PASS Information

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1. Abstract

Title: Stress Urinary Incontinence and Suicidality Seen in the United Kingdom Clinical Practice Research Database

Keywords: Duloxetine, stress urinary incontinence, suicidality

Rationale and background: Following authorisation of duloxetine in 2004, the issue of suicidality and associated use of SSRIs, notably in paediatric depression (FDA, 14 September 2004), became a topic of intense scrutiny by regulatory authorities around the world. This concern was extended to other products of a similar class including SNRIs. Given the limited number of patients with comorbid depression in SUI studies and limited sample size of the duloxetine RCT population at the time (~2005), there was a request to further study the impact of concurrent depression in the occurrence of suicide-related behaviour in SUI patients. It was assumed at that time that patients with SUI would not be subject to the extent of confounding by indication seen in the MDD licensed indication but this needed to be verified. Therefore, Lilly proposed to conduct an observational study in a large population database to assess the rate of suicide-related events among women with SUI taking duloxetine compared to controls with no exposure in a clinical practice setting in the European Union Risk Management Plan. The basis for conducting this study was 1) the issue of suicidality could not be addressed in the SUI clinical trial database, since use of antidepressants was an exclusion criterion and 2) the sample size needed for a clinical trial with an active comparator made this option unfeasible. Although the methodological challenges were acknowledged by CHMP, the possibility of performing an observational study was fully explored and a final study design was agreed upon, following an extensive evaluation of various methodologies and data sources.

Accordingly, between 2004 – 2010, Lilly conducted 4 analyses using the United Kingdom Clinical Practice Research Datalink (CPRD), (formerly known as the General Practice Research Database [GPRD]) to assess feasibility and investigate suicidality incidence among SUI patients. Although these previous analyses did not provide evidence of an association between duloxetine exposure and non-fatal suicide attempts or suicidal ideation in women with SUI, the previous results may have been limited by small sample size. As a result, Lilly was requested in 2011 by the CHMP to continue the study and conduct an additional analysis when the sample size was sufficiently large enough to detect a 2.5-fold difference in suicidal attempts as a primary study outcome. CHMP considered that the study was highly valuable as an increase in numbers of the study population (particularly, of those non-depressed and less "unconfounded" patients) could potentially rule out the possibility of an increased risk of suicidal outcomes among the duloxetine-treated SUI population.

This study presents the findings from the fifth analysis of CPRD.

Research question and objectives: This study investigated the association between duloxetine and suicidality in women with SUI. The specific objectives were the following:

- **Primary Objective:** To assess the association between suicide attempts (both non-fatal and completed) and receipt of duloxetine treatment in women with SUI compared to

women with SUI without duloxetine treatment, accounting for important demographic and medical history covariates.

- **Secondary Objective:** To study the association between suicidal ideation and receipt of duloxetine treatment in women with SUI compared to women with SUI without duloxetine treatment, accounting for important demographic and medical history covariates.
- **Exploratory Objectives:** To evaluate the association between suicidality-related outcomes and SUI case status, accounting for important demographic and medical history covariates.

Study design: This was an observational study using secondary collected data. The study utilised a retrospective cohort study design to compare suicidality outcomes between duloxetine-treated patients and untreated patients among those with or without an SUI diagnosis.

Setting: Data from the United Kingdom CPRD was utilised for this analysis. This analysis encompassed database records from September 1995 to September 2015.

Subjects and study size, including dropouts: Eligible women were those registered in active medical practices with CPRD quality-verified records, aged 18 and older, and with a minimum follow up-time of 1 year. For the primary and secondary objectives, all eligible women with a first diagnostic code for SUI identified in the CPRD dataset were included in the SUI cohort.

Variables and data sources: Important demographic and baseline characteristics were summarised for each of the comparison populations (duloxetine SUI versus non-duloxetine SUI and SUI versus non-UI). Continuous factors summarised included mean index age, mean follow-up time, and Charlson Comorbidity Index (summarised via means and standard deviations). Categorical factors were summarised via percentages and include psychiatric comorbidities, suicidal history (history of attempts, history of ideation, family history of suicidality), hospitalisation history, and psychiatric medication use (by class of medication).

Exposure variables in the study were duloxetine prescriptions. The following outcome variables were also assessed in this study: suicide attempt (which includes completed suicide and non-fatal suicide attempts), completed suicide, non-fatal suicide attempt, suicide ideation, and the combined outcome (completed suicide, non-fatal suicide attempt, and suicide ideation).

