Department of Health and Human Services
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Center for Drug Evaluation and Research
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Date:	July 11, 2007
To:	Thomas Laughren, Director, Division of Psychiatric Products (DPP)
Thru:	Dr. Mark Avigan, Director, Division of Drug Risk Evaluation (DDRE)
From:	Jenna Lyndly, R.N., Safety Evaluator Division of Drug Risk Evaluation (DDRE)
Subject:	Urinary Retention and Urinary Hesitation; NME Review Follow-up
Drug Name(s):	Duloxetine (Cymbalta)
Application Type/Number:	21-427, 21-733
Applicant/sponsor:	Lilly
OSE RCM #:	2007-1096

CONTENTS

EXECUTIVE SUMMARY

This analysis is in response to follow-up from the March 13, 2007 pilot NME review[1] for duloxetine where the multidisciplinary team identified urinary hesitation/urinary retention as a follow-up issue.

Duloxetine has a facilitatory effect on incontinence by increasing bladder capacity and urethral sphincter muscle activity. As duloxetine is unable to induce sphincter contractions, urinary retention was thought to be unlikely. No reports of urinary retention resulting in hospitalization or catheterization were seen during the duloxetine clinical trials for major depressive disorder, stress urinary incontinence, or benign prostatic hypertrophy; or during duloxetine drug interactions studies with desipramine, paroxetine, or tolterodine.[2] However, the AERS post-marketing case series had 26 of 78 cases reporting serious outcomes; with 62% of the serious outcomes in females.[3] Of the 26 cases, there were 9 catheterizations, 8 hospitalizations, and 9 cases of hospitalization + catheterization. Seven of the hospitalizations had a primary or secondary diagnosis of urinary retention/hesitation. The quality of the cases in our series is not optimal; however, the number of cases with serious outcomes describing both a temporal relationship (within one week of starting duloxetine) and a positive dechallenge, with/without treatment indicates a potential risk of urinary retention requiring hospitalization and/or catheterization for patients in the general population.

While the postmarketing labeling includes a listing for urinary retention, the current duloxetine labeling does not inform health care providers of the potential serious outcomes seen in postmarketing AERS reports.

Therefore, OSE recommends:

- Add cautionary information to the Precautions section concerning duloxetine associated urinary retention that resulted in hospitalization and/or catheterization of both males and females as seen in the AERS post-marketing cases.

- Modify the venlafaxine label to be consistent with "class labeling" as identified in the duloxetine for urinary hesitation.

[1] New Molecular Entity (NME) Postmarketing Evaluation, Duloxetine, March 13, 2007, Section J, Conclusions and Recommendations

[2] Viktrup et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence.

[3] In this review we are defining serious outcomes as death, hospitalization, life-threatening and catheterization reports without death, hospitalization or life threatening outcomes

1 BACKGROUND

1.1 INTRODUCTION

The FDA is piloting a review process for drugs classified as new molecular entities[4] (NME). As part of the pilot, duloxetine was selected as the first drug product to undergo the NME review process. The review involves a template (to guide the new review process) which was used by multidisciplinary reviewers from both the Office of Surveillance and Epidemiology (OSE), and the Office of New Drugs (OND).

On March 13, 2007, OND and OSE brought together a multidisciplinary workgroup to review the safety profile of duloxetine since approval in August of 2004; including clinical trial safety data, post-marketing adverse event data, new data from completed postmarketing commitments, and labeling changes. A portion of the OSE post-marketing review utilized a data mining analysis, drug use, and the top 50 preferred MedDRA[5] terms reported in AERS[6] to provide an overview of post-marketing adverse events. The data mining analysis highlighted urinary hesitation as the preferred term with the highest score, an EB05 of 11.[7] As a result, the multidisciplinary review team identified post-marketing duloxetine adverse event reports of urinary hesitation and urinary retention for further review, in addition to six other areas[8].

In this analysis we provide a review of post-marketing duloxetine adverse event reports retrieved from the AERS database coded with the preferred terms "urinary hesitation", and "urinary retention". Additionally, as agreed at follow-up meetings, OSE will provide separate written analyses of post-marketing cases of bleeding disorders and drug interactions prior to August 1, 2007; as well as a written analysis of duloxetine medication errors. Also, as agreed upon, to facilitate the NME review process, OND (Division of Psychiatric Drug Products) will conduct analyses of post-marketing cases of blindness, loss of consciousness, and falls.

1.2 REGULATORY HISTORY

Duloxetine is classified as a serotonin-norepinephrine reuptake inhibitor (SNRI) and was initially approved in 20, 30, and 60 mg doses for major depressive disorder (MDD) on August 3, 2004 with a trade name of Cymbalta. Another indication was approved on September 3, 2004 when duloxetine was approved for diabetic peripheral neuropathy pain (DPNP); with the third indication of generalized anxiety disorder (GAD) approved on February 23, 2007. In August of 2004, duloxetine was approved in Europe for stress urinary incontinence under the trade name Yentreve; however, [redacted] the FDA has not approved duloxetine for the indication of stress urinary incontinence.

[4] A new molecular entity (NME) means a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act.
[5] Medical Dictionary for Regulatory Affairs
[6] Adverse Event Reporting System - computerized information database designed to support the FDA's post-marketing safety surveillance program
[7] OSE Post-Marketing Data mining Analysis, Drug: Duloxetine, Marilyn Pitts, February 20, 2007
[8] The seven areas targeted for follow-up included: Urinary hesitation/retention, bleeding disorders, drug interactions, blindness, loss of consciousness, fall and medication errors

1.3 PRODUCT LABELING[9]

The current labeling addresses urinary hesitation and urinary retention in the following sections:

Under the "*Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials"* Section:

Urinary Hesitation

"Cymbalta is in a class of drugs[10] known to affect urethral resistance.[11] If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related."

Under the *"Other Adverse Events Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine"* section:

Renal and Urinary Disorders —*Infrequent:* dysuria, micturition urgency, nocturia, urinary hesitation, urinary incontinence, urinary retention, urine flow decreased, and urine odor abnormal; *Rare:* nephropathy.

2 METHODS AND MATERIALS

2.1 INTRODUCTION

We utilized adverse event reports retrieved from the AERS database, a listing of non-serious expected adverse events from the sponsor, drug use information from Verispan[12] and an analysis of the AERS database by WebVDME[13] (data mining tool) as data sources for this review. The sponsor of duloxetine was granted a waiver for non-serious labeled adverse events on February 7, 2005.[14]

2.2 DATA MINING

A data mining search of the Adverse Event Reporting System (AERS) database was performed for this analysis using WebVDME 5.2. This method uses the Multi-item Gamma Poisson Shrinker (MGPS)[15-16] algorithm which analyzes the records contained in the AERS database. The algorithm then quantifies reported drug-event associations by producing a set of values or scores which indicate varying strengths of reporting relationships between drugs and events.

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[9] Drugs@FDA, Cymbalta, NDA 021427, label approved on 02/23/2007
[10] Selective serotonin-norepinephrine reuptake inhibitors (SNRIs); currently includes duloxetine and venlafaxine
[11] The venlafaxine label includes "urinary retention" and "urination impaired", but not urinary hesitation; Drugs@FDA, Effexor, NDA 020151, label approved on 02/07/2007
[12] Verispan, LLC: Total Patient Tracker, Aug04-Dec06, Extracted Feb07. Files: TPT Cymbalta AUG04-DEC06 Aggregate Product Brand Report.xls, TPT Cymbalta aug04-dec06 Aggregate Gender Report.xls
[13] Developed by Lincoln Technologies, Inc. in cooperation with the FDA
[14] The non-serious labeled reports of urinary hesitancy and urinary retention are most likely under-represented in the AERS database, and consequently under-represented in WebVDME.
[15] DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-9; San Diego, Ca: ACM Press:67-76.
[16] Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Safety 2002;25:381-92.

These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs and events in the database. MGPS also calculates lower and upper 90% confidence limits for the EBGM values, denoted as EB05 and EB95 respectively.

On January 3, 2007, we queried WebVDME by using the Ingredient (S) run with the search criteria of duloxetine and all reports with an EB05[16] score >2, which indicates 95% confidence that the event was reported at least twice as often for duloxetine when compared to all other drugs in AERS. The result of the overall query is provided in a separate OSE document. [17]

2.3 AERS SELECTION OF CASES

We queried the AERS database as follows:

Table 1. AERS Search Strategy

SEARCH INFORMATION	
Source Database	Adverse Event Reporting System (AERS)
Date of Search	March 26, 2007
Drug Name Search Terms	Duloxetine active ingredient and related verbatim terms
MedDRA Adverse Event Search Terms	Urinary Retention, Urinary Hesitation
Search Level	Preferred Terms (PT)

We also requested the sponsor to submit the non-serious labeled event reports of urinary hesitation and urinary retention affected by the existing waiver.

2.4 LITERATURE SEARCH

We searched STAT!REF[18] for definitions of urinary retention and urinary hesitation.

We searched PubMed to determine current information regarding the potential mechanism for duloxetine to effect incontinence with the terms 'duloxetine and mechanism and incontinence' with two pertinent articles identified.[19]

We searched PubMed for urinary retention and duloxetine. The results were one article which addressed the mechanism of action of duloxetine, the incidence of urinary retention, and examined urinary retention in three duloxetine clinical studies and three drug interaction studies.[20]

We also searched PubMed with the search terms of 'urinary retention and prevalence', 'urinary retention and incidence', and 'urinary retention and epidemiology' to determine the epidemiology of urinary retention. Three relevant articles and one abstract not available in

[17] OSE Post-Marketing Data mining Analysis, Drug: Duloxetine, Marilyn Pitts, February 20, 2007
[18] STAT!Ref is an electronic resource for healthcare professionals – www.STAT!Ref.com
[19] Schuessler, B. What do we know about duloxetine's mode of action? Evidence from animals to humans, Jost, W and Marsalek. Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus
[20] Viktrup et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence

English were present in all three searches.[21] An additional search for 'urinary retention and incidence' limited to 'females and humans' was performed to identify the epidemiology of urinary retention in females. One relevant article was identified.[22]

An additional search was performed in both PubMed and Google in an attempt to identify any publications or information regarding SNRIs and urinary retention. 'SNRI and urinary retention' and 'selective serotonin and norepinephrine-reuptake inhibitors and urinary retention' were used as search terms and did not result in any applicable publications.

3 RESULTS

3.1 DATA MINING

The data mining results relevant to urinary hesitation and urinary retention are presented in Table 2 below:

Table 2. Data Mining Results[23] of AERS Cases of Urinary Retention/Hesitation from Marketing to January 3, 2007

DATA MINING RESULTS				
MedDRA Preferred Term	**N[24]**	**EB05[25]**	**EBGM**	**EB95**
Urinary hesitation	32	11.54	15.763	21.011
Urinary retention	55	2.847	3.568	4.426

3.2 AERS CASE SERIES

Case Series (78):

Our search of the AERS database on March 26, 2007 retrieved 84 reports, 78 of which comprise the case series. We excluded six reports from further analysis.[26] The overall characteristics of the included cases are detailed in table 3 below:

Table 3: Overall Characteristics of Unique AERS Cases of Urinary Retention/Hesitation from Marketing to March 26, 2007 (n=78)

Location	US (68), Foreign (10)
Report Source	Expedited (17), Direct (2), Periodic (59)
Reporter	Consumer (15), Health Care Professional (62), Foreign Study (1)
Gender	Female (42), Male (36)
Age Range1	18 to 85 years, median = 53, n = 58
Indications for Use[27]	Anxiety (2), Depression/Bipolar/MDD[28] (35), DPNP[29]/Neuropathy (10), Ill-defined disorder (1), Incontinence/ SUI[30] (5), Myoclonus (1), OCD[31] (1), Parkinson's (1), PTSD[32] (1), Unknown (22)

[21] Cathcart et al. Incidence of primary and recurrent acute urinary retention between 1998 and 2003 in England, Meigs et al Incidence rates and risk factors for acute urinary retention: the health professional follow-up study, Verhamme et al. Low incidence of acute urinary retention in the general male population: the triumph project, Abstract - Shimizu, N. Clinical study of acute urinary retention.
[22] Kavia et al. Urinary retention in women: its causes and management
[23] OSE Post-Marketing Data mining Analysis, Drug: Duloxetine, Marilyn Pitts, February 20, 2007
[24] The numbers do not represent individual cases as one case may include PT terms for both urinary hesitation and urinary retention and will be represented for both terms.
[25] EB05 is the estimated lower 90% confidence limit for the adjusted observed to expected ratio
[26] Excluded = duplicates (3), onset of symptoms after discontinuation of duloxetine (3)

Table 3: Overall Characteristics of Unique AERS Cases of Urinary Retention/Hesitation from Marketing to March 26, 2007 (n=78)

Peak Daily Dose	median = 60mg, 20mg to 120mg, n = 69
Concomitant Medication Drug Classes[33] - labeled for urinary retention/hesitation [34]	Anticonvulsants (5), Antidepressants (10), Antihistamine drugs (1), Antimuscarinics/antispasmodics (2), Antipsychotics (7), CNS Agents (1), Genitourinary smooth muscle relaxants (4), Opiate agonists (10), None (4), Unknown (28)
Co-morbid Relevant Medical Conditions[35]	BPH[36] (2), Diabetes (8), Instrumentation of GU tract (1), Kidney Stones (2) LUTS[37] (17), MS (1), Parkinson's (3), Pelvic radiation (1), Prostatitis (1), Shy bladder (1), STD (1), TURP[38] (1), UTIs (6), Negative history for GU[39] (9), Unknown (28)
Event PT	Urinary retention (46), Urinary hesitation (29), Urinary retention and urinary hesitation (3)
Onset Information	median = 6.5 days, 5 hours to 'more than a year', n = 41
Offset Information	1 to 30 days, median = 6.5 days, n = 6
Outcomes	Death (0), Hospitalization (17), Life-threatening (1)
Catheterizations	18 (9 of the catheterizations overlap with the hospitalizations)
Duloxetine Status	Discontinued (49), Continued (17), Unknown (12)
Dechallenge	Positive with treatment (10), Positive (18), Negative (4)
Rechallenge	Positive (1)

The data included two positive dechallenge cases without confounding from medications or pre-existing LUTS[40]. The narratives for the two cases are detailed below:

ISR # 5011375

A 28 year old male who denied history of urinary tract symptoms or disorders including BPH, and with no concomitant medications, including over-the-counter medications, was prescribed duloxetine 30 mg QD for major depressive disorder and anxiety. The dose was increased to 60 mg QD, and the patient subsequently experienced urinary hesitation and retention. Duloxetine was discontinued after seven days and the symptoms resolved and did not reoccur.

