen, mainly supplied by tax authorities, educational institutions, and employment services (22).

Study drugs

Included drugs were antimuscarinic drugs (tolterodine [ATC G04BD07], solifenacin [ATC G04BD08], trospium chloride [ATC G04BD09], darifenacin [ATC G04BD10], fesoterodine [ATC G04BD11], oxybutinin [ATC G04BD04], flavoxate [ATC G04BD02]), duloxetine [ATC

N06AX21] (only brand name Yentreve®), and oestrogens [ATC G03C]. Propiverine [ATC G04BD6] has not been licensed in Denmark.

Exposed and unexposed cohorts

Exposed cohort: All women ≥ 18 years undergoing a ~~primary~~first-time surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark, and having redeemed one or more prescriptions for antimuscarinic drugs or duloxetine for UI within 365 days preceding the date of surgery (index date).

Unexposed cohort: All women ≥ 18 years undergoing a ~~primary~~first-time surgical procedure for UI between 1 January 1996 and 31 December 2010 in the county of Funen/Region of Southern Denmark without having redeemed similar prescriptions within the same time frame.

Outcome data

For both exposed and unexposed women, the ~~primary~~first-time outcome was the use of symptom-relieving drugs, defined as having redeemed at least one prescription for antimuscarinic drugs or duloxetine within 1) 60 days after the index date (short term postoperatively), and 2) 61 days to 365 days after index date (long term postoperatively). These outcomes were not mutually exclusive, i.e. a woman might be classified both as a short and long term user postoperatively.

Covariates

The use of symptom-relieving drugs might be affected by age, type of procedure, use of oestrogen, comorbidity, educational level, annual income, and calendar time; therefore these variables were included in the analysis as potential confounders.

Type of procedures: The types of UI surgery were divided into four groups according to the surgical procedure code: 1) mid-urethral sling procedures with transobturator route (toMUS), 2) mid-urethral sling procedures with retropubic route (rpMUS), 3) bulking procedures, and 4) other types of UI surgeries.

Oestrogen: To adjust for preoperative oestrogen use, women were divided into those who had redeemed at least one prescription for oestrogens within 365 days prior to surgery, and those who had no preoperative oestrogen use. Both systemic and local oestrogens were included.

Comorbidity: The comorbidity was classified according to the Charlson comorbidity index (CCI) (23) – a well-known, validated and widely used quantitative measure of comorbid illness (24,25). It assigns different weights (1, 2, 3, and 6) to 19 different disease categories specified by medical condition and severity (for example, diabetes, cardiovascular diseases, chronic pulmonary, renal, liver, and connective tissue diseases). For each woman the CCI was computed based on her complete hospital discharge history from the NPR since 1977. A categorised version of the CCI with score values grouped were used: 0 (low), 1-2 (medium) and 3+ (high) (26).

Socio economic status: To measure socio economic status, information on education and annual income for each woman was retrieved. Education was categorised according to the highest attained educational level as "Basic" (basic school/high school education: 7-12 years of ~~primary~~first-time, secondary and grammar-school education), "Secondary" (vocational education, 10-12 years of education), and "Higher" (a university degree or an examination in another higher institution requiring an average a total of 13 years or more) (27).

On the basis of quartiles of annual income for each women at the year of her surgery, we categorised women in low (1st quartile), medium (2nd and 3rd quartile), and high income (4th quartile) recipients.

Statistical analysis

We describe in a flowchart the use of symptom-relieving drugs within the first 365 days after surgery for the two groups of users and non-users of drugs prior to surgery.

We also constructed contingency tables for the main study variables, and computed the odds ratio (OR), with 95% confidence intervals (CI).

To analyse the significance of preoperative symptom-relieving drug use as risk factor of postoperative use (short- and long term), adjusted ORs were estimated by means of multivariate logistic regression models. Adjustment was made for age (18-39, 40-59, ≥ 60 years (reference)), type of procedures (toMUS (reference), rpMUS, Bulking, others), education (basic (reference), secondary, higher), annual income (low (reference), middle, high), comorbidity (CCI 0 (reference), CCI 1-2, CCI 3+), calendar year (1996-2006, 2007-2008 (reference), 2009-2010), and use of oestrogen within 365 days preceding surgery (No (reference), Yes).

All analyses were performed using Stata Release 12.0.

Results

A total of 2,151 women had a ~~primary~~first-time surgical procedure for UI between 1 January 1996 and 31 December 2010 (2,073 had solitary UI surgery, and 78 had concomitant surgery for pelvic organ prolapse).

