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Research Paper

Duloxetine and Pregnancy Outcomes: Safety Surveillance Findings

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Abstract

Background: Duloxetine hydrochloride is approved for the treatment or management of major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, chronic musculoskeletal pain, and fibromyalgia in the United States. These conditions affect millions of women, including those of childbearing potential. In pregnancy, pharmacological treatment is justified only if the potential benefits outweigh potential risks to mother and fetus, neonate or infant. There are no adequate and well-controlled studies in pregnant women treated with duloxetine. Post-marketing surveillance is an important tool for the assessment of drug safety in pregnancy in a naturalistic setting.

Objective: Using safety surveillance and spontaneous adverse events reporting databases, to provide pregnancy outcomes statistics as they relate to duloxetine exposure.

Study design and Setting: This was an analysis of pregnancy outcome data captured in Lilly Safety System (LSS) (a safety database for the collection, storage, and reporting of adverse events involving Lilly Products), through October 31 2011 and the FDA Adverse Events Reporting System (AERS) database through September 30 2011. Both databases provided spontaneous reporting data from the time of first duloxetine marketing authorization in 2004; in addition, the LSS Database includes serious adverse event and pregnancy data from clinical trials since the creation of the database in 1983.

Patients: Patients who had received duloxetine during pregnancy and reported pregnancy outcomes.

Main outcome measures: Normal and abnormal pregnancy outcomes. Abnormal outcomes comprised spontaneous abortion, premature/post-term birth, congenital anomaly, perinatal/post-perinatal complication, still birth, and ectopic pregnancy. Descriptive statistics are provided for LSS data. A disproportionality analysis was performed using the Empirical Bayes Geometric Mean (EBGM) for the AERS data. The lower bound of the 90% confidence interval of EBGM (EB05) ≥1 was used as the threshold to determine disproportionality.

Results: In the LSS analysis, 400 pregnancy cases with a known pregnancy outcome were identified. Of the 233 prospectively reported cases, 170 (73%) were spontaneous reports; the remainder were reported from clinical trials (58 [25%]) or post-marketing studies (5 [2%]). In most of these cases (74%), patients received duloxetine for the treatment of depression. Pregnancy outcomes were normal in 143 cases, and abnormal in 90 cases. Abnormal pregnancy outcomes were mainly spontaneous abortions (n=41), post/perinatal conditions (n=25) or premature births (n=19). In patients with abnormal pregnancy outcomes, relevant concomitant medication use and relevant medical history were more frequently reported, compared to those with normal pregnancy outcomes ($p<0.05$). For the AERS database analysis, EB05 was less than one for all clusters

of abnormal pregnancy outcomes; there was no disproportionality of reporting adverse pregnancy outcomes for patients treated with duloxetine versus all other drugs or selected antidepressants.

Conclusion: While limitations of these data are recognized, the information available to date from these two data sources suggest that the frequency of abnormal outcomes reported in duloxetine pregnancy cases is generally consistent with the historic control rates in the general population.

Key words: safety surveillance, pregnancy outcomes, birth defects, antidepressants, duloxetine.

Introduction

Duloxetine hydrochloride (hereafter referred to as duloxetine) is a serotonin-norepinephrine reuptake inhibitor. In many countries, including the United States, it is approved for the treatment or management of major depressive disorder (MDD), generalized anxiety disorder, diabetic peripheral neuropathic pain, and fibromyalgia. In some markets, it is also approved for the treatment or management of chronic musculoskeletal pain (including in the US), and stress urinary incontinence (not in the US).

Worldwide, these conditions affect millions of women, including those of childbearing potential, and pharmacological treatment of these conditions in pregnancy is common. MDD, for example, is estimated to affect 6.6 % of the US population (1). It is more common in women, and its prevalence peaks from the age of 25 to 44 years (2). Depression has been reported in 7-13% of pregnant women (reviewed by Bennett (3)), and a large retrospective cohort study reported that 13% of pregnancies were exposed to antidepressants in 2003, with a steady increase since 1999 (4).