Statistical analysis: A Cox proportional hazard model was used to estimate adjusted hazard ratios along with the corresponding 95% confidence intervals. Estimations were based on models that incrementally included the covariates of interest. An as-treated analysis was used as a primary analysis (treated patients contributed to the analysis during the time they were exposed to duloxetine and untreated patients contributed to the analysis for the entire time they were in the database or were censored at the same time as their matches); additional pre-specified sensitivity analyses (using other follow-up lengths, intent-to-treat analysis, subgroup analysis, and other definitions for suicidal outcomes) and post hoc analyses (using propensity score stratification as well as an additional comparator group of patients with SUI treated with antidepressants other than duloxetine) were conducted.

Results: The analytical cohorts for the primary and secondary objectives were comprised of 5,255 duloxetine-treated and 20,674 untreated matched patients with SUI. The duloxetine treatment period was relatively short, therefore, an "as treated" method was utilised, which resulted in an average follow-up time of 270 days, including a 30-day wash-out period.

The mean ages were similar for duloxetine-treated and untreated patients: 56.42 (±13.92) and 56.40 (±13.81) years of age, respectively. Duloxetine-treated patients with SUI had more baseline psychiatric comorbidities compared to untreated patients; for example, more duloxetine-treated patients had baseline depression (14.44% vs.9.95%) and a history of depression (27.06% vs. 19.29%) compared to untreated patients. Furthermore, they were more likely to have been exposed to any psychiatric medication (54.14% vs. 38.23%), which may have been due to the severity of depression compared to untreated patients.

Using the as-treated analysis described above, the adjusted hazard ratios were 2.92 (1.44, 5.95, p=0.003) for duloxetine-treated compared to untreated patients followed for the entire time they were included in database and 5.06 (1.56, 16.45, p=0.007) for duloxetine-treated compared to untreated patients followed for the same amount of time as their matches, suggesting an approximately three- to five-fold increased risk of suicidal attempt with duloxetine treatment, after adjusting for measured/recorded important risk factors. Among the sensitivity and post hoc analyses, of particular interest is the comparison of duloxetine-treated patients with SUI to patients with SUI treated with other antidepressants, which identified that the baseline characteristics were comparable between the cohorts, e.g., depression (10.7% vs. 10.9% respectively) and other comorbidities. This emphasized that the large majority, approximately 89% of patients using antidepressants, did not have a recorded diagnosis of depression at baseline.

As an exploratory objective, 57,393 patients with SUI and 400,069 non-UI patients in the CPRD database were analysed after 1:7 matching. The association between suicidal outcomes and SUI diagnosis was not statistically significant after adjusting for important baseline depression and psychiatric medication use. The hazard ratios for suicide attempt and suicidal ideation were 0.90 (0.77, 1.04, p=0.169) and 1.07 (0.94, 1.21, p=0.315), respectively.

Discussion: Contrary to previous analyses conducted with the CPRD database, this study demonstrated a statistically significant association between duloxetine use and suicide-related outcomes (non-fatal suicidal attempt and suicidal ideation) as compared to untreated patients with SUI. The reasons why such findings became apparent in this analysis are considered to be due to the change in analysis type and the increased extent to which duloxetine is being prescribed for both MDD and SUI. It is clear from the data that there is an imbalance of comorbid depression within the duloxetine patient population and that patients with SUI treated with duloxetine were more likely to have depression or other psychiatric conditions than non-users within the context of a UK healthcare system setting. An earlier UK-based observational study gave some indication that duloxetine would be prescribed to SUI patients with comorbid depression which would be a reasonable clinical approach for a prescriber to take in order to avoid polypharmacy. However, the extent to which this could occur in broader clinical practice, and, hence, the inevitable impact on suicidal outcomes was not anticipated.