ISR # 4530908

A 50 year old male with a negative history of urinary tract problems, and no concomitant medications, was prescribed duloxetine 30 mg QD for mild depression with anxiety components and various pain complaints. On Day 3, he experienced a little urinary hesitancy. On Day 6, he

[27] One case may have more than one indication.
[28] Bipolar depression (1), Depression (26), MDD - Major Depressive Disorder (7), Mild depression with various complaints of pain (1),
[29] Diabetic neuropathy (2), Diabetic peripheral neuropathy (1), DPNP - Diabetic Peripheral Neuropathic Pain (2), Neuralgia (1), Neuropathic pain (1), Neuropathy (1), Peripheral neuropathy (1), Reflex sympathetic disease (1)
[30] Incontinence (2), SUI - Stress Urinary Incontinence (3)
[31] OCD - Obsessive Compulsive Disorder
[32] PTSD - Post Traumatic Stress Disorder
[33] Drug Classes from AHFS Drug Information (2007)
[34] One case may contain multiple medications labeled for urinary retention/urinary hesitation
[35] One case may contain multiple co-morbid conditions
[36] BPH – Benign Prostatic Hypertrophy
[37] LUTS – Lower urinary tract symptoms - Incontinence (8), frequent urination (1), overactive bladder (2), urinary hesitation (1), urination problems at night (1), urinary retention (2), voiding difficulties (1)
[38] TURP - Transurethral Resection of the Prostate
[39] GU - Genitourinary
[40] LUTS – Lower urinary tract symptoms

experienced increased hesitancy with nocturia. Duloxetine was discontinued and both symptoms resolved within 2 days.

Serious Outcomes - Hospitalizations and/or Catheterizations (26):

Twenty-six (16F/10M) of the AERS cases required hospitalization and/or catheterization; nine catheterization, eight hospitalization, and nine hospitalization with catheterization. As the literature noted that urinary retention in females is "uncommon" or "rare" and reports of urinary retention in the MDD, SUI and BPH clinical trials were predominantly from males, we will separate the cases by gender.[41,42]

- **Cases of hospitalization/catheterizations in females (16)**

Sixteen cases were female (16/26, 62%) with a median age of 53 years old (range 35-85, n=15). Six were hospitalized and catheterized; five were hospitalized and five were catheterized. The median time to onset was 7 days with a range of 2-365 days[43] (n=8). Two offsets were reported; both catheterized with offsets of 20 and 30 days.

Hospitalizations (11)
Eleven females were hospitalized; two with a primary diagnosis of urinary retention/hesitation, and one with a secondary diagnosis. Nine cases included concomitant medications labeled for urinary retention and/or medical conditions which might increase the risk of urinary retention. Six positive dechallenges with treatment were described.

Table 4: Overall Characteristics of Unique AERS Cases of Female Hospitalizations with/without Catheterization from Marketing to March 26, 2007 (n=11)

Age Range	median = 70, 42 to 85 years, n = 10
Peak Daily Dose	median = 40mg, 20mg to 120mg, n = 10
Indication for Use[44]	Depression (4), MDD (1), Incontinence(1), SUI (2), Unknown (3)
Concomitant Medication Drug Classes[45] - labeled for urinary retention[46]	Anticonvulsants (2), Antidepressants (3), Antipsychotics (3), CNS Agents (1), Genitourinary smooth muscle relaxants (2), Opiate agonists (2), Unknown (2)
Co-morbid Relevant Medical Conditions[47]	Diabetes (3), Parkinson's[48] (2), UTIs (4), Unknown (1)
Event PT	Urinary retention (8), Urinary hesitation[49] (2), Urinary retention and urinary hesitation (1)
Duloxetine Status	Discontinued (9), Continued (2)
Symptom Resolution	Recovered/recovering (7), Continued (1), Unknown (3)
Positive Dechallenges	(6)
Catheterizations	(6)

[41] Kavia et al: Urinary Retention in women? Its causes and management. BJU International. 2006:Feb;97(2):281-7.
[42] Viktrup et al. Urinary side effects of duloxetine in the treatment of depression and stress urinary incontinence.
[43] 210 days estimated time used for onset of "6-8 month", 365 days estimated time used for onset "more than a year"
[44] One case may have more than one indication.
[45] Drug Classes from AHFS Drug Information (2007)
[46] One case may contain multiple medications labeled for urinary retention/urinary hesitation
[47] One case may contain multiple co-morbid conditions
[48] Parkinson's (1), possible atypical Parkinson's (1)
[49] ISR #520371: urinary hesitation described as "could not pee"

The two females hospitalized with a primary diagnosis of urinary retention/hesitation were also treated for overactive bladder with oxybutynin and detail a possible drug interaction. One discontinued oxybutynin; the other discontinued duloxetine, with both reporting resolution of symptoms. The cases are summarized below:

ISR #5034786
A female of unknown age with a history of diabetes was prescribed duloxetine 20 mg QD. Over three weeks, duloxetine was increased to 100 mg QD. The patient experienced urinary hesitancy on an unknown date. Duloxetine was decreased to 60 mg QD. The patient presented to the ER with an inability to void. She was admitted to the hospital and had a foley catheter inserted for 1 week. Duloxetine was discontinued. The symptoms resolved after 1 month. Concomitant medications were insulin, hydrocodone/acetaminophen, oxybutynin, lisinopril, simvastatin, and fluoxetine.

ISR #5203711
A 45 year old female with a history of diabetes was prescribed duloxetine 30 mg BID for depression 01/2005. In 04/2006 the patient was prescribed oxybutynin, enalapril, zolpidem, and naprosyn. She was subsequently hospitalized for urinary hesitation described as "could not pee." Oxybutynin was discontinued. The patient was discharged from hospital on [redacted]. The retention resolved. The reporter felt that the combination of duloxetine and oxybutynin along with a history of diabetes caused the urinary hesitation.

Catheterizations without hospitalization (5)
Five females were catheterized without hospitalization. Four cases included concomitant medications labeled for urinary retention and/or medical conditions which might increase the risk of urinary retention. Time to onset was reported for four cases with a median of 62 days (range 2-180 days, N=4). One time to offset is reported with a recovery period of 20 days during which self-catheterization and two prescriptions – bethanechol and tamsulosin – were required before resolution of the urinary retention.

Table 5: Overall Characteristics of Unique AERS Cases of Females Catheterized without Hospitalization from Marketing to March 26, 2007 (n=5)

Age Range:	median = 38, 35 to 78 years, n = 5
Peak Daily Dose:	median = 30mg, 30mg to 60mg, n = 5
Indication for Use: [50]	Depression (1), DPNP (1), MDD (1), Neuralgia(1), Reflex sympathetic disease (1), Unknown (1)
Concomitant Medication Drug Classes[51] - labeled for urinary retention[52]	Antipsychotic (1), Opiate agonists (1), Unknown (3)
Co-morbid Relevant Medical Conditions[53]	Diabetes (1), Pelvic surgery and radiation (1), Shy bladder (1), UTI (1), Unknown (0)
Event PT	Urinary retention (5)
Duloxetine Status	Discontinued (3), Continued (1), Unknown (1)

[50] One case may have more than one indication.
[51] Drug Classes from AHFS Drug Information (2007)
[52] One case may contain multiple medications labeled for urinary retention/urinary hesitation
[53] One case may contain multiple co-morbid conditions

Table 5: Overall Characteristics of Unique AERS Cases of Females Catheterized without Hospitalization from Marketing to March 26, 2007 (n=5)

Symptom Resolution	Recovered/recovering (2), Continued (1),Unknown (2)
Positive Dechallenge	(2)

- **Cases of hospitalization/catheterizations in males (10)**

The ten males (10/26, 38%) had a median age of 68.5 years and a range of 33-83 (n=8). Four were catheterized, three hospitalized and three were hospitalized and catheterized. Median time to onset was 21.5 days with a range of 3-89 days (n=6). Offset information is provided for one case; a hospitalization without catheterization with resolution of urinary retention within 24 hours after discontinuation of duloxetine.

Hospitalizations of male patients (6)

Six males were hospitalized; four with a primary or secondary diagnosis of urinary retention. Five cases included medications labeled for urinary retention and/or medical conditions which may increase the risk of urinary retention. All six discontinued duloxetine with accounts of two positive dechallenges with treatment.

Table 6: Overall Characteristics of Unique AERS Cases of Male Hospitalizations with/without Catheterization from Marketing to March 26, 2007 (n=6)

Age Range	median = 75, 35 to 83 years, n = 5
Peak Daily Dose	median = 60mg, 30mg to 120mg, n = 5
Indications for Use[54]	Anxiety (1), Bipolar Depression (1), Depression (1), Diabetic neuropathy (1), DPNP (1), Neuropathy(1), Unknown (0)
Concomitant Medication Drug Classes[55] - labeled for urinary retention[56]	Antidepressants (3), Opiate agonists (2), Unknown (3)
Co-morbid Relevant Medical Conditions[57]	BPH (1), Diabetes (2), Unknown (2)
Event PT	Urinary retention (6)
Duloxetine Status	Discontinued (6)
Symptom Resolution	Recovered/recovering (2), Continued (1),Unknown (3)
Positive Dechallenge	(2)
Catheterizations:	(3)

[54] One case may have more than one indication.
[55] Drug Classes from AHFS Drug Information (2007)
[56] One case may contain multiple medications labeled for urinary retention/urinary hesitation
[57] One case may contain multiple co-morbid conditions

One positive dechallenge with treatment is summarized below:

ISR # 4539855
A 35 year old male was prescribed duloxetine 60 mg QD for bipolar depression. He experienced urinary retention "almost requiring catheterization." Duloxetine was discontinued. The symptoms resolved within 24 hours.

Catheterizations without hospitalization (4)
Three cases reported concomitant medications labeled for urinary retention and/or medical conditions which may increase the risk of urinary retention. Symptom resolution is reported for two cases; both with descriptions of positive dechallenges with treatment.

Table 7: Overall Characteristics of Unique AERS Cases of Males Catheterized without Hospitalization from Marketing to March 26, 2007 (n=4)

Age Range	median = 65, 33 to 72 years, , n = 3
Peak Daily Dose	median = 60mg, 30mg to 60mg, , n = 3
Indications for Use [58]	Depression (2), Unknown (2)
Concomitant Medication Drug Classes[59] - labeled for urinary retention[60]	Antipsychotic (1), Opiate agonists (2), Unknown (1)
Co-morbid Relevant Medical Conditions[61]	BPH (1), Kidney stones (1), Prostatitis (1), UTI (1), Unknown (1)
Event PT	Urinary retention (4)
Duloxetine Status	Discontinued (3), Unknown (1)
Symptom Resolution	Recovered/recovering (2), Unknown (2)
Positive Dechallenge	(2)

A positive dechallenge with treatment is summarized below:

ISR #5011384
A 33 year old male with a history of UTIs and a family history of prostate problems was prescribed duloxetine 60 mg QD. Three months later, the patient experienced urinary retention. He was seen in ER and catheterized. The results of the catheterization were normal. He was subsequently diagnosed with "prostate enlarged" and duloxetine was discontinued. The symptoms completely resolved.

