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Duloxetine Use in the Management of Stress Urinary Incontinence & Students' Survey

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Abstract

The goal of this study is to assess the knowledge and opinion of students regarding the off-label use of duloxetine in the treatment of stress urinary incontinence (SUI). The Survey questions were provided during the Drug Information Course at Howard University (HU) College of Pharmacy in a class where first-year pharmacy students learn how to conduct a literature search and a survey. A total of 39 students responded to the survey. There were more females (n=23; 56.1%) with an age range between 18 – 24 years. About two-thirds (n=29; 70.7%) had a four-year degree before starting the pharmacy program. Overall, participants scored less than the passing 70% mark on the knowledge questions, which may call for educators to make a special effort to incorporate off-label and approved indications of medication teaching therapeutic-related courses. For example, more than sixty percent of respondents (n=25; 61%) incorrectly stated that duloxetine is a narrow therapeutic drug. The majority (n=; 34; 82.9%) of the participants responded wrongly that urinary incontinence is more common in women during their childbearing age. The opinion survey showed that most participants (n=25; 61%) did not believe there were many FDA-approved effective drugs for treating SUI. Over sixty percent of participants (n=25; 61%) considered SUI a severe illness and did not agree to use a non-approved drug such as duloxetine, although several published clinical studies support its effective use. Participants were split in their opinion regarding the non-approved use of medications. Study results suggest that students may need encouragement to explore medications with non-FDA approvals.

Keywords: Duloxetine; FDA; Survey; Non-approved; Urinary incontinence; Pharmacy; Survey

1. Introduction

Approximately 15 million adult women in the United States suffer from stress urinary incontinence (SUI), the most common form of incontinence among women [1]. SUI is an involuntary leakage of urine resulting from urethral sphincter dysfunction and pelvic floor weakness, which occurs in response to increasing intraabdominal pressure when exerting effort, sneezing, or coughing, significantly impacting the patient's quality of life. Individuals can develop pelvic floor muscle loss due to chronic cough, rigorous exercise, pelvic floor trauma after vagina delivery, smoking, obesity, menopause, and constipation [2]. Behavioral, pharmacological, and surgical approaches are available to manage stress urinary incontinence. However, conservative treatment often fails to meet the needs of patients with severe SUI, and surgery is rarely an option for an elderly population with a high level of morbidity [3]. Duloxetine is effective in treating stress urinary incontinence in several studies.

Duloxetine is used off-label to treat stress urinary incontinence in both men and women. It is a serotonin and norepinephrine (5-HT and NE) reuptake inhibitor (SNRI). Duloxetine is generally approved for treating depression, generalized anxiety disorder, fibromyalgia, chronic musculoskeletal pain, and diabetic peripheral neuropathy. It has a common side effect of nausea, headache, dry mouth, drowsiness, or insomnia. Duloxetine has a possible risk of suicidal ideation in children, adolescents, and adults. The efficacy of Duloxetine for SUI is attributed to its ability to block presynaptic reuptake of 5-HT and NE in Onuf's nucleus, elevating the concentration of these neurotransmitters in the synaptic clefts [4]. The bladder sphincter is controlled by serotonergic and norepinephrine terminals in Onuf's nucleus.

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Stimulating these receptors increases guarding reflex tone, suppressing voiding when abdominal pressure increases or is triggered by coughing or sneezing.

A double-blind, randomized, placebo-controlled trial was conducted to evaluate the efficacy and safety of Duloxetine in the treatment of stress urinary incontinence. The study was done on 553 women (18 to 65 years) with SUI. Patients were administered duloxetine 20 mg/day (138), 40 mg/day (137), and 80 mg/day (140) for 12 weeks. The results showed a significant and dose-dependent reduction in incontinence episode frequency (IEF), and improvements were reported in the Patient Global Impression of Improvement scale (PGI-I) and the Incontinence Quality of Life questionnaire (I-QOL). The highest dose, 80 mg daily, was statistically significant (P <.001). Most of the discontinuations were caused by nausea [5].

A phase 3 randomized controlled study was conducted on 683 North American women (22 to 84 years) to assess the efficacy and safety of Duloxetine in women with SUI. Participants included in this trial must show symptoms of SUI with a weekly IEF of ≥7, the absence of urge incontinence (UI), regular diurnal and nocturnal frequency, a bladder capacity of ≥400 ml, and a positive cough stress test. The subjects were randomly allocated to receive Duloxetine 40mg BID or 80mg/day (344) vs. placebo (339) for 12 weeks. Compared with the placebo, there was a significant reduction in IEF with Duloxetine (50% vs. 27%, p 0.001) and a similar improvement in QOL (11.0 vs. 6.8, p 0.001). There was a significant increase in the voiding interval with Duloxetine compared to the placebo (20 vs. 2 minutes, p <0.001). Nausea was the most common side effect [6].