In addition, among depressed patients, severity of depression (usually not captured in the database) could further confound the results in the present study. This situation is further compounded by an unexpected finding that, for the large majority (89%) of non-duloxetine antidepressant users, depression was not recorded as a diagnosis in the database. Overall, this study has clearly shown that the SUI population of patients treated with duloxetine is significantly confounded by comorbid depression, which may well not even be recorded in the CPRD and to an extent that we had not anticipated. In the statistical models for this study, depression was considered to be an important effect modifier, so if this variable is poorly captured in the database, the statistical models cannot accurately adjust/account for this confounder along with other important risk factors for suicidality. This indicates that, for unanticipated reasons, the study did not succeed in identifying the sufficiently robust cohort of non-depressed and "unconfounded" SUI patients for which it was intended and, therefore, it is not possible to "rule out" the potential for an increased risk of suicidal outcomes among patients with SUI exposed to duloxetine. Given the extent of confounding in the treated population, the findings are likely to be significantly influenced by insurmountable limitations and factors, such as underdiagnosis of depression and the presence of comorbid depression, therefore, it cannot confirm any definitive causal association.

Confounding and the inability to accurately account for comorbid depression in SUI in the limited number of countries/databases where SUI is a licensed indication, is a key limitation in any observational approach to the question of whether or not concurrent depression has any impact on increasing risk of suicide-related behaviour in SUI patients. The extent to which these confounding factors account for the findings in this study vs an indication that they represent a true effect of duloxetine in increasing the risk can therefore not be determined by this or other observational approaches. Extending the study to include other databases (e.g., THIN) will also likely be subject to the same limitations as the current analysis. Additionally, another observational study with a larger sample size was conducted by MAH using comparisons between duloxetine-treated patients to general population patients with MDD and patients treated with other antidepressants. The study not only confirmed that there is no statistically significant association between duloxetine and suicide-related outcomes but also demonstrated the inability of the study to overcome confounding by indication if using a very different comparator group (i.e., non-depressed patient population) (Valuck et al. 2016).

A key advantage of using an observational research design is that it allows for larger sample sizes than those found in RCTs. We anticipated that this study would be sufficiently powered to address the request to rule out the possibility of an increased risk of suicidal outcomes among duloxetine-treated patients. In practice, the CPRD database included less than 6,000 patients and a small number of total events, which is appreciably lower than the accumulated patient exposures from randomised clinical trials (RCT) (14058 total duloxetine-treated patients and 2646.8 patient years (PY) of exposure using the cut-off date 21 February 2017). Findings from placebo-controlled RCT data (psychiatric and non-psychiatric trials) did not show an increase in the risk of recorded adverse events related to suicidal thoughts and behaviour with antidepressant use in patients over age 24.

Given all the reasons discussed above, Lilly does not see a viable option to further study the potential association between duloxetine treatment and suicidality within the SUI population. The totality of evidence in adult patients treated with duloxetine does not support any definitive causal association with treatment and significant methodological limitations precludes any further evaluation that would alter current knowledge or existing risk management activities. Therefore, the results from this study do not change the benefit/risk of using duloxetine for the treatment of SUI.

Marketing Authorisation Holder(s): Eli Lilly and Company

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2. List of abbreviations

Term	Definition
CCI	Chartson comorbidity index
CL	confidence level
CPRD	Clinical Practice Research Datalink
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GP	general practitioner
GPRD	General Practice Research Database
HIPAA	Health Insurance Affordability and Accountability Act of 1996
IR	incidence rate
ITT	intent-to-treat
LCL	lower confidence level
LUTD	lower urinary tract disorders
MAH	Marketing authorization holder
MDD	major depressive disorder
NA	not applicable
PEM	Prescription-Event Monitoring
PY	patient years
RR	relative risk
SMQ	Standardized MedDRA Query
SNRI	serotonin norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
SUI	stress urinary incontinence
TCA	Tricyclic antidepressants
UCL	upper confidence level

UI	urinary incontinence
UK	United Kingdom

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4. Other responsible parties

Not applicable.

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	01 December 2015	27 January 2016	
End of data collection	30 June 2016	30 January 2017	
Registration in the EU PAS register	NA	NA	The study protocol and four analyses were initiated prior to GVP guidance
Final report of study results	31 March 2017	31 July 2017	

6. Rationale and background

Stress urinary incontinence (SUI) is the most common type of urinary incontinence reported by women, affecting more than 1 in 7 women worldwide (Fultz et al. 2003). Stress urinary incontinence incidence appears to increase with age up until 50-60 years of age and is more common in women than in men. In addition to female gender and age, childbirth and obesity are established risk factors for SUI. There is no direct evidence that SUI is a risk factor for suicidality, although there is a link between SUI and depression.