Waived Cases (198):

We requested and received from the sponsor a line listing of non-serious labeled waived reports which included 198 domestic cases of urinary retention and/or hesitation.[62] The line listings

[58] One case may have more than one indication.
[59] Drug Classes from AHFS Drug Information (2007)
[60] One case may contain multiple labeled for urinary retention/urinary hesitation
[61] One case may contain multiple co-morbid conditions
[62] Waived reports from 02/03/05-05/02/07, submitted 05/25/07

consist of 7 fields and provide limited information. The overall characteristics of the cases are detailed in Table 8 below:

Table 8: Overall Characteristics of Unique Waived Non-serious Labeled Cases from February 3, 2005 to May 2, 2007, Received from Eli Lilly Inc (n=198)

Location	US (198)
Gender	Female (74), Male (122), Unknown (2)
Age Range	median = 50, 17 to 87 years, n = 134
Peak daily dose	median = 60, 20-120 mg per day, n = 171
Indications for use	Anxiety (5), ADHD[63] (1), Depression/MDD[64] (62), Fibromyalgia (3), Neuralgia/Neuropathy[65] (23), Pain (11)[66], Panic disorder (2), Unknown (91)
Event PT[67]	Urinary hesitation (64), Urinary retention (123), Urinary hesitation/retention (11) ,
Event Outcome	Recovered/Recovering (77), Not recovered (26), Worsened (1), Unknown (94),
Catheterizations	Male (6), Female (6), n = 12

Urinary retention was reported in 134 of the waived cases. We provide information concerning these reports below:

- ***Unique Non-serious Labeled Waived Cases of Urinary Retention in Females from February 3, 2005 to May 2, 2007 (n=51)***

Fifty-one (51/134, 38%) of the urinary retention cases were female with a median age of 45 (range 17-80, n=31) and a median dose of 60 mg (range 20-90, n=44). Nineteen (19/51, 37%) reported improvement or resolution of urinary retention. Six of the female patients reported catheterization with three describing a positive dechallenge (n=3).

- ***Unique Non-serious Labeled Waived Cases of Urinary Retention in Males from February 3, 2005 to May 2, 2007 (n=82)***

Eighty-two (82/134, 56%) of the urinary retention cases were male with a median age of 55 (range 25-87, n=57). [68] The median dose was 60 mg (range 20-60, n=68). Thirty-three (33/82, 40%) reported improvement or resolution of urinary retention. Six of the male patients reported catheterization with four describing a positive dechallenge (n=4).

Drug Use

The Duloxetine NME Postmarketing Review performed on March 13, 2007 included drug use information stratified by gender which is summarized in Table 9 below:

[63] Attention deficit/hyperactivity disorder
[64] Depression (56), MDD (6)
[65] Neuralgia (6), Neuropathy (9), Diabetic neuropathy (3), Neuropathy peripheral (2), Peripheral sensory neuropathy (1), Radiculitis brachial (1), Trigeminal neuralgia (1),
[66] Pain (5), Back Pain (2), Bone pain (1), Complex Regional Pain Syndrome (1), Myofascial pain syndrome (1), Pain in extremity (1)
[67] PT = Preferred Term
[68] Gender was not reported for one urinary retention waived case.

Table 9: Duloxetine Drug Use[69]; Total Prescriptions (TRX) Volume by Gender

	Drug Use – TRx % from August 2004 through December 2006
Female	73% (10,198,586/14,016,887)
Male	26% (3,684,624/14,016,887)

3.3 LITERATURE SEARCH RESULTS

Definition of Urinary Hesitation/Retention:
Urinary hesitation or hesitancy is defined by Stedman's Medical Dictionary[70] as "an involuntary delay or inability in starting the urinary stream." The Merck Manual[71] defines urinary retention ranging from incomplete emptying of the bladder to inability to void, acute or chronic and notes that acute urinary retention may be accompanied by pain.

Proposed Mechanism of Duloxetine on Bladder Function:
We reviewed three articles describing the proposed mechanism of duloxetine on bladder functions.

Jost and Marsalek[72] noted duloxetine was shown to exhibit a dose dependent five fold increase in bladder capacity and eight fold increase in striated urethral sphincter muscle activity in the cat model. The increased striated muscle is the result of inhibiting reuptake of both serotonin (5-hydroxytrytamine, 5-HT) and norepinephrine at Onuf's nucleus in the pudendal nerve; thus increasing striated muscle contraction in the urethral sphincter. Jost and Marsalek's proposed mechanism for the increase in bladder capacity was central afferent modulation. Phase III human studies showed dose dependent decreases in urinary incontinence episodes and micturition intervals.

Schuessler's article reviewed the animal studies which described a limited modulatory effect of serotonin and norepinephrine with glutamate as the primary neurotransmitter for excitation of the pudendal nerve and sphincter contraction. He noted that in the absence of glutamate, serotonin and 5-HT do not have the ability to induce sphincter contractions; therefore, increased levels of serotonin and norepinephrine would not effect voiding. Human studies by Boy et al and Bump et al were referenced by Schuessler who concluded that human studies confirm the proposed mechanism from animal studies. The study by Bump et al assessed females at 4 weeks and seven months. Schuessler highlighted the lack of impact on voiding in the human studies and also the five-fold increase in cough activity after seven months seen in one woman which was suggestive of a progressive effect of duloxetine on sphincter activity.[73]

The final journal article reviewed was by Viktrup et al, Lilly Research Laboratories, which reiterated the same proposed mechanism discussed in the previous articles and reviewed the clinical trials for MDD concluding the risk for urinary obstruction should be "negligible" since

[69] Source: Verispan, LLC: Vector One®: National, Aug04-Dec06, Extracted March 2007. File: VONA 2007-69 Cymbalta NME Report TRx AgeGender.qry
[70] Stedman's Medical Dictionary, 2006 Lippincott & Wilkins, through STAT!Ref
[71] Merck Manual of Diagnosis and Therapy, The – 18th Ed. (2006), through STAT!Ref
[72] Jost W, Marsalek P: Duloxetine: mechanism of action at the lower urinary tract and Onuf's nucleus. Clin Auton Res. 2004 Aug:14(4):220-7.
[73] Schuessler B: What do we know about duloxetine's mode of action? Evidence from animals to humans. BJOG. 2006 MAY;113 Suppl 1:5-9.

5-HT and norepinephrine enhances sphincter activity during the storage phase but not during micturition phase.

Epidemiology of Urinary Retention:
We reviewed four articles and one abstract related to the epidemiology of urinary retention Three of the articles discuss urinary retention in men. Meigs et al noted an overall background rate for acute urinary retention in men of approximately 5 to 7/1000 per year. Cathcart and Verhamme saw slightly lower rates while Viktrup et al referred to obstructive voiding difficulties in men as "common." Shimizu noted that 85% of the patients seen by the department of Urology for acute urinary retention from 1993-2005 were male. Two articles discussed acute urinary retention in females. Kavia stated that urinary retention in women is "not a common complaint" and Viktrup et al described urinary retention as "rare" in females. (See Appendix II)

Published duloxetine clinical study review:
Viktrup et al reviewed 3 duloxetine studies and 3 duloxetine drug interaction studies in one article. The article reviewed clinical studies and provided an in-depth analysis of urinary retention reported during the duloxetine clinical trials for MDD, SUI, and Benign Prostatic Hyperplasia (BPH). There were a total of 4788 patients (3990F/798M) with 22 (16M/6F) reporting subjective symptoms of urinary retention. OSE summarized the case details in a table. (See Appendix II, Table 2)

Females (6)
The females had a median age of 68.5 years (range 33-83, n=6). Three patients received a dose of 80mg daily, and three received a dose between 80 and 120mg daily. The median time to onset was 2.5 days with a range of 1-175 days (n=6). Two reported concomitant medications or medical conditions which may increase the risk of urinary retention. One case discontinued duloxetine during the study due to urinary retention. A positive dechallenge occurred for one case when duloxetine was discontinued at the end of the study; the patient had remained on duloxetine for 57 days, while experiencing urinary retention during the treatment time. When the study ended the patient's urinary retention resolved within one day.

Males (16)
The 16 males had a median age of 53.5 years (range 35-85, n=16); a median time to onset of 8.5 days (range 1-117 days, n=16) and a median time of offset of 1.5 days (range 1-8 days, n=4). The patients received doses ranging from 30 to 120mg daily. Nine cases detailed medical conditions and/or concomitant medications which may increase the risk of urinary retention. Four positive dechallenges were noted; one who discontinued during the study due to urinary retention symptoms and three with resolution of symptoms when the study ended and duloxetine was discontinued.

Drug Interaction Studies:
Viktrup et al also reviewed three studies of potential drug interactions with duloxetine with desipramine, a tricyclic antidepressant, paroxetine, a selective serotonin reuptake inhibitor, and tolterodine, an antimuscarinic agent. The three studies did not result in reports of urinary retention in the "healthy subjects." But Viktrup et al noted that caution should be used with any

agent such as duloxetine with "the potential to induce or exacerbate an obstructive voiding symptom."[74]

4 DISCUSSION

4.1 DATA MINING

OSE utilized data mining, which scores drug-event combinations based on disproportional analysis comparing a drug-event against the AERS database. An elevated score does not imply or prove causality, or an increased relative risk of the event for that drug. Because AERS is a spontaneous adverse events reporting system and confounding is not evaluated prior to inclusion in the database, the actual risk for a drug-event cannot be determined from data mining. Data mining provides a signal which must be further investigated. Additionally, the sponsor was granted a waiver for non-serious, labeled adverse events such as urinary hesitation and urinary retention. As such, in respect to urinary retention and urinary hesitation, the AERS database and data mining are under-represented, as confirmed by the additional 198 non-serious cases submitted from the sponsor's database.

Even with the under-representation of the waived reports, data mining for duloxetine still showed at least a greater than 2-fold increase in both urinary retention and urinary hesitation with a 95% confidence interval.

4.2 AERS CASE SERIES CHARACTERISTICS

A total of 276 post-marketing reports are included in our review; 78 from AERS and 198 waived reports received from the sponsor. Urinary retention was reported in 169 cases, urinary hesitation in 93 and both urinary retention, and urinary hesitation in 14. Of the 276 reports, 116 were female (42%), 158 male (57%).[75] The males had a median age of 55 (range 21-87, n=111) compared to the females (median 45.5, range 17-85, n=82). The median dose was 60 mg with a range of 20-120 mg (n=69). The median time to onset was 6.5 days with a range of 5 hours to more than a year (n=41). Forty nine discontinued duloxetine with 18 positive dechallenges and one positive rechallenge. The median time to offset was 6.5 days, (range 1 to 30 days, n=6). The data included two positive dechallenge cases without confounding from medications or co-morbid medical conditions.

The postmarketing AERS case series included 26 cases with serious outcomes. We include in this definition cases reporting death, hospitalization, life-threatening outcomes, with or without catheterization; as well as catheterization cases that did not report death, hospitalization and/or life-threatening outcomes. There were no death cases; however, eight were hospitalized, nine catheterized, and nine hospitalized and catheterized. Seven of the hospitalizations had a primary or secondary diagnosis of urinary retention/hesitation. In the AERS reports more females (16/26) than males (10/26) had serious outcomes. Twenty of the twenty-six cases included medical conditions and/or medications which may potentially increase the risk for urinary retention.

[74] Viktrup et al, p. 73.
[75] Gender was not reported for 2 cases.

The females had a median age of 53 years old (range 35-85, n=15); with a median time to onset of 7 days, with a range of 2-365 days[76] (n=8). The median peak daily dose for the hospitalized and/or catheterized females was 40 mg (range 20-120); while the median in females catheterized without hospitalization was 30 mg (range 30-60); both lower than the median of 60 mg for the AERS case series. Thirteen of the sixteen (81%) included concomitant medications and/or medical conditions which might increase the risk of urinary retention. Eight positive dechallenges with treatment were described among the 11 (73%) reporting symptom resolution. Two females reported offsets; both catheterized with offsets of 20 and 30 days.

The males had a median age of 68.5 years and a range of 33-83 (n=8); with a median time to onset approximately three times longer than the females at 21.5 days, (range of 3-89 days, n=6). The hospitalized and/or catheterized males had a median peak daily dose of 60 mg (range 30-120); the same as the median in the males catheterized without hospitalization (range 20-120) and the case series median. Eight of ten (80%) reported concomitant medications, or medical conditions which might increase the risk of urinary retention. Offset information was provided for one case with resolution in one day. Four of the five reporting symptom resolution described positive dechallenges with treatment.

In addition, twelve catheterizations (6F/6M) were included in the 198 waived reports received from the sponsor with 3 females and 4 males detailing positive dechallenges (n=7).

4.3 LITERATURE SEARCH

The literature describes a mechanism of action of duloxetine for a dose-dependent increase in urinary sphincter activity that has been demonstrated in the cat model. Also noted in cats is a proposed potential mechanism for the dose-dependent increase in bladder capacity. Studies have shown duloxetine's action to be modulatory as duloxetine alters neurotransmitters (serotonin and 5-HT) which are unable to induce sphincter contractions in the absence of glutamate. Human studies have reinforced the mechanisms seen in animal models.

To assess the adequacy of the current labeling, we compared the urinary retention reports from the MDD, SUI and BPH clinical trials with our AERS postmarketing case series. Viktrup et al examined the three clinical studies and noted 22 reports of subjective urinary retention. Viktrup's review did not include any reports of urinary retention which required catheterization or hospitalization. They determined it unlikely that duloxetine would result in objective urinary retention or retention which would require catheterizations. In comparison, our postmarketing cases series had twenty-six cases with serious outcomes including nine catheterizations, nine catheterizations with hospitalization and eight hospitalizations; with seven of the seventeen hospitalizations having a primary or secondary diagnosis of urinary retention/hesitation.