Pharmacological treatment of any condition is justified only if the potential benefits outweigh potential risks. In pregnancy, risks reach beyond the treated individual to the fetus, neonate or infant; these potential additional risks include teratogenicity, perinatal syndromes, neonatal toxicity, or abnormal behavioral development of the infant. While pooled clinical trial data provide important safety information on a drug entity used in a controlled environment, studies to identify potential pregnancy-related risks with pharmacologic agents are challenging. Pregnant women are often excluded from clinical trials and unlikely to volunteer to participate in clinical trials of new drug entities. Post-marketing surveillance is a complementary tool for detecting potential safety signals associated with drug use during pregnancy. Its value lies in its potential to detect safety signals in a large sample population in a naturalistic setting.

Since it was first marketed in 2004 through October 31 2012, more than 45 million patients have received duloxetine; this number includes more than 32 million women, approximately 11 million of whom were of childbearing age (Data on file, Eli Lilly and Company).

In this paper, we report cumulative information regarding outcomes of duloxetine-exposed pregnancies as captured in the Lilly Safety System (LSS) and the FDA Adverse Events Reporting System (AERS) database. The aim was to provide descriptive data from safety surveillance and spontaneous adverse events reporting databases, and to put the findings in the context of population statistics for abnormal pregnancy outcomes.

Methods

Data sources used for this report were the LSS, and the AERS databases. Both databases provide spontaneous reporting data from the time of US duloxetine marketing authorization in August 2004; in addition, the LSS includes serious adverse event and pregnancy data from clinical trials since the creation of the database in 1983. These databases are not mutually exclusive and the same event may have been reported to both.

Lilly Safety System (LSS)

The LSS is a global pharmacovigilance database in which Lilly collects information regarding adverse events (AEs) from various sources, and monitors and evaluates the information for subsequent communication to regulatory agencies, investigators, and internal departments. The current system was implemented in 2005, and contains data from 1983 onward. It contains serious and non-serious events reported spontaneously from post-marketing experience (including from the published literature and regulatory reports) and serious events from clinical trials and post-marketing studies. Medical Dictionary for Drug Regulatory Affairs (MedDRA®) (version 14.0) terms were used for analysis of all AEs.

A cumulative search was conducted of the case reports in LSS through October 31 2011. Both prospectively-identified (i.e., at time of initial report, fe-

tus still in utero and no evidence of fetal abnormality) and retrospectively-identified (i.e., at time of initial report, infant has been born or there is evidence of fetal abnormality in utero) cases are reported.

All pregnancy cases with a known outcome were analyzed based on the outcome of the pregnancy. Normal pregnancy outcomes were defined as those reports of pregnancy where birth was full term and fetal outcome was normal. Abnormal pregnancy outcomes were defined as those reports of pregnancy with one or more of the following outcomes: spontaneous abortion (fetal death), premature or post-term birth (regardless of fetal outcome), congenital anomaly, perinatal or post-perinatal complication, stillbirth (intrauterine death), or ectopic pregnancy. Specific pregnancy outcome definitions are as follows: *Normal* - infants born at 37-42 weeks gestation or unspecified gestation, with no problems noted; *Spontaneous Abortion* - failure of embryonic development, fetal death in utero, and/or expulsion of all or any part of the product of conception before the 20th week of gestation or expulsion of a fetus weighing less than 500 grams; *Premature* - infants born <37 weeks gestation or reported as "premature"; *Post-Term* - infants born >42 weeks or reported as "post-term"; *Congenital Anomaly* - infants born at 37-42 weeks gestation or unspecified gestation with a congenital abnormality (resulting from abnormal tissue formation) at birth, and reports of therapeutic abortions due to congenital abnormalities in the fetus; *Post/Perinatal Condition* - infants born at 37-42 weeks gestation or unspecified gestation with an AE <7 days of birth (perinatal) or >7 days after birth (post-perinatal); *Stillbirth/Intrauterine Death* - death of a fetus any time after the 20th week of pregnancy; the fetus has not taken any breath or shown any other evidence of life such as a beating heart after birth; *Ectopic Pregnancy* - an abnormal pregnancy in which the embryo implants outside the uterus.

Select patient characteristics were compared between prospectively-identified cases with normal pregnancy outcomes and those with abnormal pregnancy outcomes. Continuous variables were analyzed using ANOVA and dichotomous variables were analyzed using chi-square test. The level of statistical significance was defined as $p<0.05$. All the tests were conducted using SAS 9.1 (SAS, Inc., Cary, NC).