Of the 2,151 women, 358 (16.6%) were exposed to symptom-relieving drugs within 365 days before surgery, and 1,793 (83.4%) were not. The use of symptom-relieving drugs within 365 days after surgery is detailed in both these cohorts (Figure 1).

Women having redeemed prescriptions for symptom-relieving drugs before surgery (exposed)

Out of the 358 women with prior drug use of antimuscarinic drugs or duloxetine, 110 (30.7%) women redeemed prescriptions for these drugs within 0-60 days after surgery, and 98 out of the 358 women (26.8%) even within 61-365 days after surgery (Figure 1). On the other hand, 248 (69.3%) women did not redeem a prescription for symptom-relieving drugs within 0-60 days after surgery, and the majority of these women (192/358=53.6%) also abstained from symptom-relieving drugs during the time frame 61-365 days after surgery (Figure 1). For the exposed women, the number of redeemed prescriptions was 1,360 preoperatively (DDD 174.6 (SD ±202)), postoperatively 126 (DDD 32.3 (SD ±63.5)) within 0-60 days, and 984 (DDD 140.4 (SD ±234.3)) within 61-365 days.

Women with no usage of symptom-relieving drugs before surgery (unexposed)

Only 25 of the 1,793 (1.4%) women redeemed a first time prescription for symptom-relieving drugs within 0-60 days after surgery, and these women typically continued their use within 61-365 days after surgery (20 women) (Figure 1). Of the 1,793 women who did not redeem prescription before surgery, 1,768 (98.6%) women remained non-users within 0-60 days after surgery, and the vast majority of these women (1,643/1,793=91.6%) continued as non-users also within 61-365 days after surgery (Figure 1). For the unexposed women, the number of redeemed prescriptions postoperatively was 129 (DDD 0.8 (SD ±8.8)) within 0-60 days, and 403 (DDD 11.9 (SD ±54.8)) within 61-365 days.

Baseline characteristics of exposed and unexposed are presented in Table 1. The most commonly used procedures were rpMUS or toMUS. The exposed women were more likely to have had a trans-obturator mid-urethral sling or a bulking agent injection compared to unexposed women, where retropubic mid-urethral sling was the preferred procedure. The most commonly prescribed drugs prior to surgery were solifenacin and tolterodine. Compared to unexposed women, the exposed women tended to be older, to be more frequent oestrogen-users, to have higher comorbidity, a lower educational level, and a lower annual income.

Among women with prior drug use, the unadjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 31.1 (95% CI 19.9-49.4), and 8.4 (95% CI 6.4-11.0), respectively. The adjusted OR of being short or long term user of symptom-relieving drugs after surgery, was 33.0 (95% CI 20.0-54.7), and 7.2 (95% CI 5.4-9.6), respectively. The details from logistic regression models are presented in Table 2 showing the impact of each risk factor included. Preoperative use of antimuscarinic drugs or duloxetine was the absolutely strongest risk factor of

postoperative use (both short and long term); i.e. compared to preoperative drug use no other factors contributed considerably to the OR of being short or long term postoperative user.

Discussion

Among 2,151 women undergoing first-time surgery for UI less than 20% had redeemed prescriptions for antimuscarinic drugs or duloxetine prior to surgery, and nearly 30% of these continued using the drugs within 2 months after surgery and typically stayedid long term users. Among the women without drug use before surgery, the vast majority continued being non-users after surgery, with lessfewer than 9% redeeming a first time prescription of the drugs.

Our study has several strengths: 1) it is a population-based study in the sense that this study covers all the relevant surgeries in a well-defined geographic area in Denmark, 2) The source of procedure has high coverage and validity. The NPR records 99.4% of all discharges from hospitals in Denmark, and the procedures in the NRP have been validated showing a moderate-to-high quality of the data with positive predictive values of 94-100% (28–30), 3) the access to high quality data on prescriptions from the OPED that are representative for the Danish population (21), 4) information on several confounders such as comorbidity and socio economic status, 5) complete information in the follow up period for all included women, 6) outcome data on postoperative drug prescriptions were obtained independently of exposure assessment preventing differential misclassification of the outcome, and finally 7) the drugs and the surgical procedures included in our study do not have other indications than UI, which strongly limits the number of alternative interpretations of our findings.