While the clinical studies had roughly the same gender distribution as the postmarketing drug use, with 83% females in the clinical studies and 73% of females in the postmarketing drug use, the AERS postmarketing cases with serious outcomes included more females than males (16F/10M) with eleven females requiring catheterization; compared to Viktrup's urinary retention cases which were predominantly male (16M/6F) and did not result in any serious

[76] 210 days estimated time used for onset of "6-8 month", 365 days estimated time used for onset "more than a year"

outcomes. Given the literature describing urinary retention in females as rare or uncommon, OSE did not expect to see more females than males with serious outcomes. Our postmarketing females with serious outcomes detailed more positive dechallenges (73%) than Viktrup's urinary retention females (17%). Eighty-one percent of our postmarketing females with serious outcomes reported concomitant medications and/or medical conditions which might increase the potential for urinary retention compared to thirty-three percent in Viktrup's urinary retention cases. Our females described a longer onset (median 7 days) versus Viktrup's median of 2.5 days. Both describe a wide range of onset; 2-365 days in the postmarketing females with serious outcomes; 1-175 days for Viktrup's urinary retention females. One possible explanation for the delayed onset may be the progressive increase on sphincter activity after seven months seen in the Bump study.[77]

In the AERS postmarketing case series, the males with serious outcomes are older; with a median of 68.5 years old in our case series compared to 53 in Viktrup's. Our median time to onset was longer, a median of 21.5 days compared 8.5 days for Viktrup but both had wide ranges; ours with a range of 3-89 days and Viktrup's with a range of 1-117 days. Eighty percent of our males with serious outcomes reported concomitant medications and/or medical histories which may increase the potential for urinary retention compared to 56% of Viktrup's males with urinary retention. Eighty percent of the males with serious outcomes who reported symptom resolution documented a positive dechallenge with treatment; compared to four of 16 (25%) in Viktrup's males with urinary retention.

5 CONCLUSION

Voiding is a complex mechanism which is not fully understood. Duloxetine resulted in a dose-dependent eight fold increase in striated sphincter muscle activity in the cat model and was shown to have similar results in human studies. Duloxetine was also shown to have a dose-dependent five fold increase in bladder capacity in cats. In clinical studies, duloxetine demonstrated a dose-dependent decrease in incontinence episodes and a dose dependent increase in time between voids. Duloxetine has been shown to impact urethral closure; however duloxetine's mechanism of action is considered facilitatory and thus, unlikely to result in urinary retention. However, urinary retention was seen in the clinical studies but serious outcomes such as catheterization or hospitalization were not reported.

The OSE case series indicates that duloxetine use in the general population may result in urinary retention with serious outcomes including hospitalization and catheterization. Although the quality of the cases in our series is not optimal; the cases with serious outcomes with both a temporal relationship to duloxetine, and a positive dechallenge support a risk of urinary retention for patients using duloxetine. While the current labeling includes a listing of urinary retention, the labeling does not inform health care providers of the serious outcomes seen in our case series.

Health care providers may find the potential for urinary retention resulting in catheterization and/or hospitalization, particularly in female patients, helpful information when considering

[77] Schuessler p, 8.

duloxetine for their patients. In addition, the information concerning the delayed onset of urinary retention seen in both the clinical studies and our postmarketing case series may assist health care providers when assessing duloxetine patients with urinary retention.

RECOMMENDATIONS

- Add cautionary information to the Precautions section concerning duloxetine associated urinary retention that resulted in hospitalization and/or catheterization of both males and females as seen in the AERS post-marketing cases.

- Modify the venlafaxine label to be consistent with "class labeling" as identified in the duloxetine for urinary hesitation.

Concur,

Marilyn R. Pitts, Pharm.D., Safety Evaluator, Team Leader Date

cc: DPP: Hughes/Saini/Glass
OSE: Robinson/Drug File

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7 APPENDIX

Appendix I: Limitations of AERS

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Appendix II: Literature Search Results

Urinary retention was seen predominantly in males (85%) over the 12 year period reviewed by Shimizu et al in the Kinki University Hospital (n=206).[78] An incidence rate of acute urinary retention for males of 2.2/1000 man years was reported by Verhamme et al following a retrospective cohort study in the Netherlands. (n=56,958)[79] A prospective cohort study of male health professionals was performed by Meigs et al who calculated a crude incidence of 5.2/1000 person-years and an adjusted incidence of 4.5/1000 person-years with reports of 82 catheterizations in 6,100 men[80]; consistent with studies of similar populations such as the Olmstead County study. The incidence increased with age. Calcium channel blockers, beta blockers, nondiuretic antihypertensive and antiarrhythmia medications were accompanied by a 2-3 fold increased risk. A diagnosis of BPH or pre-existing lower urinary tract symptoms was also associated with an increased risk of acute urinary retention. There was no association between clinical risk factors such as smoking, diabetes, or hypertension and an increased risk. Cathcart et al. found an incidence rate of 3.06/1000 men yearly.[81] While there are several studies on the epidemiology of urinary retention in males, we were unable to find similar population based studies in women. Kavia et al described urinary retention in women as "not a common complaint."[82] Viktrup et al noted that urinary retention in women is "usually related to pharmaceutical agents," genital organ prolapse, multiple sclerosis (MS), Parkinson's disease, Diabetes Mellitus or vessico-urethral sphincter dyssynergia. Benign Prostatic Hypertrophy (BPH), prostatic cancer were listed as unique risk factors for the common obstructive voiding symptoms in men along with pharmaceuticals and the same neurologic disorders which pose a risk for females.[83]

Adverse events reported during duloxetine clinical trials for MDD, SUI and Benign Prostatic Hyperplasia (BPH) were reviewed by Viktrup et al; a total of 4788 patients (3990F/798M) (see table 1) with 22 reporting subjective symptoms of urinary retention (female=6, male=16). The MDD trial was comprised of 8 double-blind 8-9 week placebo-controlled studies with 1139 patients (age 18-77, 761F/378M); followed by an open-label study with 1279 enrolled (age18-87, 928F/351M). Patients received duloxetine at doses from 40-120mg with a median duration of 91 days; 41.1% with a duration of more than 180 days. Gender was not provided. The SUI study included 4 double-blind placebo-controlled studies and 4 open-label studies (age 20-87) with longer exposures to duloxetine 40 mg b.i.d.; 191 having more than 12 months of exposure and 818 more than 6 months of exposure; (n=2301). Sixty-nine men with pre-existing symptoms of obstruction were subjects in the BPH placebo-controlled study receiving 30-40 mg of duloxetine for 4-8 weeks. The BPH study included 69 men who had documented mild to moderate obstruction during uroflowmetry, irritative symptoms such as frequency, nocturia or urgency and were either currently in medical therapy for BPH or were a candidate for therapy. Two of the sixty-nine reported urinary retention during the study; one with retention symptoms resulting in discontinuation of duloxetine after the second episode of urinary retention. Per Viktrup et al, a history of BPH or other prostate conditions did not appear to increase subjective symptoms of urinary retention. Viktrup et al concluded obstructive voiding symptoms occurred significantly more often with duloxetine – 1% versus placebo 0.4% ($p<.05$). While the MDD, SUI, and BPH studies included 4788 patients (3990F/798M) with 22 reporting urinary retention symptoms, none of the subjects were catheterized or hospitalized due to urinary retention. Viktrup et al concluded the risk for duloxetine associated urinary retention was limited as was the likelihood of discontinuation due to obstructive voiding symptoms.

Table 1. Abstracted Data from Urinary Retention/Urinary Hesitation in MDD, SUI and BPH Clinical Trials

Action	MDD placebo (n=1139)	MDD Open-label (n = 1279)	SUI placebo (n = 1913)	SUI Open-label (n=1877[84])	BPH placebo (n = 69)	Total n = 4788 (3990F/798M)
Reported Urinary Retention	4 1 F - 0.1% 3M – 0.8%	14 3F -0.3% 11M – 3.2%	0	2F – 0.1%	2M– 2.8%	22 – 0.5% 6 F 16 M
Reported Urinary Hesitation	5[85]	1[86]	2F	3F	NA[87]	11

[78] Shimizu et al: Clinical Study of Acute Urinary Retention. Nippon Hinyokika Gakkai Zasshi. 2006 Nov;97(7):839-43.
[79] Verhamme et al: Low incidence of acute urinary retention in the general male population: the triumph project. European Urology. 2005 Apr;47(4):494-8.
[80] Excluded history of acute urinary retention and/or TURP. Meigs et al. p 377.
[81] Cathcart et al: Incidence of Primary and recurrent Acute Urinary Retention Between 1998 and 2003 in England. Journal of Urology. 2006 Jul;176(1):200-4.
[82] Kavia et al: Urinary Retention in women? Its causes and management. BJU International. 2006:Feb;97(2):281-7.
[83] Viktrup et al: Urinary Side Effects of Duloxetine in the Treatment of Depression and Stress Urinary Incontinence, Prim Care Companion J Clin Psychiatry. 2004;6(2):65-79.
[84] 3 open-label studies extensions of placebo-controlled studies. 1 open label study (n = 658) not preceded by placebo controlled study.
[85] Gender not available in Viktrup et al
[86] Gender not available in Viktrup et al

Discontinued due to urinary symptoms	0	2M	0	1F	1M	4 (3M/1F)

Viktrup et al also reviewed studies of potential drug interactions with duloxetine. Small studies for drug interactions with desipramine (n=7), a tricyclic antidepressant, paroxetine (n=12, duration 5 days), a selective serotonin reuptake inhibitor and tolterodine (n=16, duration 5 days), an antimuscarinic agent, did not result in any reports of urinary retention in healthy subjects. But Viktrup et al noted that caution should be used with any agent such as duloxetine with "the potential to induce or exacerbate an obstructive voiding symptom."[88]

Table 2. Summary of Characteristics for Clinical Trial Subjects Report Urinary Retention

Study	Age	Gender	Total Daily Dose	Onset in Days	Offset in Days	Duration in Days	Discontinued due to retention	Positive Dechallenge	Relevant History
MDD	56	f	80	1	1	57		Y	Pseudoephedrine
MDD	41	f	*80-120	2	35 while on duloxetine	34			
MDD	42	f	*80-120	8	17 while on duloxetine	10			Diabetes
MDD	60	f	*80-120	1	8 while on duloxetine	8			
SUI	29	f	80	175	Continued after dc	>50	Y		
SUI	83	f	80	3	Continued after dc	>40			
MDD	28	m	40	8	Continued after dc	>70			Urinary hesitation, decreased urinary flow
MDD	52	m	80	3	26 while on duloxetine	24			
MDD	63	m	120	1	72 while on duloxetine	24			
MDD	59	m	*80-120	15	2	352		Y	Pygeum africanum
MDD	46	m	*80-120	14	182 while on duloxetine	169			Multiple pain meds
MDD	30	m	*80-120	117	362 while on duloxetine	247			
MDD	44	m	*80-120	1	1	10		Y	
MDD	57	m	*80-*120	3	Continued after dc	>320			Dsyuria, burning on urination
MDD	50	m	*80-120	2	102 while on duloxetine	101			
MDD	62	m	*80-120	9	13 while on duloxetine	5			Polyuria
MDD	58	m	*80-120	1	Continued after dc	>91	Y		Dysuria, shrinkage of urinary canal, pollakiuria, nocturia
MDD	46	m	*80-120	15	Continued after dc	>212			
MDD	47	m	*80-120	23	116 while on duloxetine	94			
MDD	65	m	*80-120	2	Continued after dc	12	Y		Diabetes
BPH	55	m	30	11	8	25		Y	Diabetes, BPH

[87] Known obstructive voiding symptoms, Viktrup et al, p 71.
[88] Viktrup et al, p. 73.