Another study compared Duloxetine alone, pelvic floor muscle training (PFMT) alone, combined therapy, and placebo in women with stress urinary incontinence. This randomized controlled trial enrolled 201 women (18–75 years) with predominant symptoms of SUI. Based on the analysis, the efficacy of Duloxetine was indicated, and it was more effective when used with PFMT than when used independently. Duloxetine alone and Duloxetine in combination with PFMT significantly ($p < 0.05$) reduced the median IEF by 57% vs. 35% PFMT alone vs. 29% placebo. The mean total I-QOL score also improved. The median declines in pad usage; were 46% for the combination, 35% for Duloxetine alone, 25% for PFMT alone, and 10% for placebo [7].

A meta-analysis of 4 randomized placebo-controlled trials of Duloxetine was performed on 1913 patients. A proposal for approval was submitted to the European Medicines Agency to treat women with stress urinary incontinence. Multiple clinical study reports were used to assess the benefits and adverse effects. Duloxetine significantly reduced weekly incontinence episodes compared to placebo (mean difference of 13.56%, 95% [CI] −21.59% to −5.53%). The NNT for a PGI-I of "much better or very much better" was 8 (95% CI 6 to 13). The NNH was 7 (95% CI 6 to 8) for discontinuing due to an adverse event. The was no report of suicidal events, violence, or akathisia [8].

Off-label drug use (OLDU) involves prescribing medications currently on the market but for an indication that has not yet been approved by the Food and Drug Administration (FDA). Several factors may also contribute to the use of off-label drugs. For instance, if a specific patient population such as pediatric, geriatric, pregnant patients or dosages are not analyzed in clinical studies. In a patient suffering from a life-threatening disease, a healthcare professional may administer any appropriate treatment, irrespective of FDA approval [9]. Therefore, it is crucial that healthcare providers educate themselves about off-label drug use to prevent medication errors. A study showed the frequency of off-label use among office-based physicians; approximately 21% of OLDU was reported in the trial [10]. In general, antidepressants, anticonvulsant medications, and antipsychotic medications are commonly used off-label, as observed in a retrospective analysis of Georgia Medicaid recipients [11].

A study was conducted to assess prescribing physicians' knowledge and perception of off-label drug use in a tertiary care hospital. A validated questionnaire was given to interns, junior residents, and faculty members. About 69% of the participants indicated that they had used a drug in an off-label manner primarily (36.5%) related to therapeutic purposes. Almost half of the study participants (48.2%) considered prescribing an off-label drug illegally, and only 29.3% of respondents believed that they had adequate Knowledge regarding off-label drug use [12].

Another study reported the perceptions and attitudes of hospital-based pharmacists in Jordan towards off-label dispensing for pediatric patients. Pharmacy staff at 250 hospitals were randomly selected to complete a validated questionnaire regarding off-label dispensing to pediatric patients. The questionnaires were returned with 150 completed responses. Only 44% of respondents (n = 66) said they were familiar with off-label dispensing, stating their expertise mainly came from their dispensing experience. The survey found that 36% of respondents dispensed off-label drugs knowingly within their practices. There were concerns over the efficacy (82%, n = 123) and safety (98%, n = 147) of off-label medicines among respondents [13].

Several studies show that most healthcare providers need to be more knowledgeable about off-label medicines before acquiring knowledge from their professional experiences. Off-label medicines are also subject to concerns regarding their efficacy and safety, especially in pediatric patients, due to the increase in adverse drug reactions (ADRs). We could not find research regarding the knowledge and opinions of OLDU pharmacy students. Pharmacists play a vital role in drug dispensing and patient outcomes. Thus, off-label use of medication should be integrated into the pharmacy curriculum. This study aims to assess the Knowledge and Opinions of Pharmacy Students regarding the off-label use of Duloxetine in managing Stress Urinary Incontinence.

2. Materials and methods

This study enrolled 39 incoming first-year students from Howard University College of Pharmacy with a 100% response rate. The survey was optional and provided to students during the Drug Information course. All questions, demographics, and responses were analyzed using Qualtrics. The survey consisted of 8 demographic questions and ten opinion and knowledge questions and was administered using the Likert scale (Strongly agree to strongly disagree). Demographic data, including age, gender, residence state before the pharmacy program, prior work experience, annual income, and level of education, was collected through the survey. All results were analyzed using IBM SPSS, and statistical analysis was completed using crosstab and chi-square Pearson analysis, with a p-value of less than 0.05 considered significant.