AERS Database

The AERs database was designed to support the FDA's post-marketing safety surveillance program for all approved drug and therapeutic biologic products. The FDA uses AERS to monitor for new AEs and medication errors that might occur with marketed products. Reporting of AEs is voluntary in the United States. Reports are received directly from healthcare professionals and consumers, but these individuals may also report AEs to the products' manufacturers. If a manufacturer receives an AE report, it is required to send the report to FDA as specified by regulations.

Data analyzed from the AERS database were those available as of September 30 2011. Analyses were performed for five groups of MedDRA Preferred Terms (PTs) - Spontaneous Abortion, Induced Abortion, Still Birth, Ectopic Pregnancy, and Congenital Malformation. All PTs were from the System Organ Classes (SOCs) of 'Pregnancy, Puerperium, and Perinatal Conditions' and 'Surgical and Medical Procedures' and the Standard MedDRA Queries (SMQs) of Reproductive Toxicity, Pregnancy Complications, Disorders of the Offspring, And Congenital, Familiar and Genetic Disorders.

The Empirical Bayes Geometric Mean (EBGM), a data mining measure of disproportional reporting (software, PhaseForward), was used to analyze pregnancy-related outcomes. Following the widely used approach by the FDA and others (5, 6), the 90% confidence interval (CI) of Empiric Bayes Geometric Mean (EBGM) was calculated in a disproportionality analysis. A lower bound of the 90% CI for the EBGM (EB05) ≥1 was used as a threshold to determine disproportionality. Disproportionality may suggest an association between a drug and an event, but does not establish causality.

The analyses were based on the entire AERS data background (i.e., events with duloxetine in context of events with any other drug) as well as a customized antidepressant background (i.e., events with duloxetine in context of events with these other antidepressants: amitriptyline, imipramine, bupropion, citalopram, escitalopram, fluoxetine, paroxetine, sertraline, venlafaxine, venlafaxine slow release, desvenlafaxine, doxepin, and nefazodone).

RESULTS

Lilly Safety Database

The cumulative search for case reports in the LSS through October 31 2011 identified a total of 1149 pregnancy cases, of which 400 contained pregnancy outcome information. Of these 400 cases with a known outcome, 233 were prospectively reported and 167 were retrospectively reported. Table 1 summarizes the cases by normal and abnormal outcomes. Prospectively reported cases had a numerically low proportion of abnormal outcomes.

Since prospectively-reported cases are less influenced by reporting bias and thus provide a more accurate representation of the reported pregnancy

outcomes, we explored these cases further. Of the 233 prospectively reported cases with a known pregnancy outcome, the majority (170 [73%]) were spontaneous reports; the remainder were reported from clinical trials (58 [25%]) or post-marketing studies (5 [2%]). In most of these cases (74%), patients received duloxetine for the treatment of depression or post-partum depression; the remainder reported anxiety, other psychiatric disorders, urinary incontinence, pain or neuropathy, or fibromyalgia as indications for use.

Table 2 summarizes the details of the pregnancy outcomes of prospectively identified cases. Table 3 shows patient characteristics of the prospectively identified cases by outcome. In patients with abnormal pregnancy outcomes, concomitant medication use and relevant medical history were more frequently reported, compared to those with normal pregnancy outcomes ($p<0.05$).

AERS Database

EB05 for all PT clusters from the disproportionality analysis was less than 1 in all cases (Table 4); that is there was no disproportionality of reporting adverse pregnancy outcomes (congenital anomaly, spontaneous abortion, induced abortion, ectopic pregnancy, and still birth) in patients treated with duloxetine versus all other drugs or selected antidepressants.

Table 1. Pregnancy outcomes of cases identified in the LSS.

Identification	Normal	Abnormal	Total
Prospective	143	90	**233**
Retrospective	47	120	**167**

Table 2. Specific pregnancy outcomes of cases prospectively identified in the LSS.

Pregnancy Outcome	Report Source		Total[a]
	Clinical Trial or Post-Marketing Study	Spontaneous	
Normal	37	106	**143**
Spontaneous Abortion	3	38	**41**
Post/Perinatal Condition	15	10	**25**
Premature	5	14	**19**
Congenital Anomaly	1	5	**6**
Ectopic Pregnancy	0	3	**3**
Stillbirth/Intrauterine Death	3	0	**3**
Post-Term	0	1	**1**

[a]Each case could have more than one listed abnormal outcome (e.g., premature *and* congenital anomaly), so the total column of the table does not add up to 233.

Table 3. Characteristics of pregnancy cases prospectively identified in the LSS.