In 2004, duloxetine was approved for the SUI indication in the European Union. The integrated safety analysis of 4 placebo-controlled clinical trials formed the basis for the marketing application of duloxetine as a treatment of SUI in the European Union. In 1913 women with SUI randomised to placebo (N=955) or duloxetine 40 mg twice daily (N=958), it was reported that there were no incidences of suicide, suicidal behaviour, or mania in any of the studies (Hurley et al. 2006). Following authorisation in 2004, the issue of suicidality and associated use of SSRIs, notably in paediatric depression (FDA, 14 September 2004), was a topic of intense scrutiny by regulatory authorities around the world. This concern was extended to other products of a similar class including SNRIs. Given the limited number of patients with comorbid depression in SUI studies and limited sample size of the duloxetine RCT population at the time (~2005) there was a request to further study the impact of concurrent depression in the occurrence of suicide-related behaviour in SUI patients. Lilly proposed to conduct an observational study in a large population database to assess the rate of suicide-related events among women with SUI taking duloxetine compared to controls with no SUI in a clinical practice setting in the European Union Risk Management Plan. The basis for this request was that 1) the issue of suicidality could not be addressed in the SUI clinical trial database, since depression was an exclusion criterion and 2) the sample size needed for a clinical trial with an active comparator made this option unfeasible. Although the methodological challenges were acknowledged by CHMP, the possibility of performing an observational study was fully explored and a final study design was agreed, following an extensive evaluation of various methodologies and data sources.

Accordingly, Lilly conducted a series of 4 preliminary analyses of the CPRD database to assess the rate of suicide-related events among women with SUI taking duloxetine compared to controls with no SUI in a clinical practice setting. These feasibility results were communicated to the EMA's Committee for Medicinal Products for Human Use (CHMP) between 2004 and 2010. Although no evidence of an association between duloxetine exposure and non-fatal suicide attempts or suicidal ideation in women with SUI has been demonstrated in these analyses, the previous results may have been limited by small sample size. CHMP interpreted that the non-significant result was due to low statistical power of the analyses and not a lack of effect. In 2011, CHMP required that this study continue as a pharmacovigilance action of the RMP for duloxetine and that Lilly conduct an additional analysis when the sample size was sufficiently large enough to detect a 2.5-fold difference in suicidal attempts as a primary study outcome. CHMP considered that the study was highly valuable as an increase in numbers of the study population (particularly, of those non-depressed and less "unconfounded" patients) could

potentially rule out the possibility of an increased risk of suicidal outcomes among the duloxetine-treated SUI population.

This report presents the results of the fifth analysis of CPRD.

7. Research question and objectives

The research question is whether or not duloxetine treatment increases the risk of suicide-related outcomes among SUI patients and this study was undertaken to rule out the possibility of a 2.5-fold increased risk of non-fatal suicide attempts among patients with SUI exposed to duloxetine.

The specific objectives were assessed as follows:

- Primary Objective: To assess the association between suicide attempts (both non-fatal and completed) and receipt of duloxetine treatment in women with SUI compared to women with SUI without duloxetine treatment, accounting for important demographic and medical history covariates.
- Secondary Objective: To study the association between suicidal ideation and duloxetine by comparing women with SUI who received duloxetine and women with SUI who did not receive duloxetine, accounting for important demographic and medical history covariates.
- Exploratory Objectives: To evaluate the association between suicidality-related outcomes and SUI case status or not, accounting for important demographic and medical history covariates.

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	03 May 2017	Data analyses	Update	Statistical analysis plan was updated to include proposed new analyses.

9. Research methods

The present study was based on the same protocol as the 4 previous analyses. The statistical analysis was updated to include new developments (updated READ codes, use of an "as-treated" study design in place of an "intent-to-treat design" [see Section 9.3.2]), and amended due to a better understanding of patients' baseline characteristics (2 post-hoc analyses were added [see Section 9.9.5].

9.1. Study design

F1J-MC-B056 was an observational study using secondary collected data. The study utilised a retrospective cohort study design to compare suicidality outcomes between duloxetine-treated patients and untreated patients among those with SUI diagnoses.

9.2. Setting

Data from the United Kingdom (UK) CPRD, formerly known as the UK GPRD, was utilised for this analysis. This analysis encompassed database records from September 1995 to September 2015.

9.3. Subjects

9.3.1. Study population

Eligible women were those registered in active medical practices with CPRD quality-verified records, aged 18 and older, and with a minimum follow up-time of 1 year.