3. Results and discussion

A total of 39 students participated in this study. Most of the survey respondents (n=32; 78%) were 18 to 34 years (Table 1). There were more female respondents (n=23; 56.1%) than males (n=16; 39.0%). Twenty-nine (n=29; 70.7%) had a four-year degree before starting the pharmacy program. About (n=19; 46.6%) reported living in the Maryland/Virginia/Washington D.C. metropolitan area. Other demographic data are also summarized (Tables 1 and 2).

Table 1 Demographic characteristics of respondents

Characteristics	**Respondents (n, %)**
Age (years)	
18 – 24	18 (43.9)
25 – 34	14 (34.1)
≥35	7 (17.1)
Gender	
Male	16 (39.0)
Female	23 (56.1)
Education	
Some College	4 (9.8)
2 Year Degree	3 (7.3)
4 Year Degree	29 (70.7)
Professional Degree	3 (7.3)
Resident	
Washington DC	2 (4.9)
Maryland	10 (24.40
Virginia	7 (17.1)
Other States	20 (48.8)

Table 2 Work-Related Characteristics of the respondents

Worked	
Yes	34 (82.9)
No	5 (12.2)
Type of Job	
Non-Pharmacy or Non-Healthcare Related	8 (19.5)
Pharmacy Related	13 (31.7)
Non-Pharmacy but Healthcare Related	12 (29.3)
Years Worked	
< 1 Year	3 (7.3)
1-3 Years	19 (46.3)
4-5 Years	2 (4.9)
>5 Years	11 (26.8)
Annual Income	
<$10,000	12 (29.3)
$10,000 - $19,000	2 (4.9)
$20,000 - $29,000	5 (12.2)
$30,000 - $39,000	7 (17.1)
$40,000 - $49,000	4 (9.8)
>$49,000	6 (14.6)

Students were asked 5 knowledge and 5 opinion questions. The knowledge questions then were graded against the correct answers. According to the overall scoring of the knowledge section, sixty-five percent (n=23; 65%) of the respondents correctly answered the questions regarding duloxetine. The score is much lower than the passing scale, which is 70 percent or higher. The highest number of correct responses (n=34; 82.9%) was reported in the following knowledge question: Duloxetine has been shown to cause adverse side effects such as nausea, constipation, and dry mouth. The statement is true. The question with the least (n=4; 9.8%) correct answers was: Urinary incontinence is prevalent among women of childbearing age. The statement is incorrect (Table 3).

Duloxetine is a medication used to manage major depressive disorder (MDD), generalized anxiety disorder (GAD), fibromyalgia, diabetic peripheral neuropathy, and chronic musculoskeletal pain. Over three-fourths (n=31; 75%) of participants answered this question correctly. On the other hand, over sixty percent of participants (n=25; 61%) believed that the drug is considered a narrow therapeutic drug. Drugs are considered to have a narrow therapeutic index when there is only a small difference between the minimum effective concentrations and the minimum toxic concentrations in the blood. However, duloxetine is not considered one of them.

Over 25 million adult Americans experience temporary or chronic UI. This condition although can occur at any age, it is more common in women over the age of 50. However, the participants in our study (n=; 34; 82.9%) believed it is more common in women during their child-bearing age. On the other majority of the participants correctly answer about the black box warning and other adverse effects of the drug.

More than half of the participants (n=19; 51.5%) agreed with the statements regarding duloxetine based on their overall opinions. The survey revealed the highest response rate (n=31; 75.6%) in the group that agreed to the statement: Duloxetine has many adverse effects and thus should be reserved for only those indications approved by the FDA. The first and second statements had the lowest agreement rate (n= 13; 31.7%); the majority (n=25; 61%) of the respondents

disagreed with these statements. Most of the participants do not believe in the off-label use of duloxetine in stress urinary incontinence (Table 4).

Table 3 Responses to Knowledge - Related Survey Questionnaire Statements (n=39)

Survey Statement		**Response [n, (%)]**		**LK (m±SD)**
		T. Correct Responses	**T. Incorrect Responses**	
1.	Duloxetine is approved for the treatment of major depressive disorder	31 (75.6)	7 (17)	3.34±0.85
2.	Duloxetine is considered a narrow therapeutic drug and patients should be told not to exceed the maximum dose	13(31.7)	25 (61)	2.87±1.04
3.	Urinary incontinence is very common among childbearing-age women	4 (9.8)	34 (82.9)	3.29±0.65
4.	Duloxetine has a black box warning that it increases suicidal thoughts and actions in children, adolescents, and young adults	33 (80.5)	5 (12.2)	3.39±0.72
5.	Duloxetine is well known to cause adverse effects that include nausea, dry mouth, and constipation	34 (82.9)	4 (9.8)	3.29±0.65

Abbreviations: T. Correct Responses= Total correct Responses; T. Incorrect Responses: Total incorrect Responses; LK = Likert score; m±SD=mean± standard deviation.