	Normal (N=143)	Abnormal (N=90)	P value
Age, mean (SD)	31.2 (6.0)	32.0 (5.7)	NS
[a]Advanced maternal age, n (%)	29 (27%)	26 (32%)	NS
[b]Relevant concomitant medication, n (%)	19 (13%)	23 (26%)	0.02
[c]Relevant medical history, n (%)	25 (17%)	27 (30%)	0.03

[a]Advanced age is 35 years of age or greater.

[b]Relevant concomitant medications are those with positive evidence of human fetal risk (pregnancy category D or X, as classified by the FDA). Benzodiazepines (n=20), non-steroidal anti-inflammatory drugs (n=15), anti-convulsants (n=6), as well as angiotensin converting enzyme (ACE) inhibitors and other class D drugs (n<5 in both cases).

[c]Relevant medical history factors were miscarriage (n=23), smoking (n=21), substance abuse (n=8), pregnancy complication (n=6), as well as abortion, diabetes, congenital anomaly, ectopic pregnancy, stillbirth, AIDS, Factor V deficiency (n<5 in all cases).

Table 4. Disproportionality analysis for duloxetine and pregnancy cases identified in the AERS database.

Group indicating:	Number of cases		EB05
	Duloxetine	Other drugs	
Full AERS background			
Congenital anomaly	89	42,520	0.69
Spontaneous Abortion	66	12,469	0.55
Induced Abortion	11	4,620	0.20
Ectopic Pregnancy	4	1,603	0.14
Still Birth	6	3,973	0.15
Customized antidepressant background			
Congenital anomaly	89	6,028	0.21
Spontaneous Abortion	66	862	0.60
Induced Abortion	11	358	0.28
Ectopic Pregnancy	4	66	0.31
Still Birth	6	351	0.17

EB05 = the lower bound of 90% confidence interval of empirical Bayes geometric mean.

Discussion

In this paper, we provide descriptive data on pregnancy outcomes of duloxetine-exposed pregnancies as captured in the LSS and the AERS databases. The frequency of abnormal outcomes reported in prospectively-identified duloxetine pregnancy cases captured within the LSS is generally consistent with the historic control rates in the general population. Spontaneous abortions were reported in 18% of pregnancy cases; in the general US population, prevalence of spontaneous abortion is 12%-15% (7). Pregnancies resulting in a premature infant, a congenital anomaly, ectopic pregnancy, or stillbirth/intrauterine death, occurred in 8%, 3%, 1%, and 1% in the present analysis, versus 12% (8), 3% (9), 2% (10, 11), 0.6% (12) in the general population. It is recognized that such comparisons with population rates have limitations. These include a bias towards reporting abnormal versus normal outcomes where outcomes are reported as potential safety signals. There is also a higher prevalence of risk factors for abnormal pregnancy outcomes, including smoking and alcohol use, in depressed individuals than in the general population.

We attempted to identify patient characteristics that were associated with an increased risk of abnormal pregnancy outcomes in those receiving duloxetine. As shown in table 3, more patients with abnormal pregnancy outcomes had a history of using concomitant medications with positive evidence of human fetal risk (pregnancy category D or X, as classified by the FDA). In our analysis, these medications included benzodiazepines, non-steroidal anti-inflammatory drugs, anti-convulsants, as well as angiotensin converting enzyme (ACE) inhibitors and other class D drugs. Consideration was given to conducting an analysis of outcomes based on the timing of duloxetine exposure within the gestational period. However, unlike in the instances of age and concomitant illness, if trimester of exposure information was missing, the data collection method involved imputing missing values and assigning these exposures to all three trimesters. These data are thus unreliable for use in assessment of any association between the timing of duloxetine exposure and pregnancy outcomes.

Disproportionality analysis of AERS data as a signal detection method, as employed here, has been widely used (13, 14). Findings from the analysis of the AERS data showed no apparent disproportionality in abnormal pregnancy outcomes in patients treated with duloxetine versus all other drugs or selected antidepressants.