Study population in the primary and secondary study objectives:

All eligible women with a first diagnostic code for SUI identified in the GPRD dataset were included in the SUI cohort (Read codes K586.00, K198.00, 1A24.00, 1A24.11, 1593.00, 7B33800, and 7B33C00).

- Duloxetine-treated SUI cohort: Among these SUI patients, women prescribed duloxetine (at least 1 prescription) for SUI were identified and considered "exposed". The pool of eligible controls was restricted to those unexposed patients in a practice that had experience in diagnosing a case of SUI.
- Duloxetine-untreated SUI cohort (comparison cohort): The comparison cohort of women with SUI who did not receive a duloxetine prescription, was constituted through an approximately 4:1 random sample of eligible patients with SUI who matched duloxetine-exposed patients on the basis of year of birth, clinical practice, index date (± 30 days) (definition Section 9.3.2) and diagnosis of SUI (± 90 days). The matching variables were selected to account for the age distribution of SUI, as well as for the clustering of women within a practice to account for unobserved practice variation. To further adjust for immortal time bias, the index date of SUI unexposed patients was reassigned (see Section 9.3.2).

- The cohort including patients treated with other antidepressants was evaluated in a post hoc analysis.

Study population in the exploratory study objectives:

- SUI diagnosed cohort: All eligible women with a first diagnostic code for SUI identified in the CPRD dataset were included in the SUI cohort, regardless of duloxetine treatment.
- Non-UI cohort (comparison cohort): Women without urinary incontinence of any type were eligible as participants in the comparison non-UI cohort. This analytic comparison cohort will be constituted through a 7:1 matching of non-UI to SUI diagnosed women by year of birth, clinical practice, and Duloxetine prescription. Among non-UI patients, the corresponding index date will be re-assigned to match the date of SUI diagnosis date.

9.3.2. Observation period/drug exposure

Baseline period was defined as no drug exposure during 1 year prior to index date.

Index date was defined as the following:

Primary and secondary study objectives:

- Index date of duloxetine treated SUI cohort was the first prescription date of duloxetine;
- Index date of non-duloxetine treated SUI cohort was randomly assigned, and derived from the distribution of the number of days from the initial SUI diagnosis to the prescription date of initial duloxetine use among treated patients. The index date was selected at random and assigned to the nonusers according to the distribution of time between diagnosis and prescription derived from the treated cohort. Therefore, the overall distribution of the index date of the non-users matched that of the users' time for the first duloxetine prescription. This approach for matching prescription time between duloxetine users and non-users at cohort entry was considered reasonable given SUI is a chronic condition and has been reported as a way to control for time-related bias (Zhou 2005).

Exploratory study objectives:

- Index date of SUI diagnosed cohort was the first SUI diagnosis date;
- Index date of non-UI cohort was reassigned based on the SUI diagnosis date of the matched SUI cases.

End of duloxetine exposure was defined as last prescription plus duration of the prescription and wash out period (30 days). In addition, sensitivity analyses have been proposed to evaluate various wash out periods (e.g., 60 days, 90 days, etc.). The duloxetine exposure of interest ranged from the marketing approval date of 04 August 2004 through 30 June 2014.

End of the follow-up was defined as the following:

Based on observations from previous executions of the study protocol, an "as-treated (without censoring)" analysis was chosen as the primary exposure condition for the main analysis. This

was decided based on the observation that some patients in the duloxetine-treated cohort who would be included in an "intent-to-treat" analysis had considerable lengths of time (sometimes months to years) between stopping duloxetine and an event of interest. When a considerable gap in exposure existed, this would suggest the event likely had little to do with duloxetine exposure. It was thereafter observed that patients not treated with duloxetine often had significantly greater periods of observation compared to the duloxetine-treated cohort, so an "As-treated (censoring)" analysis was adopted to attempt to equalise the "exposure" intervals.

1. As-treated analysis (without censoring): incidence of the analysed suicidality events, or until a first date of 1 of the following events: death or loss to follow-up was observed in the data, or end of duloxetine exposure, or end of study period. For patients with multiple outcomes of interest, the first outcome was considered.
2. As-treated analysis (with censoring): In addition to the above-mentioned bullet 1, the follow-up interval was truncated to match the time of the exposed patients.
3. Intent-to treat analysis: incidence of the analysed suicidality events, or until a first date of 1 of the following events: death or loss to follow-up was observed in the data or end of study period. For patients with multiple outcomes of interest, the first outcome was considered.