Table 4 Responses to Opinion-Related Questionnaire Statements

Survey Statement	**Response [n, (%)]**		**LK (m±SD)**
	Agreed	**Disagreed**	
I believe in the use of duloxetine outside of FDA-approved indications since there are not many effective drugs	13 (31.7)	25 (61)	2.08±0.78
Urinary incontinence is a major illness that affects the well-being of patients and I do not recommend the use of unapproved drugs	13 (31.7)	25 (61)	2.08±0.91
Duloxetine has many adverse effects and thus should be reserved for only those indications approved by FDA	31 (75.6)	7 (17.1)	3.11±0.83
Non-approved drugs overall should be abounded from being used	18 (43.9)	20 (48.8)	2.61±1.03
I do not believe duloxetine has enough evidence to use in women with stress urinary incontinence	22 (53.6)	16 (39)	2.66±0.85

The majority of the survey participants (n=25; 61%) did not believe that there are many FDA-approved effective drugs for the treatment of UI although we know that there are over 20 drugs currently on the market including but not limited to oxybutynin (Ditropan XL), tolterodine (Detrol), darifenacin (Enablex), fesoterodine (Toviaz), solifenacin (Vesicare) and trospium chloride. Mirabegron (Myrbetriq). However, when it comes to SUI, there are no medications that have been approved in the United States although multiple medications have been evaluated.

Over sixty percent of participants (n=25; 61%) consider UI as a major illness and they did not agree with using a non-approved drug such as duloxetine. However, as stated in the introduction section of this manuscript, there are several excellent studies in support of its use.

Three-quarters of the participants (n=31; 75.6%) believed that duloxetine has many adverse effects. However, compared to currently FDA-approved drugs, this drug is either less than or to the same level of adverse effects.

Participants were split in half in their opinion regarding the non-approved use of medications. Off-label prescribing is when a provider prescribes a drug that the FDA has not approved to treat a condition. This practice is legal and common. One in five prescriptions written today is for off-label use.

Over half of the participants did not believe there are enough supporting documents for the use of duloxetine in UI. That may be true to some extent, but the studies discussed in the introduction section are evident that the drug is very effective in SUI.

We combined the knowledge and opinion questions responses, categorized each demographic into two values, and took the average scores. The only significant and the highest (n= 30; 78.9%; P<0.001) overall knowledge score was reported in participants who had pharmacy or other healthcare-related experience before pharmacy school compared to the respondents (n= 8; 21.1%) with non-pharmacy or non-healthcare-related jobs.

Unfortunately, respondents' opinions and knowledge about the off-label use of Duloxetine in SUI were not significantly affected by the type of demographic factors collected in this study. The only factors that reached statistical significance is the type of work experience as shown in Table 5. The general lack of knowledge about the off-label use of drugs could explain this.

Table 5 Type of Job as one of the Predictive Factors to Determine Response

Demographic	**Overall score**	**P-Value**
Type of Job		
Knowledge Related Questions	Non-Pharmacy or Non-Healthcare Related (n= 8; 21.1%) Pharmacy or Other Healthcare Related (n= 30; 78.9%)	P<0.001

4. Conclusion

A survey of thirty-nine incoming first-year professional students at Howard University College of Pharmacy indicated that the majority had a poor level of knowledge regarding the overall score. However, they have a better handle on two of the five items on the knowledge-based questionnaire. The highest amount (n=34; 82.9%) was obtained for correct responses when asked about Duloxetine's adverse effects, including nausea, dry mouth, and constipation. Most participants (n=33; 80.5%) correctly identified that d has a black box warning related to increased suicidal thoughts and behaviors in children, adolescents, and young adults. However, approximately thirty-four students (n=34; 82.9%) incorrectly answered the question regarding the prevalence of urinary incontinence among childbearing-age women. The overall results of the opinions statements showed that more than half of the participants (n = 19, 51.5%) did not accept the off-label use of Duloxetine in stress urinary incontinence. This study shows that students may need to be encouraged to explore non-FDA-approved indications, particularly in conditions such as UTIs where no effective FDA-approved medications are lacking.

Limitations

This study is limited by a small sample size of 39 participants in the survey. Therefore, a more extensive study that includes students from other schools may be needed to confirm the finding of this study

Compliance with ethical standards

Disclosure of conflict of interest

All the authors have no conflict of interest, and there is nothing to disclose.

Statement of informed consent

The study was approved by the Howard University IRB and done as a part of a course. Therefore, there was no need to obtain informed consent from all individual participants included in the study.

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