Our study also has limitations. Data on redeemed prescription are only a surrogate for drug intake. However, antimuscarinic drugs and especially duloxetine are expensive drugs with significant patient co-payment, and we find it unlikely that these drugs to any major extent would be bought and not consumed. We had no data on patient symptomatology, i.e. whether stress UI, urgency UI, mixed UI, or overactive bladder syndrome were predominant, just as there was no available data on findings in urodynamic studies. The exposed cohort were receiving symptom-relieving drugs, and

thus these women most likely had predominantly mixed UI, whereas the unexposed women most likely had predominantly stress UI. We were not able to control for potential confounders such as body mass index, parity, grade of concomitant cystocele, severity of UI symptoms, intrinsic sphincter ~~factor~~ deficiency, or menopausal status, which are well-known risk factors for persistent UI after surgery for UI (31–35). One might speculate whether duration of time with UI symptoms and preoperative conservative treatment could impact our estimates of postoperative drug use, as women in the exposed cohort could have longer disease duration before surgery than women in the unexposed cohort. This could be due to a more extensive preoperative evaluations including urodynamic studies, as well as waiting time to evaluate the effect of drug treatment in the exposed cohort. However, to our knowledge no studies have indicated that disease duration or conservative treatment of UI is a risk factor for postoperative drug use, and therefore we do not believe our estimates of postoperative drug use are influenced by duration of time with UI symptoms.

Currently available drugs for UI are expensive, have many side effects (36), and the long term persistence of the use of antimuscarinic drugs as well as duloxetine is low (without regarding surgery) (37–39). All the latter may contribute to the cessation of the drugs; and thus a reduction in the drug usage may not be explained entirely by the surgery. The reasons for cessation of drug use after surgery can be influenced by other factors as well. For example, misinterpretation of symptoms/investigations may lead to treatment of stress UI with symptom-relieving drugs.

The risk of initiating medical treatment after surgery for UI (based on de-novo surgery) is small, but well-known (40).

There was a low rate of concomitant pelvic reconstructive surgery, as was expected given the current practice in Scandinavia with a conservative approach of addressing the predominant problem of either pelvic organ prolapse or UI in sequential surgery (41). Age was higher among exposed than among unexposed, and therefore expectedly, we found a higher proportion of women

with high comorbidity in the exposed group – and furthermore not surprisingly a higher proportion of Bulking procedures among exposed as this procedure often is preferred in women with high comorbidity.

To our knowledge, this is the largest study addressing the changes in use of symptom-relieving drugs in relation to surgery for UI, and with a large number of possible risk factors of postoperative use. Our results in this larger population are consistent with the previous smaller studies (13–15). Compared to the previous studies, our study included a larger number of women with UI surgery, estimated the risk of postoperatively symptom-relieving drug use with adjustment for a number of relevant covariates, and assessed the risk of both short term and long term use. Our study also showed that educational level, personal income, and type of procedure did not seem to influence the risk of postoperative drug use. High comorbidity was found to significantly increase the risk, but it did not influence the estimates as much as the preoperative drug use, which was the strongest risk factor of postoperative drug use.

More studies are needed to examine the possible impact of body mass index, menopausal status, the predominant type of incontinence, and the relationship between time from diagnosis of UI to performed surgery and the following probability of receiving symptom-relieving drugs.

In conclusion, we found that a substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority (8.1%) of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to preoperative drug use no other factors in the regression model contributed considerably to the OR of being short or long term postoperative user of symptom-relieving drugs. Counselling women prior to UI surgery should therefore include information on a high risk of continuing use after surgery for preoperative users of symptom-relieving drugs, and preoperative non-users have a risk – although it is low – of becoming a user

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Competing interests "All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years.

Ethical approval The study was approved by the Danish Data Protection Agency (no. 2009-41-3564). According to Danish law, ethical review board approval or patient consent are not required for register-based studies.

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Data sharing According to the Danish Data Detection Agency, we are not allowed to share our data from the Danish National Patient Registry. This would require a special approval from both the Danish Data Detection Agency and the Statens Serum Institut who delivers the data from the Danish National Patient Registry.

Article Summary:

Article focus: Urinary incontinence is a prevalent disorder among women. This study focus on both surgical and medical treatment of urinary incontinence. We examined the effect of preoperative use of antimuscarinic drugs or duloxetine on the risk of being a postoperative user of these drugs.

Key messages: A substantial number of women will continue to be prescribed symptom-relieving drugs after surgery for UI within a year of follow-up. Only a minority of preoperative non-users initiated usage of symptom-relieving drugs after surgery. Compared to other included factors, preoperative use of antimuscarinic drugs or duloxetine was the strongest risk factor of postoperative use.