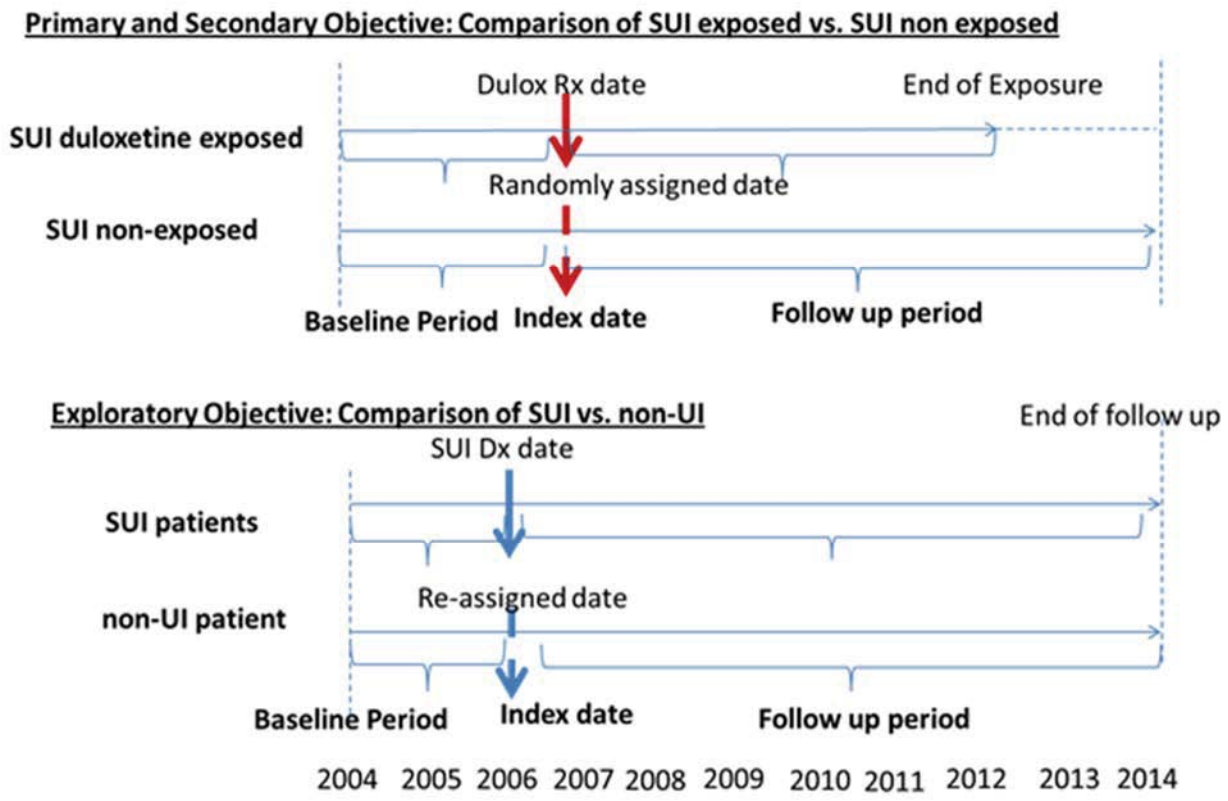
Study observation period was defined as the following:

Primary and secondary study objectives:

Study observation period for the comparison between SUI exposed patients and the SUI non-exposed patients began with index date (duloxetine initiation for women exposed and the randomly assigned index date for the unexposed SUI patients) until end of the study follow-up (see above). The study observation periods of both comparisons is shown in Figure 9.1.

Exploratory study objectives:

Similarly, for the comparison between SUI patients and non-UI patients, the study observation period began with index date (SUI diagnosis date for SUI patients, and corresponding date for non-UI patients) until end of the follow-up.



Abbreviations: SUI = stress urinary incontinence; UI = urinary incontinence.

Figure 9.1. Study observation period.

9.4. Variables

9.4.1. Baseline variables

Demographic and baseline characteristics were summarised for each of the comparison populations (Duloxetine SUI versus Non-Duloxetine SUI and SUI versus Non-SUI). Continuous factors summarised included mean index age, mean follow-up time, and Charlson Comorbidity Index (summarised via means and standard deviations). Categorical factors were summarised via percentages and included psychiatric comorbidities, suicidal history (history of attempts, history of ideation, family history of suicidality), hospitalisation history, and psychiatric medication use (by class of medication).