Study	Age	Gender	Total Daily Dose	Onset in Days	Offset in Days	Duration in Days	Discontinued due to retention	Positive Dechallenge	Relevant History
BPH	62	m	30	17	1	3	Y	Y	BPH

*Specific prescribed dose unavailable. Open-label extension study with 80-120 mg

Appendix III: Line Listing of Waived Reports

Table 3: Line Listing of Waived Reports of Urinary Retention and Urinary Hesitation from 02/03/05-05/02/07, Submitted by Eli Lilly, Inc, submitted 05/25/07

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA0509109470	26 Years	Female	05-Oct-2005	30 mg, daily (1/D)	Anxiety	Urinary hesitation	Not Recovered
S200612001169	56 Years	Female	07-Dec-2006	30 mg, each evening	Depression	Urinary hesitation	Not Recovered
USA0509107492	Unknown	Female	09-Sep-2005	60 mg, daily (1/D)	Fibromyalgia	Urinary hesitation	Not Recovered
USA050597390	69 Years	Female	13-May-2005	60 mg, each evening	Fibromyalgia	Urinary hesitation	Not Recovered
USA050598026	64 Years	Female	23-May-2005	30 mg, each evening	Depression	Urinary hesitation	Recovered
US200610000859	18 Years	Female	05-Oct-2006	30 mg, UNK	Depression	Urinary hesitation	Recovered
USA0511112820	Unknown	Female	05-Nov-2005	30 mg, unknown	Depression	Urinary hesitation	Recovering
USA050495219	38 Years	Female	16-Apr-2005	60 mg, daily (1/D)	Depression	Urinary hesitation	Unknown
USA0507102143	40 Years	Female	13-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
USA0507102145	40 Years	Female	13-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
US200606002343	25 Years	Female	09-Jun-2006	Unknown	Depression	Urinary hesitation	Unknown
US200605001837	54 Years	Female	09-May-2006	30 mg, UNK	Neuropathy	Urinary hesitation	Unknown
US200512000366	Unknown	Female	02-Dec-2005	20 mg, CAPSULE	Pain	Urinary hesitation	Unknown
USA050598361	45 Years	Female	23-May-2005	20 mg, daily (1/D)	Unknown	Urinary hesitation	Unknown
US200512000359	Unknown	Female	02-Dec-2005	30 mg, CAPSULE	Unknown	Urinary hesitation	Unknown
USA0507103433	42 Years	Female	21-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary hesitation	Unknown
US200607002694	50 Years	Female	17-Jul-2006	30 mg, UNK	Unknown	Urinary hesitation	Unknown
US200607002695	Unknown	Female	17-Jul-2006	30 mg, UNK	Unknown	Urinary hesitation	Unknown
US200602001376	55 Years	Female	07-Feb-2006	60 mg, UNK	Unknown	Urinary hesitation	Unknown
USA050597284	Unknown	Female	11-May-2005	UNK, unknown	Unknown	Urinary hesitation	Unknown
US200607003370	Unknown	Female	19-Jul-2006	Unknown	Unknown	Urinary hesitation, Dysuria	Unknown
USA0507102484	41 Years	Female	18-Jul-2005	60 mg, daily (1/D)	Myofascial pain syndrome	Urinary hesitation, Dysuria	Not Recovered
US200602004323	57 Years	Female	22-Feb-2006	60 mg, daily (1/D)	attention deficit/hyperactivity disorder	Urinary hesitation, Micturition urgency, Urine flow decreased	Not Recovered
US200702003529	Unknown	Female	16-Feb-2007	30 mg, daily (1/D)	Depression	Urinary retention	Not Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
US200702005464	57 Years	Female	27-Feb-2007	30 mg, unknown	Depression	Urinary retention	Not Recovered
USA0507102290	Unknown	Female	15-Jul-2005	60 mg, daily (1/D)	Major depression	Urinary retention	Not Recovered
US200701000733	19 Years	Female	04-Jan-2007	30 mg, daily (1/D)	Panic disorder	Urinary retention	Not Recovered
US200607005094	33 Years	Female	28-Jul-2006	30 mg, UNK	Anxiety	Urinary retention	Recovered
US200611000660	43 Years	Female	03-Nov-2006	30 mg, UNK	Anxiety	Urinary retention	Recovered
US200611003378	17 Years	Female	17-Nov-2006	20 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA0507102915	48 Years	Female	24-Aug-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA050496703	Unknown	Female	04-May-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
US200601005167	40 Years	Female	30-Jan-2006	60 mg, CAPSULE	Depression	Urinary retention	Recovered
US200602004300	55 Years	Female	22-Feb-2006	60 mg, UNK	Depression	Urinary retention	Recovered
USA0507102757	Unknown	Female	21-Jul-2005	60 mg, unknown	Depression	Urinary retention	Recovered
USA0506101574	60 Years	Female	08-Jul-2005	80 mg, daily (1/D)	Depression	Urinary retention	Recovered
US200604001240	65 Years	Female	07-Apr-2006	60 mg, UNK	Neuralgia	Urinary retention	Recovered
USA0506101542	55 Years	Female	07-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
USA0507102084	Unknown	Female	14-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
US200702002045	18 Years	Female	12-Feb-2007	30 mg, UNK	Unknown	Urinary retention	Recovered
USA050393293	58 Years	Female	24-Mar-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
USA0511112824	80 Years	Female	05-Nov-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
USA050597863	44 Years	Female	16-May-2005	60 mg, unknown	Unknown	Urinary retention	Recovered
US200604004482	79 Years	Female	27-Apr-2006	60 mg, daily (1/D)	Pain in extremity	Urinary retention	Recovering
US200605004422	39 Years	Female	22-May-2006	30 mg, each evening	Trigeminal neuralgia	Urinary retention	Recovering
USA0507102394	Unknown	Female	14-Jul-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Recovering
US200611004244	48 Years	Female	22-Nov-2006	40 mg, daily (1/D)	Depression	Urinary retention	Unknown
USA050392586	29 Years	Female	15-Mar-2005	60 mg, daily (1/D)	Depression	Urinary retention	Unknown
US200604003907	55 Years	Female	25-Apr-2006	60 mg, UNK	Depression	Urinary retention	Unknown
USA050393437	Unknown	Female	26-Mar-2005	60 mg, unknown	Depression	Urinary retention	Unknown
US200608000940	45 Years	Female	04-Aug-2006	90 mg, UNK	Depression	Urinary retention	Unknown
USA0508105484	57 Years	Female	16-Aug-2005	UNK, unknown	Major depression	Urinary retention	Unknown
US200604001241	68 Years	Female	07-Apr-2006	60 mg, UNK	Neuralgia	Urinary retention	Unknown
US200606001134	Unknown	Female	05-Jun-2006	20 mg, UNK	Unknown	Urinary retention	Unknown
US200609001777	44 Years	Female	08-Sep-2006	30 mg, UNK	Unknown	Urinary retention	Unknown
US_0506118105	38 Years	Female	01-Jun-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
USA050290450	45 Years	Female	19-Feb-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA0509109559	Unknown	Female	04-Oct-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
US200704000222	19 Years	Female	02-Apr-2007	60 mg, UNK	Unknown	Urinary retention	Unknown
US200609005529	36 Years	Female	22-Sep-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200511000444	Unknown	Female	15-Nov-2005	60 mg, UNK	Unknown	Urinary retention	Unknown
US200605003917	Unknown	Female	18-May-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200606001394	Unknown	Female	06-Jun-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200609005062	Unknown	Female	21-Sep-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
USA0510110897	23 Years	Female	18-Oct-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
US_0503114496	49 Years	Female	22-Mar-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0509108508	Unknown	Female	27-Sep-2005	90 mg, unknown	Unknown	Urinary retention	Unknown
US200611002621	78 Years	Female	14-Nov-2006	UNK mg, UNK	Unknown	Urinary retention	Unknown
USA050189379	Unknown	Female	11-Feb-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050291000	Unknown	Female	25-Feb-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495117	Unknown	Female	14-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA0506101677	Unknown	Female	08-Jul-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA0509108509	Unknown	Female	27-Sep-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA0507101964	Unknown	Female	13-Jul-2005	60 mg, daily (1/D)	Unknown	Urinary retention, Urinary hesitation	Not Recovered
US200611003172	Unknown	Male	16-Nov-2006	120 mg, daily (1/D)	Major depression	Urinary hesitation	Not Recovered
US200603004373	59 Years	Male	16-Mar-2006	120 mg, UNK	Neuralgia	Urinary hesitation	Not Recovered
US200611003863	84 Years	Male	21-Nov-2006	30 mg, daily (1/D)	Neuralgia	Urinary hesitation	Not Recovered
USA0508106374	68 Years	Male	26-Aug-2005	60 mg, daily (1/D)	Peripheral sensory neuropathy	Urinary hesitation	Not Recovered
US200602004065	31 Years	Male	21-Feb-2006	30 mg, CAPSULE	Anxiety	Urinary hesitation	Recovered
US200606001156	30 Years	Male	05-Jun-2006	60 mg, UNK	Back pain	Urinary hesitation	Recovered
US200605004217	45 Years	Male	19-May-2006	60 mg, UNK	Back pain	Urinary hesitation	Recovered
USA0508106522	59 Years	Male	29-Aug-2005	30 mg, daily (1/D)	Bone pain	Urinary hesitation	Recovered
US200612004398	61 Years	Male	27-Dec-2006	20 mg, daily (1/D)	Depression	Urinary hesitation	Recovered
US200605000883	36 Years	Male	04-May-2006	60 mg, UNK	Depression	Urinary hesitation	Recovered
US200605006808	44 Years	Male	31-May-2006	60 mg, UNK	Depression	Urinary hesitation	Recovered
USA0507102109	33 Years	Male	14-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Recovered
US200612001651	21 Years	Male	11-Dec-2006	60 mg, UNK	Pain	Urinary hesitation	Recovered
USA0510111918	62 Years	Male	29-Oct-2005	60 mg, unknown	Pain	Urinary hesitation	Recovered
US200610004710	51 Years	Male	26-Oct-2006	120 mg, UNK	Panic disorder	Urinary hesitation	Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
US200701004311	46 Years	Male	23-Jan-2007	30 mg, daily (1/D)	Radiculitis brachial	Urinary hesitation	Recovered
USA0507103055	41 Years	Male	21-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary hesitation	Recovered
US200605003669	50 Years	Male	17-May-2006	60 mg, UNK	Unknown	Urinary hesitation	Recovered
US_0511123661	27 Years	Male	07-Nov-2005	60 mg, unknown	Unknown	Urinary hesitation	Recovered
US200702003397	77 Years	Male	16-Feb-2007	60 mg, unknown	Unknown	Urinary hesitation	Recovered
USA050597356	55 Years	Male	13-May-2005	30 mg, daily (1/D)	Depression	Urinary hesitation	Recovering
USA050597578	Unknown	Male	13-May-2005	30 mg, daily (1/D)	Depression	Urinary hesitation	Recovering
US200701005370	Unknown	Male	26-Jan-2007	60 mg, UNK	Unknown	Urinary hesitation	Recovering
US200608004554	32 Years	Male	22-Aug-2006	30 mg, 2/D	Complex regional pain syndrome	Urinary hesitation	Unknown
US200608003595	53 Years	Male	17-Aug-2006	30 mg, daily (1/D)	Depression	Urinary hesitation	Unknown
USA0507102146	30 Years	Male	13-Jul-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
US_0412109056	53 Years	Male	13-Dec-2004	60 mg, unknown	Depression	Urinary hesitation	Unknown
USA050495611	Unknown	Male	20-Apr-2005	60 mg, unknown	Depression	Urinary hesitation	Unknown
US200605002157	55 Years	Male	10-May-2006	30 mg, UNK	Unknown	Urinary hesitation	Unknown
US200609001795	Unknown	Male	08-Sep-2006	60 mg, daily (1/D)	Unknown	Urinary hesitation	Unknown
US200609002337	21 Years	Male	11-Sep-2006	60 mg, UNK	Unknown	Urinary hesitation	Unknown
US200511000527	50 Years	Male	15-Nov-2005	60 mg, UNK	Unknown	Urinary hesitation	Unknown
US200605000406	Unknown	Male	02-May-2006	60 mg, UNK	Unknown	Urinary hesitation	Unknown
US200611003176	Unknown	Male	16-Nov-2006	Unknown	Unknown	Urinary hesitation	Unknown
USA050188985	Unknown	Male	07-Feb-2005	30 mg, 2/D	Neuropathy	Urinary hesitation, Dysuria	Not Recovered
US200608006336	Unknown	Male	29-Aug-2006	30 mg, daily (1/D)	Depression	Urinary hesitation, Dysuria	Not Recovered
US200606002988	Unknown	Male	13-Jun-2006	60 mg, UNK	Unknown	Urinary hesitation, Dysuria	Unknown
USA0510110777	77 Years	Male	17-Oct-2005	30 mg, unknown	Neuropathy peripheral	Urinary hesitation, Dysuria	Recovered
US200605003650	42 Years	Male	17-May-2006	60 mg, UNK	Unknown	Urinary hesitation, Dysuria	Recovered
US200611002845	52 Years	Male	15-Nov-2006	Unknown	Unknown	Urinary hesitation, Urinary incontinence	Recovered
US200702004967	53 Years	Male	23-Feb-2007	20 mg, UNK	Depression	Urinary retention	Not Recovered
US200612003178	47 Years	Male	18-Dec-2006	30 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
USA0507103807	52 Years	Male	29-Jul-2005	60 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
US200703005406	62 Years	Male	26-Mar-2007	60 mg, daily (1/D)	Depression	Urinary retention	Not Recovered
US200702004105	Unknown	Male	20-Feb-2007	60 mg, unknown	Depression	Urinary retention	Not Recovered
USA050393646	43 Years	Male	30-Mar-2005	UNK, unknown	Depression	Urinary retention	Not Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA041184374	44 Years	Male	01-Dec-2004	20 mg, 2/D	Anxiety	Urinary retention	Recovered
USA0509108455	87 Years	Male	22-Sep-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA0510110268	Unknown	Male	11-Oct-2005	30 mg, daily (1/D)	Depression	Urinary retention	Recovered
US_0501110700	45 Years	Male	20-Jan-2005	30 mg, unknown	Depression	Urinary retention	Recovered
USA0507103144	73 Years	Male	22-Jul-2005	30 mg, unknown	Depression	Urinary retention	Recovered
USA0507101881	60 Years	Male	12-Jul-2005	60 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA0510111687	Unknown	Male	26-Oct-2005	60 mg, daily (1/D)	Depression	Urinary retention	Recovered
USA050291723	67 Years	Male	25-Feb-2005	UNK, unknown	Depression	Urinary retention	Recovered
USA050290991	85 Years	Male	25-Feb-2005	UNK, unknown	Depression	Urinary retention	Recovered
USA050597035	38 Years	Male	09-May-2005	60 mg, daily (1/D)	Major depression	Urinary retention	Recovered
US200607004351	Unknown	Male	25-Jul-2006	60 mg, UNK	Major depression	Urinary retention	Recovered
USA0506101113	70 Years	Male	29-Jun-2005	30 mg, daily (1/D)	Neuropathy	Urinary retention	Recovered
US200511002532	50 Years	Male	23-Nov-2005	30 mg, capsule	Unknown	Urinary retention	Recovered
USA0507102913	27 Years	Male	25-Jul-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
US200704005974	54 Years	Male	26-Apr-2007	30 mg, daily (1/D)	Unknown	Urinary retention	Recovered
US200605005734	70 Years	Male	26-May-2006	30 mg, each evening	Unknown	Urinary retention	Recovered
USA050393296	70 Years	Male	24-Mar-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
USA0507103006	Unknown	Male	22-Jul-2005	30 mg, unknown	Unknown	Urinary retention	Recovered
US200601005285	Unknown	Male	31-Jan-2006	60 mg, UNK	Unknown	Urinary retention	Recovered
USA0508106867	70 Years	Male	01-Sep-2005	60 mg, unknown	Unknown	Urinary retention	Recovered
USA041183340	38 Years	Male	10-Nov-2004	60 mg, daily (1/D)	Depression	Urinary retention	Recovering
US200605002338	65 Years	Male	11-May-2006	60 mg, UNK	Diabetic neuropathy	Urinary retention	Recovering
US200605002339	65 Years	Male	11-May-2006	60 mg, UNK	Diabetic neuropathy	Urinary retention	Recovering
USA050495566	57 Years	Male	19-Apr-2005	60 mg, daily (1/D)	Neuropathy peripheral	Urinary retention	Recovering
US200603005299	73 Years	Male	21-Mar-2006	60 mg, UNK	Unknown	Urinary retention	Recovering
US200611003201	Unknown	Male	16-Nov-2006	60 mg, UNK	Unknown	Urinary retention	Recovering
US200612001539	62 Years	Male	11-Dec-2006	30 mg, UNK	Depression	Urinary retention	Unknown
USA0507103080	40 Years	Male	21-Jul-2005	60 mg, daily (1/D)	Depression	Urinary retention	Unknown
US200604003908	58 Years	Male	25-Apr-2006	60 mg, UNK	Depression	Urinary retention	Unknown
USA0510110430	59 Years	Male	13-Oct-2005	60 mg, unknown	Depression	Urinary retention	Unknown
USA0507102505	Unknown	Male	21-Jul-2005	UNK, unknown	Depression	Urinary retention	Unknown
USA0510109908	50 Years	Male	06-Oct-2005	60 mg, unknown	Diabetic neuropathy	Urinary retention	Unknown
USA0509109451	40 Years	Male	30-Sep-2005	60 mg, unknown	Fibromyalgia	Urinary retention	Unknown