Much of the existing published literature on the safety of antidepressants in pregnancy is focused on epidemiological study findings. The topic has been reviewed by Yonkers et al (15). Briefly, while these studies have been an essential vehicle for increasing our understanding of antidepressant safety, their limitations are recognized; the studies rely on clinical reports or self reports, there is often a lack of information on diagnosis of depression and antidepressant use and, in some cases, there is lack of control for confounding factors. While findings from some studies do suggest an association between antidepressant use and adverse birth outcomes including miscarriage, low birth weight infants, preterm deliveries, congenital abnormalities (particularly heart defects), pulmonary hypertension of the newborn and adverse effects on neonatal neurobehavior, other studies have found no such associations. Considering all published findings to date, a causal relationship between antidepressant use and adverse pregnancy outcomes has not been established.

Importantly, potential risks of treatment should be weighed against the risks of untreated depression (i.e., benefit of treatment) to mother, fetus, neonate and infant. The literature on this topic is heterogeneous and suffers from similar limitations to those outlined above. Antidepressant discontinuation may increase the risk of a new or worsening episode of major depressive disorder in pregnant women (16), although this has not been found in all studies (17); discontinuation of antidepressant treatment may in turn increase exposure to risk factors for adverse pregnancy outcomes (inadequate nutrition, increased exposure to additional medications, and increased alcohol and tobacco use in the mother). In some studies, untreated maternal depression has been associated with adverse pregnancy outcomes, including miscarriage, low birth weight infants, and preterm delivery (reviewed by Yonkers et al (15)). Maternal depression has also been documented to negatively impact a child's emotional development. Newborns of women with untreated depression during pregnancy cry more and are more difficult to console (18). Children of mothers with depression have poor adaptive skills, are at risk of emotional and behavioral problems and are more prone to suicidal thoughts and behavior (19, 20).

There are some limitations to the databases used in this paper. For cases not captured in the clinical trial setting, details surrounding a pregnancy or pregnancy outcomes that might help in assessing possible association with a suspect drug (e.g., potential confounders) are often incomplete. Although it is

probable that the majority of pregnant women taking duloxetine are doing so to treat a depressive disorder, this cannot be confirmed; duloxetine has other approved uses in addition to treatment of major depressive disorder, including management of diabetic peripheral neuropathic pain and fibromyalgia, and may also be used in an off label manner; these individual diseases are likely to be associated with different levels of risk for abnormal pregnancy, which cannot be addressed in this study. Calculating the incidence of abnormal pregnancy outcomes is problematic, even for prospectively-identified cases, with a recognized bias towards reporting abnormal outcomes over normal outcomes. Further bias exists as a result of more diagnostic tests being employed in women with depression, such that there is increased potential for detecting anomalies that would not necessarily be detected in women who are not depressed (21). Additional factors can influence whether or not an AE will be reported and thus the calculated incidence of the event (e.g., length of time product has been available in the marketplace, publicity surrounding the specific AE). In the case of the AERS database, challenges exist in determining the time at which an exposure occurred in relation to when an AE was observed and reported and thus identification of prospective versus retrospective cases is not possible.

Despite these limitations which restrict their use in the determination of causality or the incidence of an event, post-marketing surveillance data do have strengths over those from clinical trials. They are from a naturalistic setting rather than the controlled environment of a clinical trial, and the number of patients exposed to a medicine after it is commercialized can be considerable compared to that feasible in clinical trials, particularly in situations where drugs have been marketed for some time.

In conclusion, while limitations of these data are recognized, the information available to date from these two data sources suggest that the frequency of abnormal outcomes reported in duloxetine pregnancy cases is generally consistent with the historic control rates in the general population. It is recognized that numbers are small, and the monitoring of the safety of duloxetine in pregnancy will continue. As data continue to accrue, our understanding of the safety of duloxetine use in pregnancy will increase. Patient and healthcare provider reports to manufacturers and to the FDA through MedWatch (22) are valuable for continuing data gathering. Information relating to use of drugs in pregnancy may also be reported through pregnancy registries, including the Cymbalta Pregnancy Registry (23), designed to collect prospective data about potential risks of duloxetine exposure during pregnancy. As with all medications, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Abbreviations

AERS: Adverse Events Reporting System; LSS: Lilly Safety System; EBGM: Empirical Bayes Geometric Mean; MDD: Major depressive disorder; AE: Adverse event; MedDRA®: Medical Dictionary for Drug Regulatory Affairs; PT: Preferred Term; SMQ: Standard MedDRA Query; SOC: System Organ Class; NS: Not statistically significant.

Competing Interests

These analyses were performed by Eli Lilly and Company. All authors are full time employees at Eli Lilly and Company.

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