Strengths and limitations of this study:

A population-based study.

2,151 included women.

High quality of data sources and complete information in the follow-up period for all included women.

Adjustment for several factors: age, procedure type, preoperative oestrogen use, comorbidity, educational level, and personal annual income.

Redeemed prescriptions were used as a proxy for drug use.

No data on type of urinary incontinence or urodynamic studies

Table 1 Baseline characteristics of all included women (N=2,151) having ~~primary~~first-time surgery for urinary incontinence in Denmark, 1996-2010.

	Exposed n= 358 (16.6%)	Unexposed n=1,793 (83.4%)
Mean age (±SD), years (At time of first UI surgery)	60.9 (±12.7)	54.5 (±12.6)
Age groups n (%)	13 (3.6)	199 (11.1)
18-39	151 (42.2)	956 (53.3)
40-59	194 (54.2)	638 (35.6)
60-		
Procedures n (%)		
rpMUS	73 (20.4)	602 (33.6)
toMUS	172 (48.0)	800 (44.6)
Bulking	101 (28.2)	259 (14.4)
Others	12 (3.4)	132 (7.4)
Concomitant prolapse surgery n (%)	11 (3.1)	67 (3.7)
Symptom-relieving medications n (%)*		
Solifenacin	176 (49.2)	-
Tolterodine	84 (23.5)	-
Fesoterodine	63 (17.6)	-
Trospium chloride	32 (8.9)	-
Obybutynin	29 (8.1)	-
Darifenacin	14 (3.9)	-
Emepronium	6 (1.7)	-
Duloxetine	6 (1.7)	-
Oestrogen users n (%)**		
No	135 (37.7)	1,073 (59.8)
Yes	223 (62.3)	720 (40.2)
Comorbidity (CCI) n (%)		
0	214 (59.8)	1,298 (72.3)
1-2	107 (29.9)	413 (23.0)
3+	37 (10.3)	82 (4.6)
Educational level n (%)***		
Basic	178 (51.7)	739 (41.8)
Secondary	125 (36.3)	645 (36.5)
Higher	41 (11.9)	383 (21.7)
Annual income n (%)		
Low (1st quartile)	100 (27.9)	437 (24.4)
Middle (2nd-3rd quartile)	206 (57.6)	871 (48.6)
High (4th quartile)	52 (14.5)	485 (27.0)
Year of surgery n (%)		
1996-2006	50 (14.0)	409 (22.8)
2007-2008	118 (33.0)	673 (37.5)
2009-2010	190 (53.0)	711 (39.7)

*Does not sum up to 100%. Some women redeemed more than one type of the drugs during the time period.
**Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
***Unknown highest attained educational level: 40 women
Abbreviations: SD = standard deviation, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Table 2 Risk factors of postoperative use of antimuscarinic drugs/duloxetine. Results from multivariate logistic regression models on i) short term (0-60 days after surgery) and ii) on long term (61-356 days after surgery)

	Post op non-use Number	Post op short term use		Post op non-use Number	Post op long term use	
		Number	OR (95% CI)		Number	OR (95% CI)
Preoperative use						
No	1,768	25	reference	1,648	145	reference
Yes	248	110	33.0 (20.0-54.7)	145	152	7.2 (5.4-9.6)
Age group						
18-39	209	3	0.3 (0.1-1.4)	204	8	0.3 (0.1-0.7)
40-59	1,063	44	0.6 (0.3-0.9)	999	108	0.6 (0.4-0.8)
60-	744	88	reference	651	181	reference
Procedure						
rpMUS	659	16	0.6 (0.3-1.2)	612	63	0.6 (0.4-0.9)
toMUS	894	78	reference	842	130	reference
Bulking	322	38	1.2 (0.7-2.0)	262	98	0.5 (0.3-0.7)
Others	141	3	0.5 (0.1-2.6)	138	6	0.3 (0.1-1.0)
Preoperative use of oestrogen*						
No	1,159	49	reference	1,090	118	reference
Yes	857	86	0.8 (0.5-1.4)	764	179	1.0 (0.7-1.4)
Comorbidity (CCI)						
0	1,442	70	reference	1,352	160	reference
1-2	467	53	1.5 (0.9-2.4)	419	101	1.5 (1.1-2.0)
3+	107	12	0.9 (0.4-1.9)	83	36	1.9 (1.2-3.2)
Educational level**						
Basic	846	71	reference	761	156	reference
Secondary	727	43	0.9 (0.6-1.5)	674	96	0.9 (0.6-1.2)
Higher	407	17	1.1 (0.6-2.3)	385	39	0.8 (0.5-1.3)
Annual income						
Low	489	48	reference	442	95	reference
Middle	1,010	67	0.7 (0.4-1.2)	929	148	0.9 (0.6-1.2)
High	517	20	0.9 (0.4-1.8)	483	54	1.1 (0.7-1.9)
Year of surgery						
1996-2006	448	11	0.7 (0.3-1.7)	427	32	0.5 (0.3-0.9)
2007-2008	739	52	reference	675	116	reference
2009-2010	829	72	0.9 (0.6-1.4)	752	149	1.0 (0.7-1.4)