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA050291234	55 Years	Male	01-Mar-2005	60 mg, daily (1/D)	Neuralgia	Urinary retention	Unknown
US200602001094	Unknown	Male	06-Feb-2006	60 mg, UNK	Neuralgia	Urinary retention	Unknown
USA050188877	65 Years	Male	03-Feb-2005	30 mg, unknown	Neuropathy	Urinary retention	Unknown
USA050496062	43 Years	Male	27-Apr-2005	30 mg, daily (1/D)	Unknown	Urinary retention	Unknown
US200603003388	Unknown	Male	14-Mar-2006	30 mg, UNK	Unknown	Urinary retention	Unknown
USA050393504	55 Years	Male	26-Mar-2005	30 mg, unknown	Unknown	Urinary retention	Unknown
USA0506101672	Unknown	Male	07-Jul-2005	30 mg, unknown	Unknown	Urinary retention	Unknown
USA050598701	42 Years	Male	25-May-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
USA050291656	Unknown	Male	04-Mar-2005	60 mg, daily (1/D)	Unknown	Urinary retention	Unknown
US200605004117	40 Years	Male	19-May-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200512001838	50 Years	Male	12-Dec-2005	60 mg, UNK	Unknown	Urinary retention	Unknown
US200605003918	Unknown	Male	18-May-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
US200609002950	Unknown	Male	13-Sep-2006	60 mg, UNK	Unknown	Urinary retention	Unknown
USA0509109445	41 Years	Male	30-Sep-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA050598688	45 Years	Male	25-May-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
US_0511123830	50 Years	Male	08-Nov-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0508105514	57 Years	Male	17-Aug-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0508105414	65 Years	Male	15-Aug-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0506100284	80 Years	Male	15-Jun-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA0509109555	Unknown	Male	04-Oct-2005	60 mg, unknown	Unknown	Urinary retention	Unknown
USA050291255	50 Years	Male	01-Mar-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495029	Unknown	Male	13-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495537	Unknown	Male	13-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050495546	Unknown	Male	13-Apr-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050597042	Unknown	Male	09-May-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050598141	Unknown	Male	07-Jul-2005	UNK, unknown	Unknown	Urinary retention	Unknown
USA050598926	Unknown	Male	26-May-2005	UNK, unknown	Unknown	Urinary retention	Unknown
US200512004204	Unknown	Male	28-Dec-2005	Unknown	Unknown	Urinary retention	Unknown
US200612002766	71 Years	Male	15-Dec-2006	30 mg, UNK	Neuropathy	Urinary retention	Worsened
US200702005703	Unknown	Male	28-Feb-2007	60 mg, UNK	Neuropathy	Urinary retention, Micturition urgency	Unknown
US200607001863	67 Years	Male	12-Jul-2006	30 mg, UNK	Pain	Urinary retention, Urinary hesitation	Not Recovered

Manufacturer Control Number	Age	Gender	Date of Report	Dose	Indication	Event PT	Event Outcome
USA050189300	84 Years	Male	11-Feb-2005	UNK, unknown	Neuropathy	Urinary retention, Urinary hesitation	Not Recovered
USA050393935	48 Years	Male	24-Mar-2005	UNK, unknown	Unknown	Urinary retention, Urinary hesitation	Recovered
USA0508105172	29 Years	Male	12-Aug-2005	60 mg, unknown	Depression	Urinary retention, Dysuria	Recovered
US200601004520	63 Years	Male	26-Jan-2006	20 mg, daily (1/D)	Major depression	Urinary retention, Pollakiuria	Recovered
US200610001591	69 Years	Male	10-Oct-2006	60 mg, UNK	Neuropathy	Urinary retention, Pollakiuria	Not Recovered
US200604001928	56 Years	Male	12-Apr-2006	60 mg, UNK	Neuropathy	Urinary retention, Urinary hesitation	Unknown
US200605003649	70 Years	Male	17-May-2006	60 mg, daily (1/D)	Unknown	Urinary retention, Urinary hesitation	Recovered
USA050495406	Unknown	Male	19-Apr-2005	60 mg, unknown	Unknown	Urinary retention, Urinary hesitation	Recovered
USA050393342	48 Years	Male	24-Mar-2005	UNK, unknown	Unknown	Urinary retention, Urinary hesitation	Recovered
USA0507104189	53 Years	Male	02-Aug-2005	30 mg, unknown	Depression	Urinary retention, Urinary hesitation	Unknown
USA050291653	Unknown	Male	04-Mar-2005	60 mg, daily (1/D)	Unknown	Urinary retention, Urinary hesitation	Unknown
USA0510111398	25 Years	Male	21-Oct-2005	30 mg, daily (1/D)	Pain	Urinary retention, Urinary hesitation, Pollakiuria	Recovered
US_0502113494	Unknown	Unknown	28-Feb-2005	30 mg, unknown	Unknown	Urinary hesitation	Unknown
US200702003542	Unknown	Unknown	16-Feb-2007	60 mg, UNK	Depression	Urinary retention	Unknown

Appendix IV: Postmarketing AERS Case Series

Table 4. Included Post-Marketing Cases from AERS, Search Date = 03/26/07

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
5034786 US	DC Hospitalized for urinary retention admitted through ER, Cathed	Temporal relationship to duloxetine. Duloxetine dc. Positive dechallenge with treatment.	Female of unknown age with hx of diabetes prescribed duloxetine 20 mg QD. Increased by 20 mg increments up to 100 mg QD over unknown time frame. C/O urinary hesitancy. Duloxetine decreased to 60 mg QD. Presented to ER with c/o inability to void. Admitted. Foley inserted for 1 week. Duloxetine dc. Symptoms resolved after 1 month.	Hx of diabetes. Oxybutynin and fluoxetine labeled for urinary retention; hydrocodone/acetaminophen - opiate agonists may cause urinary retention. Symptoms resolved after 1 month; half life of duloxetine 12 hours. Unclear information regarding date of dc.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
5002380 FOR	DC Hospitalized for urinary retention Cathed	Medical confirmation of retention. No previous dx of BPH – new dx. Reported hx neg for UTI and renal failure. Duloxetine dc.	77 yo male prescribed duloxetine 60 mg QD for diabetic polyneuropathy. Developed urinary retention over 2 months. Duloxetine dc. Hospitalized for urinary retention. Cathed. Overflow bladder dx with .5 L residual. Distinctive BPH dx – previously unknown. Symptoms did not improve after 2 weeks without duloxetine. Surgery performed.	Hx of diabetes. New dx: BPH. Symptoms continued after dc and required surgical intervention. Negative dechallenge.
5036331 US	DC/Restarted Hospitalized with acute urinary retention	Duloxetine dc.	62 yo male prescribed duloxetine 60 BID for neuropathy. Hospitalized with acute urinary retention. Duloxetine dc. Prescribed 2 new meds for BPH. Duloxetine restarted. Neurologist and urologist managing patient.	New dx: BPH; Restarted duloxetine. Insufficient information. Concomitant meds, medical hx, and symptom resolution not reported.
5145483 5117308 US	DC Hospitalized for hyponatremia and acute urinary retention Cathed	H&P from admission included. Medical confirmation of retention. Hx of incontinence. Rechallenge: With restart, symptoms appear to have increased since cathed after restarted. Symptoms resolving after dc. Positive dechallenge with treatment.	76 yo female with distant hx of UTI and current hx of incontinence. Prescribed duloxetine 30 mg QD. On an unknown date, c/o urinary retention with additional CNS, GI and musculoskeletal complaints. Duloxetine dc. Restarted duloxetine 30. C/O urinary retention. Cathed. Developed UTI. Continued to decline. Duloxetine dc. Hospitalized one day after duloxetine dc for confusion and weakness. Dx – hyponatremia and acute urinary retention. UA – nml. Urine C&S – no growth. Recovering. NOTE: conflicting information regarding hx of retention vs. incontinence.	No information of resolution with first dc. Unclear if catheter removed prior to discharge.
5044966 US	DC Hospitalization for fecal impaction and urinary retention Cathed	Reported hx neg for BPH, urethral stricture, or frequent UTI. Symptoms resolved after dc Positive dechallenge with treatment.	83 yo male prescribed duloxetine 30 mg for depression. No previous hx of BPH. Day 8, hospitalized for urinary retention and fecal impaction. Cathed. Duloxetine dc. Hx of "constipation with many psychotropic drugs." Symptoms resolved.	Dextropropoxyphene - opiate agonists may cause urinary retention; concurrent dx of fecal impaction.
5203711 5023132 US	Continued Hospitalized for "urinary hesitation"	Oybutynin indicated for overactive bladder.	45 yo female with hx of diabetes prescribed duloxetine 30 mg BID for depression. Over 1 year late, hospitalized for c/o urinary "hesitation" described as "could not pee." Oxybutynin dc. Resolved.	Hx of diabetes. Oxybutynin labeled for urinary retention. Symptoms resolved after oxybutynin dc. Symptoms did not result in dc of duloxetine.
4683860 US	DC Hospitalized for urinary retention	Duloxetine dc. No report of hx of BPH.	Male of unknown age prescribed duloxetine for DPNP. Hospitalized for c/o urinary retention.	Hx of diabetes. Insufficient information. Concomitant meds and symptom resolution not reported
4908994 US	DC Hospitalized for pyelonephritis Cathed	Hx of incontinence. Duloxetine dc. Positive dechallenge with treatment.	78 yo female with hx of frequent UTIs and incontinence. Prescribed duloxetine 20 mg QD for depression. Increased to 60 on unknown date. 6-8 months later hospitalized with pyelonephritis. In hospital, c/o urinary retention. Cathed. Urine C&S – pseudomonas. Duloxetine dc. Resolved.	Hx of UTIs; pseudomonas in urine; concurrent dx of pyelonephritis; aripiprazole labeled for retention;
5177220 US	DC Hospitalized for suicidal ideation Cathed	Duloxetine dc.	75 yo male with hx of BPH. Hospitalized for depression. While hospitalized, prescribed duloxetine 60 mg QD for depression and anxiety. 35 days later hospitalized for suicidal ideation. C/O urinary retention while hospitalized. Cathed. TUR performed approximately 6 weeks after discharge. Duloxetine dc 2.5 weeks after the TUR.	Hx of BPH; required surgical intervention to resolve symptoms. TUR while on duloxetine. Reason for DC not reported. Fluoxetine, sertraline hydrochloride and olanzapine labeled for urinary retention.
5007901 FOR	DC Hospitalization "serotonergic delirium/ serotonine syndrome" Cathed	Medical confirmation of retention. Symptoms resolving after dc. Positive dechallenge with treatment.	79 yo female prescribed duloxetine 30 mg QD for depression. Day 3, hospitalized. Cathed for urinary retention. – 800cc residual. Dx with "serotonergic delirium/serotonine syndrome." Prolonged hospitalization. Duloxetine dc. Mirtazapine held for 1 week. Recovering.	Reboxetine labeled for urinary retention; concurrent dx of serotonergic delirium/serotonine syndrome.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
5152361 FOR	Continued Hospitalized for exacerbation of depressive symptoms Cathed	After dose increase.	44 yo female prescribed duloxetine 60 mg QD for bipolar affective disorder with severe depressive episodes. Hospitalized for exacerbation of depressive symptoms. Olanzapine prescribed. While hospitalized, duloxetine increased to 120 mg QD. Day 3 after dose increase, c/o urinary retention. I&O Cath. Continued to c/o urinary retention intermittently.	olanzapine, gabapentin and aripiprazole labeled for retention. Temporal relationship to olanzapine. Symptoms did not result in dc of duloxetine.
4687690 US	DC Hospitalized for major depressive disorder Cathed	Hx of incontinence; medical confirmation of retention. Duloxetine dc.	53 yo female with hx of urinary incontinence. Prescribed duloxetine 30 mg QD for major depressive disorder. Day 6, UA pos for klebsiella and proteus mirabilis. Day 7, c/o urinary retention. Foley inserted. 1200cc residual. Duloxetine increased to 60 mg QD. Day 8, renal US – R pelvis caliectasis. Duloxetine decreased to 30 mg QD. Day 9, foley dc. Abx prescribed. Day 11, cathed with 1975cc residual. Day 12, phenoxybenzamine prescribed. Day 14 phenoxybenzamine decreased due to incontinence. Day 17, cathed. Day 18, duloxetine dc. Day 21, phenoxybenzamine increased. Bethanechol prescribed. Day 27, UA 3+ bacteria. Abx prescribed. Urology consult.	Underlying UTI; ultram labeled for retention. Insufficient information: symptom resolution not reported.
4999908 FOR	DC Hospitalized for acute abdomen life threatening	Hx of incontinence. Medical confirmation of retention. Resolved after dc Positive dechallenge with treatment.	STUDY: 81 yo female with hx of UTI. Prescribed duloxetine 20 mg QD for stress incontinence. Day 13, increased to 40 mg QD. Day 15, hospitalized with dx of acute abdomen with subfebrile temperature. US of abdomen – urinary retention and "subileus of small intestine," liver cyst and inconspicuous abdominal findings. Duloxetine dc. Treated with laxative, food abstention, and abx. After treatment, dysuria resolved. US – no urinary retention, UA – nml. Recovered. Note: symptoms occurred after dose increase.	UTI 2 weeks PTA. Concurrent dx of sub-ileus/acute abdomen. Insufficient information: Concomitant meds not reported.
4607585 FOR	DC Hospitalized for depressed level of consciousness	Hx of stress urinary incontinence Medical confirmation of retention. Resolved after dc Positive dechallenge with treatment.	64 yo female prescribed duloxetine 40 mg QD for stress urinary incontinence. On the 5th day, c/o depressed LOC, unable to eat and drink. Duloxetine dc. Hospitalized with hyponatremia, hypokalemia, and dehydration. Diagnosed with urinary retention while hospitalized. Recovered.	Urinary retention reported while hospitalized for treatment of electrolyte imbalance. Insufficient information of treatment provided during hospitalization.
4539855 US	DC Hospitalized for suicidal ideation	Resolved within 24 hours after dc. Positive dechallenge	35 yo male prescribed duloxetine 60 mg QD for bipolar depression. C/O urinary retention "almost requiring urinary catheterization." Duloxetine dc. Resolved within 24 hours. Hospitalized for suicidal ideation – unknown time. Note: unclear if urinary retention occurred during hospitalization.	Insufficient information: Concomitant meds and medical hx not reported.
4546436 FOR	DC Hospitalized for increased Parkinson 's symptoms	Hx of incontinence. Duloxetine dc.	85 yo female with hx of Parkinson's prescribed duloxetine for urinary incontinence. Day 6 admitted for increased Parkinson's symptoms. Treated for pneumonia. C/O urinary retention. E. coli in urine. Treated with abx. CLL suspected.	Hx of Parkinson's. Underlying UTI. Levodopa labeled for urinary retention; Tilidin - Opiate agonists may cause urinary retention. Insufficient information: symptom resolution not reported.
5036025 US	DC Hospitalized with SJS	Duloxetine dc.	42 yo female prescribed duloxetine 60 mg QD. Topiramate increased – time frame unknown. Approximately 4 weeks after first dose of duloxetine, hospitalized with SJS. Also c/o of urinary hesitation with additional GI symptoms, restless leg syndrome and restlessness. Duloxetine dc.	Topiramate and buproprion labeled for urinary retention. hydrocodone/acetaminophen - Opiate agonists may cause urinary retention. Insufficient information: symptom resolution not reported. Concurrent dx: SJS.
4877214 US	DC ER Cathed	Duloxetine dc. Positive Dechallenge with treatment.	45 yo female prescribed duloxetine 30 mg QD for DPNP. C/O urinary retention 2 days later. Went to ER. Cathed for urinary retention. Retention resolved. Note: duloxetine dc for increased HR. Date of DC not reported. Unclear if duloxetine dc prior to resolution of urinary retention.	Hx of diabetes. Risperidone labeled for urinary retention. Unclear information regarding dc and resolution of urinary retention.
4531324 US	DC Cathed	Medical confirmation of retention. Duloxetine dc.	Male of unknown age prescribed duloxetine. C/O urinary retention. Cathed – "2300 cc" residual. Duloxetine dc.	Insufficient information. Concomitant meds, med hx, and symptom resolution not reported.
5007826 FOR	NR ER Cathed	No previous dx of BPH	72 yo male prescribed olanzapine and duloxetine for depression and bipolar disorder. Day 7, c/o urinary retention. ER. Cathed. Referred to urologist. Possible BPH - still evaluating.	New dx: BPH; olanzapine labeled for urinary retention. Insufficient information: duloxetine status and symptom resolution not reported.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4533068 US	DC Cathed	Hx negative for urinary retention. Medical confirmation of retention. Duloxetine dc. Positive dechallenge with treatment.	65 yo male with hx of BPH, prostatitis and "urinary problems at night." Prescribed duloxetine 60 mg QD for depression. On the 3rd day, c/o urinary retention. Duloxetine dc on the 3rd day. Day 11, cath with 800cc of residual per urologist. Day 11, prescribed ciprofloxacin and tamsulosin. Recovering.	Hx of BPH and LUTS. Propoxyphene/acetaminophen - opiate agonists may cause urinary retention. Retention continued and worsened. Cathed 8 days after duloxetine dc. Required abx and medication to treat ongoing symptoms after dc of duloxetine. Duloxetine half-life 12 hours.
4683967 US	DC Cathed	Medical confirmation of retention. Duloxetine dc. Positive dechallenge with treatment.	35 yo female with hx of UTI and shy bladder. Meds: phenazopyridine hydrochloride, trimethoprim/sulfamtehoxazole. Prescribed duloxetine 30 mg QD for depression. DC duloxetine on day 2. On day 4, cathed with 1000cc residual. Cathed on day 5 with over 1000cc residual. C/O paresthesia and numbness of perineum and perirectum. On day 10, Bethanechol chloride prescribed. Self-cath initiated. On day 13, Foley inserted. Urine C&S neg. Day 16, Foley removed. Unable to void. Day 18, prescribed tamsulosin. Day 20, numbness resolved. Voiding. Self-cath dc.	Hx of UTI and shy bladder. Underlying UTI; required significant medical intervention after dc of duloxetine to treat ongoing retention. Symptoms continued for 16 days after dc. Duloxetine half-life 12 hours.
5049084 US	DC Cathed	Duloxetine dc.	78 yo female with hx of pelvic radiation. Prescribed duloxetine 30 mg QD for DPNP. Approximately 4 months later, c/o urinary retention. Cathed. No flank or suprapubic discomfort/mass. Referred to urologist. Duloxetine dc. Symptoms continued.	Hx of pelvic radiation. Symptoms continued after dc. Negative dechallenge. Insufficient information. Concomitant meds not reported.
4682705 US	NR ER Cathed		38 yo female prescribed duloxetine 60 mg QD. C/O urinary retention. Sent to ER from PCP's office. "Through surgical procedure, the patient had a tube implanted in her bladder."	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
5011384 US	DC ER Cathed	No previous dx of BPH. Results of cath - nml. Symptoms completely resolved after dc. Positive Dechallenge.	33 yo male with hx or UTI and family hx of prostate problems. Prescribed duloxetine 60 mg QD. 3 months later, c/o urinary retention. Seen in ER. Cathed. Results of the catheterization were normal. Dx with "prostate enlarged." Duloxetine DC. Symptoms completely resolved. Note: conflicting information – one report – no meds	New dx: enlarged prostate; Hydrocodone/acetaminophen - opiate agonists may cause urinary retention.
4876289 US	Continued Cathed	Reported neg hx for UTIs.	38 yo female prescribed duloxetine 60 mg for MDD. 6 months later, c/o urinary retention. PE – discomfort in pelvis. Cath – 450ml. Duloxetine continued. Retention not resolved. Unwilling to dc duloxetine because it had been so helpful.	6 month onset Concomitant – methadone – opiate agonists may cause retention
4683086 US	DC/Restarted	Temporal relationship to duloxetine. Positive dechallenge/rechallenge Dose response – increased symptoms with increased dose.	46 yo female prescribed duloxetine 30 mg QOD for PTSD. C/O urinary frequency and bladder not emptying. Duloxetine DC. Resolved. Duloxetine 30 mg QOD restarted. Urinary symptoms recurred. Dose increased to 30 mg QD. C/O increased urinary retention/frequency with onset of burning with urination. Also c/o GI, CNS and ocular symptoms after dose increase. Continued duloxetine with continued c/o urinary symptoms.	Concomitant – diphenhydramine -anticholinergic effect may include urinary retention
4530908 US	DC	No prior hx of any urinary problems. No concomitant meds. Resolved within 48 hours of dc. Positive dechallenge.	50 yo male prescribed duloxetine 30 mg QD for mild depression with anxiety. No prior hx of any urinary problems. No concomitant meds. On the 3rd day, c/o "a little urinary hesitancy." On the 6th day, experienced increased hesitancy and nocturia. Duloxetine dc by MD. Symptoms resolved after 2 days.	
5011375 US	DC	No hx of urinary problems or BPH. No concomitant meds. Resolved after dc and did not reoccur. Positive dechallenge.	28 yo male prescribed 30 mg QD for major depressive disorder and anxiety. No hx of urinary problems or BPH. No concomitant meds. Increased to 60 mg QD. C/O urinary retention and hesitation. Duloxetine dc after 7 days. Symptoms resolved and did not reoccur.	
4532754 US	DC	Temporal relationship to duloxetine. Symptoms resolved by next day. Positive dechallenge.	46 yo female prescribed duloxetine 60 mg QD for depression. Long term use of lasix. C/O urinary retention within 1-2 days. Duloxetine dc within first week. Symptoms resolved by next day.	zolpidem labeled for urinary retention
4533031 US	DC	Temporal relationship to duloxetine. Resolved after dc. Positive Dechallenge	84 yo male with hx of TURP X 2. Prescribed duloxetine 60 mg QD for diabetic peripheral neuropathy. Day 3, c/o urinary hesitation. Day 4, Duloxetine dc. Symptoms resolved.	Hx of TURP X 2. Insufficient information: Concomitant meds not reported.