*Women with at least one redeemed prescription of oestrogen within 365 preceding surgery.
**Unknown highest attained educational level: 40 women
Abbreviations: post op = postoperative, OR = odds ratio, CI = confidence interval, rpMUS= retropubic mid-urethral sling, toMUS= trans-obturator mid-urethral sling, CCI = Charlson comorbidity index

Figure 1 Women (N=2,151) with ~~primary~~first-time surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.

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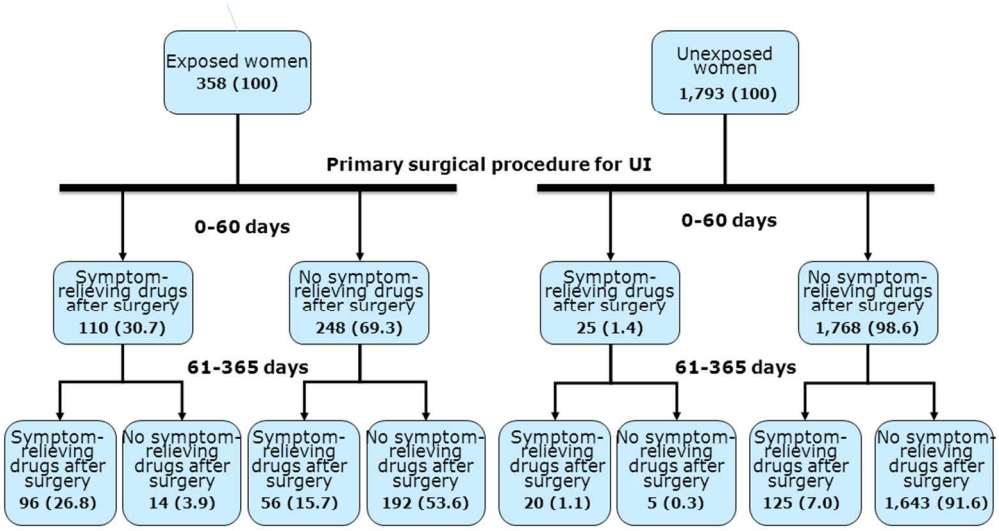

Women (N=2,151) with first-time surgery for urinary incontinence (UI) and their use of symptom-relieving drugs for UI (antimuscarinic drugs and duloxetine) before and after surgery for UI. Exposed women had redeemed one or more prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery, and unexposed women had not redeemed prescriptions of antimuscarinic drugs or duloxetine within 365 days preceding the date of surgery.
286x199mm (96 x 96 DPI)

Appendix 1 Surgical procedures according to the Danish Nordic Medico-Statistical Committee

KDG00 = Retropubic suspension of urethra
KDG01 = Percutaneous endoscopic retropubic suspension of urethra
KDG10 = Abdominovaginal suspension of bladder neck
KDG30 = Suprapubic sling urethrocystopexy
KDG31 = Percutaneous endoscopic suprapubic sling
KDG40 = Suprapubic urethrocystopexy
KDG50 = Transabdominal plastic repair of pelvic floor for urinary incontinence
KDG96 = Other operation on urethra or bladder neck for incontinence
KDG97 = Other percutaneous endoscopic operation on urethra or bladder neck for incontinence
KDV20 = Submucous urethral injection
KDV22 = Transluminal endoscopic submucous urethral injection
LEG00 = Vaginal urethrocystorrhaphy
LEG10 = Vaginal urethrocystopexy with use of sling
LEG10A = Vaginal urethrocystopexy with use of sling through foramen obturatum
LEG20 = Plastic repair of female pelvic floor with levator division
LEG96 = Other vaginal operation for incontinence