ISR LOC	Medication Status/Medical intervention	Factors which increase strength of signal	Case Summary/Notes	Factors which decrease strength of signal
4938502 FOR	DC	No previous hx. Resolved after dc Positive dechallenge	43 yo male prescribed duloxetine 30 mg QD for depression, increased to 60 mg QD after 1 week. Per MD, no previous micturition problems. After increase, c/o "partial urinary retention" and pain over scrotum. Duloxetine dc. Symptoms resolved after 11 days. Note: Symptoms occurred after dose increase.	Resolution of symptoms took 11 days. Half-life 12 hours.
4653817 US	DC	Unclear information: no hx of BPH. C&S neg. Improved after dc. Positive dechallenge.	75 yo male with hx of BPH, prescribed duloxetine 30 mg QD for depression and anxiety. Also received influenza vaccine. 5 hours after the initial dose of duloxetine, c/o urinary hesitancy and fever, extreme fatigue, sweating and multiple CNS and GI symptoms. Day 2, duloxetine increased to 60 mg QD. Urine C&S neg – date unknown. Day 4, duloxetine dc. Symptoms improved. Note: conflicting information –no hx of BPH vs. hx/concurrent BPH. Constellation of symptoms reported in conjunction with urinary hesitancy.	Unclear information :Hx of BPH Constellation of symptoms including fever
5010058 US	DC	Resolved after dc Positive dechallenge	62 yo male prescribed duloxetine 30 mg QD for depression. C/O urinary retention. Duloxetine dc. Symptoms resolved.	Insufficient information: Concomitant meds not reported.
4771494 US	DC	Resolved after dc Positive dechallenge	78 yo male prescribed duloxetine 60 mg QD. C/O urinary retention. Duloxetine dc. Symptoms abated.	Insufficient information: Concomitant meds not reported.
4533564 US	DC	? No relevant hx. Symptoms resolved after dc Positive dechallenge	Male of unknown age prescribed duloxetine 30 mg QD for major depressive disorder. Increased to 60 mg QD after unknown time frame. After increase, c/o urinary hesitation. Duloxetine dc "during the second week." Symptoms resolved. Note: conflicting information – no relevant hx vs. did not ask. symptoms after dose increase	Insufficient information: Concomitant meds not reported.
4532267	DC	No relevant hx. Symptoms resolved after dc Positive dechallenge	Male of unknown age prescribed duloxetine 30 mg QD for major depressive disorder. No relevant hx. Increased to 60 mg QD after unknown time frame. After increase, c/o urinary hesitation. Duloxetine dc "during the second week." Symptoms resolved. Note: symptoms occurred after dose increase.	Insufficient information. Concomitant meds not reported.
5092345 US	DC	Duloxetine dc. Positive dechallenge.	39 yo female prescribed duloxetine 30 mg QD for depression. Day 8, c/o urinary retention and extreme somnolence. PE neg for flank or suprapubic discomfort/fullness. Duloxetine dc. Day 16, UA WNL. Day 18, abdominal CT neg. Dx with elevated ALT/AST. Hx of ITP, liver failure, right heart failure. Events resolved.	Topiramate, buproprion, oxycodone – Topiramate and buproprion labeled for urinary retention; opiate agonists may cause urinary retention
4683134 US	DC	Symptoms resolving after dc Positive dechallenge	48 yo female with hx of urinary retention. Prescribed duloxetine 60 mg QD. After unknown time frame, c/o increased urinary retention and UTI. Also c/o musculoskeletal symptoms. Duloxetine dc. Symptoms resolving.	Hx of urinary retention, underlying UTI.
4599915 FOR	DC	Hx of incontinence Symptoms resolving after dc Positive dechallenge	43 yo female with hx of voiding difficulties, frequent UTIs and prior instrumentation of GU tract. Prescribed duloxetine 40 mg BID for stress incontinence. Within 1st week, c/o urinary retention. Duloxetine dc. Recovering. Also c/o severe nausea, vomiting, fainting. Hx of MS.	Hx of voiding difficulties, frequent UTIs, prior instrumentation Insufficient information. Concomitant meds not reported.
4683065 US	DC	Symptoms resolved after dc Positive dechallenge	58 yo female prescribed duloxetine 30 QD for neuropathic pain after neck surgery. After unknown time frame, c/o "delay in urination." Duloxetine dc. GU symptoms resolved. Also c/o GI, cardiac, CNS and ocular symptoms. GI, cardiac, and ocular symptoms resolved. CNS symptoms continued.	Morphine - opiate agonists may cause urinary retention; c/o concurrent CNS symptoms which continued after dc. No dx provided.
4877189 US	DC	Duloxetine dc. Positive dechallenge.	53 yo male with hx of urinary hesitation. Prescribed duloxetine 60 mg QD for OCD and depression. After 6-8 weeks, c/o increasing urinary hesitation. Also c/o musculoskeletal and lip pain. Duloxetine dc. Symptoms resolving.	Hx of urinary hesitation
4683130 US	DC	Duloxetine dc.	33 yo female prescribed duloxetine 60 mg. C/o hesitation, dysuria and UTI with E. coli, treated with cipro. UTI resolved with clear culture. Dysuria and hesitation continued. Duloxetine dc. Symptoms continued.	UTI; Symptoms continued after dc. Negative dechallenge. Insufficient information. Concomitant meds not reported.

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5049634 US	DC	Duloxetine dc.	53 yo female prescribed duloxetine 30 mg QD for depression. Increased to 60 mg QD after 1 week. After dose increase, c/o urinary retention. Duloxetine dc. Symptoms continued. Note: date of duloxetine conflict – 2005 vs. 2006. Dose and duration information also conflicting in narrative vs. Section C.	Atomoxetine labeled for urinary hesitation and retention. Negative dechallenge. Unclear information regarding concomitant.
5044251 US	? DC – see note	Duloxetine dc.	Female of unknown age prescribed duloxetine 120 mg QD. C/O urinary retention. Duloxetine dc at unknown time. Symptoms resolved. Note: reporter unaware if duloxetine continued at time of retention.	Insufficient information. Concomitant meds not reported. Unclear information status of duloxetine at onset of retention.
4876839 US	DC	Duloxetine dc.	Male of unknown age with hx of urinary retention. Prescribed duloxetine 60 mg QD. C/O worsening of urinary retention and elevated PSA. Duloxetine dc.	Hx of urinary retention; Insufficient information. Concomitant meds and symptom resolution not reported.
4533504 US	DC	Duloxetine dc.	Female of unknown age prescribed duloxetine 30 mg QD. Within first week, c/o urinary hesitation. Duloxetine dc.	Insufficient information. Concomitant meds and symptom resolution not reported
4876467 US	DC	Duloxetine dc.	Male of unknown age prescribed duloxetine. C/O urinary hesitancy and STD. Treated with abx for STD. Duloxetine dc.	Underlying STD; Insufficient information. Concomitant meds and symptom resolution not reported.
4533185 US	DC	Duloxetine dc.	Male of unknown age prescribed duloxetine. C/O urinary hesitation. Duloxetine dc.	Insufficient information. Concomitant meds and symptom resolution not reported.
4533782 US	DC	Duloxetine dc.	Male in 50s prescribed duloxetine 60 mg QD for depression. On same day, c/o urinary retention. Duloxetine dc.	Buproprion labeled for urinary retention. Insufficient information: symptom resolution not reported.
4651623 US	DC ER for ruptured ovarian cyst	Duloxetine dc.	18 yo female with hx of kidney stones. Prescribed duloxetine 30 mg QD for depression. Approximately 10 days later, c/o urinary retention. A few days after onset of urinary retention, seen in ER and dx with ruptured ovarian cyst. Duloxetine dc the same day.	Concurrent dx of ruptured ovarian cyst. Buproprion labeled for urinary retention. Anticholinergic effect of hyoscyamine sulfate may include urinary retention. Insufficient information: symptom resolution not reported.
4654426 US	DC	Duloxetine dc.	55 yo male prescribed duloxetine 30 mg QD for major depressive disorder. Increased to 30 mg BID after 10-14 days. During the second week, experienced multiple symptoms (GI, CNS, respiratory, musculoskeletal, neurologic, ocular, dermatologic) including urinary hesitation and retention. Duloxetine dc.	Topiramate labeled for urinary retention. Insufficient information: symptom resolution not reported.
4876603 US	DC	No concomitant meds. Duloxetine dc.	28 yo female prescribed duloxetine 30 mg QD for depression. No concomitant meds. 6.5 hours after first dose, c/o urinary retention. Multiple unrelated symptoms reported. Day 3, DC.	Insufficient information: symptom resolution not reported.
4531331 US	DC	Duloxetine dc.	Female of unknown age prescribed duloxetine 30 mg QD. C/O urinary hesitation within the first week. Duloxetine dc.	Insufficient information. Concomitant meds and symptom resolution not reported.
5050004 US	Continued	No concomitant meds. Symptoms continued.	46 yo female prescribed duloxetine 20 mg BID for depression. No concomitant meds. C/O hesitation.	Symptoms did not result in dc of duloxetine.
4531179 US	Continued	No concomitant meds. Symptoms continued.	45 yo female prescribed duloxetine 60 mg QD for major depressive disorder. No concomitant meds. C/O mild urinary hesitancy.	Symptoms did not result in dc of duloxetine.
4531344 US	continued		55 yo female prescribed duloxetine 60 mg QD for depression. DC caffeine from diet. C/O urinary retention. Restarted caffeine in diet. Symptoms resolved.	Symptoms resolved while on duloxetine. Symptoms did not result in dc of duloxetine.
4531777 US	continued		36 yo female prescribed duloxetine 20 mg BID for depression. Same night, c/o urinary hesitation. Also c/o CNS and GI symptoms. Urinary hesitation resolved on Day 2.	Dicyclomine - antimuscarinic /antispasmodics may cause urinary hesitancy. Symptoms resolved while on duloxetine. Symptoms did not result in dc of duloxetine.
4683645 US	continued		58 yo female prescribed 60 mg QD for depression. C/O urinary hesitation with multiple bouts of being unable to void. Also nocturia. PE neg for distension. Hesitation gradually resolved over 3 weeks. UA neg.	Symptoms resolved while on duloxetine. Insufficient information. Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
5044934 US	DC/Continued		27 yo female prescribed duloxetine 60 mg QD for major depression. C/O “difficulty urinating”. Also c/o multiple GI and CNS symptoms.	Symptoms did not result in dc of duloxetine.
4533771 US	Continued		Male of unknown age prescribed duloxetine 30 mg QD for depression. Increased to 60 mg QD after 1 week. C/O urinary retention.	Buproprion labeled for urinary retention. Symptoms did not result in dc of duloxetine.

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4877968 US	Continued		75 yo male prescribed duloxetine 20 mg QD for myoclonus. C/O urinary hesitancy.	Insufficient information: Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4682962 US	Continued		50 yo female prescribed duloxetine 60 mg QD. C/O urinary retention.	Insufficient information: Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4531366 US	Continued	no hx of prostate or urinary problems	68 yo male prescribed duloxetine 30 mg QD for peripheral neuropathy. Two days after first dose, c/o urinary hesitancy. Dose increased to 60 mg QD. Urinary hesitancy "improved slightly." Note: no hx of prostate or urinary problems	Insufficient information: Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4877974 US	Continued		77 yo male prescribed duloxetine 30 mg QD. After one week, increased to 60 mg QD. Prior to the dose increase, c/o urinary retention.	Insufficient information. Concomitant meds not reported. Symptoms did not result in dc of duloxetine.
4683635 US	Continued		57 yo female prescribed duloxetine 120 mg QD. C/O urinary retention. Chose to remain on duloxetine.	Fluphenazine labeled for urinary retention. Insufficient information: symptom resolution not reported. Symptoms did not result in dc of duloxetine.
4878063 4878055 US	Continued		45 yo male prescribed duloxetine 30 mg QD. Increased to 60 mg QD. After dose increase, co of urinary hesitancy. Decreased to 30 mg QD.	Insufficient information. Concomitant meds and symptom resolution not reported. Symptoms did not result in dc of duloxetine.
4531719 US	Continued		Female of unknown age prescribed duloxetine 30 mg QD. C/O urinary hesitation.	Insufficient information. Concomitant meds and symptom resolution not reported. Symptoms did not result in dc of duloxetine.
4613323 FOR	NR		31 yo female prescribed duloxetine 40 mg QD for urinary incontinence. Day 3, unable to void. Hx of spasticity by birth. Spasticity also increased in upper body to degree unable to care for self. Symptoms resolved.	Insufficient information: duloxetine status not reported.
4876395 US	NR		64 yo female with hx of not being able to urinate with other antidepressants. Prescribed duloxetine 20 mg QD for depression. Within first few days, c/o trouble urinating with additional CNS, GI and ocular symptoms. Duloxetine continued for 11 days. Trouble urinating increased to not being able to urinate.	Hx of not being able to urinate with other antidepressants. Unclear information re: duloxetine status.
4929414 US	NR		Male of unknown age prescribed duloxetine and pregabalin. C/O urinary retention.	Insufficient information: duloxetine status and symptom resolution not reported.
4877183 US	NR		80 yo male with hx of frequent urination. Prescribed duloxetine "30-60 mg" QD for Parkinson's disease. After 2 weeks, c/o difficulty urinating, increased nocturia. Duloxetine decreased to 30 mg QD.	trospium labeled for urinary retention. Insufficient information: duloxetine status and symptom resolution not reported.
4532937 US	NR		Female of unknown age prescribed duloxetine 30 mg QD. C/O urinary retention. Note: indicates no concomitant meds provided. Conflicts with statement "atomoxetine continued".	atomoxetine labeled for urinary hesitation and retention. Insufficient information: duloxetine status and symptom resolution not reported.
4682991 US	NR		53 yo female prescribed duloxetine 30 mg QD for major depressive disorder. C/O urinary retention, blood in urine and "slight discomfort" during urination.	Fluoxetine and tiagabine labeled for urinary retention. Insufficient information: duloxetine status and symptom resolution not reported.
4531304 US	NR		80 yo male prescribed duloxetine 30 mg QD for depression. C/O urinary hesitation.	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
4533132 US	NR		Male of unknown age prescribed duloxetine. C/O urinary retention.	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
4531218 US	NR		Male of unknown age prescribed duloxetine. C/O "severe urinary hesitation."	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.
4531216 US	NR		Male of unknown age prescribed duloxetine. C/O "severe urinary hesitation."	Insufficient information. Concomitant meds, duloxetine status and symptom resolution not reported.

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/s/

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