9.4.2. Exposure variables

Duloxetine prescription.

9.4.3. Outcome variables

The following outcomes of interest were assessed in this study:

- Suicide attempt (included completed suicide and non-fatal suicide attempts)
- Completed suicide

- Non-fatal suicide attempt
- Suicide ideation
- Combined outcome of completed suicide, non-fatal suicide attempt, or suicide ideation.

A comprehensive list of suicidality-related Read codes is provided in Section 8.2 of the B056 statistical analysis plan (Annex 2).

9.4.4. Other study variables

Covariates of interest that were known predictors of suicidality included diagnosis of depression and other psychiatric conditions, past history of non-fatal suicide attempts, a diagnosis of other psychiatric conditions, history of psychiatric hospitalisations, and use of antidepressants as documented in the available medical records (pertinent Read or OXMIS Medical Codes specified in Section 8.2 of the B056 statistical analysis plan [Annex 2]).

Independent variables of interest were baseline depressive diagnosis, other comorbid psychiatric conditions (bipolar, anxiety disorder, schizophrenia, and borderline personality), history of psychiatric hospitalisations, number of previous non-fatal suicide attempts, and number and type of anti-depressants used, if any (please refer to Annex 2 for related codes). Other nonpsychiatric comorbidities captured via the Charlson comorbidity index (CCI) were considered as confounders of the association between SUI and suicidality as well as between duloxetine use and suicidality, if appropriate.

9.5. Data sources

The CPRD database is an anonymised, longitudinal, primary care medical record database in the UK. It contains information on all medical care including diagnoses and treatments provided by general practitioners (GPs) in the United Kingdom. The CPRD also captures information on diagnoses and treatments from specialists through GP's electronic medical records. In the UK, more than 99% of patients are registered with a GP through the National Health Service. Currently the database captures information from 685 practices, representing approximately 8% of the UK population. Data from the CPRD is subjected to checks for continuity and completeness, and data from individual practices are flagged to ensure that researchers are aware of any data quality issues.

Diseases are classified in the CPRD using Read Codes. Read Codes are diagnostic codes used by the GPs as part of the patient's electronic medical record. The quality of the data is monitored and patients are labelled as 'acceptable' for use in research by a process that identifies and excludes patients with non-contiguous follow-up or patients with poor data recording. The overall quality of data from individual practices is mediated by use of an "up to standard" date, which is the date at which audits demonstrate that at least 95% of relevant patient encounters are recorded and data are determined to be suitable for epidemiologic research.

9.6. Bias

Due to lack of randomisation, an observational study can result in biased findings. For example, the data source did not capture the indication of any medication use. Although the studied

duloxetine prescription was the first prescription after SUI diagnosis, it is unclear why the prescription was given and it was not possible to differentiate the indication across all duloxetine indications (SUI, MDD, diabetic neuropathy, etc.).

The present study is the fifth attempt to analyse the CPRD database to address the research question of whether duloxetine use is associated with an increased suicidality risk among patients with SUI. The protocol was developed in 2006, shortly after duloxetine was initially marketed, and there was an assumption made at the beginning of the study that the statistical models could account for any imbalance in baseline characteristics, e.g., comorbid depression, etc., between duloxetine-treated and untreated patients with SUI. Although confounding by indication was noted then, the magnitude of its impact was not largely understood until the additional post hoc analysis was conducted in this study to compare duloxetine treated patients to other antidepressant treated SUI patients. We found a lower than expected proportion of recorded depression diagnoses in the antidepressant control cohort, which is an indicator that depression diagnoses were not reliably captured in the CPRD. This analysis was not conducted in the previous preliminary analyses, thus this limitation had not been previously identified. Additional sensitivity analyses were proposed to improve validity leveraging new statistical methods (e.g., propensity score stratification). However, despite sophisticated statistical methods being implemented to adjust for confounding by indication, biases in the study design (described below) could fundamentally influence the results:

1. Confounding by indication: It is possible that duloxetine was more likely to be prescribed to patients with SUI with psychiatric conditions, e.g., depression (recorded MDD diagnosis) and depressive symptoms (unrecorded MDD diagnosis) than to those without depression. For example, a physician making a decision about whether to offer pharmaceutical treatment to address a patient's symptoms of SUI may be more likely to prescribe duloxetine, which is also an antidepressant, if he/she felt that the patient also had depressive symptoms – even in absence of a recorded depression diagnosis. It was noted that the diagnosis of depression among other antidepressant users was as low as 11%. The pre-specified analyses could not overcome this problem as, based on the finding above, it is apparent that health care providers (HCPs) did not record the diagnosis for patients with depressive symptoms or the diagnosis was made elsewhere and was not recorded in the general practical database. Thus, post hoc analyses using the addition of an antidepressant comparator cohort were proposed to improve the balance of measured confounding factors.
2. Confounding by severity: An imbalance in severity of depression, social factors, and other psychiatric conditions are additional potential concerns. The CPRD did not encompass all suicidality risk factors, e.g., family history of suicide or self-harm, exposures to suicidal behaviour of others, feeling stressed or hopeless, and other factors that were not recorded in the medical records, etc. Therefore, it is possible that the association could be overestimated because duloxetine will likely be prescribed to patients with more severe depressive symptoms compared to untreated patients with SUI.

9.7. Study size

The sample size was computed based on a 2-sample noninferiority log-rank test, using the methodology of Jung et al. (2005). The constants input into the sample size calculation were: 80% power, 2-sided alpha = 0.05, null hypothesis: hazard ratio ≥2.5, ratio of untreated to duloxetine is 4:1. The formula of Jung and colleagues was used to determine that 49 events were needed in order to achieve the specified power with these constants (Jung et al. 2005).

In order to convert the events needed into the approximate number of patient-years follow-up, the event rate was estimated based on the 2010 report (Khan et al. 2010). In that report, there were 22 events with 33 315 years follow-up, which is an event rate of 0.00066 per patient-year. If the event rate persisted, we would need 74 243 patient years follow-up to have accrued 49 events.

Consistent with the protocol specifications, the follow-up for duloxetine-treated SUI patients started from the first duloxetine prescription, until the outcome (i.e., non-fatal suicide attempts or completed suicide) or the end of the data availability. The total duloxetine-treated SUI patients' follow-up time was 17 349 patient years, which indicates that the overall follow-up time was approximately 86 745 patient years. This exposure yielded more than the requisite 49 events.

9.8. Data transformation

The Statistical Analysis System (SAS® Version 9.2 proprietary software, (Copyright © 2002-2008 by SAS Institute Inc., Cary, NC, USA) was used for both data management and analysis. Datasets and analytic programs were stored on a secure server and were archived per Lilly record-retention procedures.

9.9. Statistical methods

9.9.1. Main summary measures

Baseline characteristics for the duloxetine-exposed and unexposed populations and SUI and non-UI populations are presented. Exposure-adjusted incidence for each suicide-related event, and for all events combined, with corresponding 95% confidence intervals was calculated for the analytic cohorts overall and stratified by age group and depression status.

Both crude and adjusted hazard ratios (adjusted based on independent variable values listed in Section 9.4.4) will also be presented to compare duloxetine-treated to untreated patients, or SUI patients to non-UI patients, with corresponding 95% confidence intervals. Subgroup analyses and sensitivity analyses will also be presented (for details, see Annex 2).

9.9.2. Main statistical methods

9.9.2.1. Primary analysis

For the primary comparison of suicide attempt (non-fatal attempt and complete suicide) rates between SUI patients exposed to duloxetine versus SUI patients not exposed to duloxetine, a Cox proportional hazard model was used to estimate adjusted hazard ratios along with the

corresponding 95% confidence intervals. Estimations were based on models that incrementally included the covariates of interest (as detailed below in Table 9.1).

Table 9.1. Cox Regression Models for each Suicidality Outcome within Women with an SUI Diagnosis, Contrasting Women taking Duloxetine with those that did not take Duloxetine

Covariates	Base model	Base model + Depression	Full model
Duloxetine Status	X	X	X
Current depression		X	X
Psych comorbidities			X
History of depression		X	X
History of psychiatric hospitalisation			X
History of suicide attempt			X

Cox Proportional Hazards models were also used to assess the association between each of the other suicide-related outcomes listed in Section 9.4.1 and receipt of duloxetine treatment in the subpopulation of women with SUI, following the same procedure used for the primary comparisons.

9.9.2.2. Secondary analyses

For comparison of suicidal ideation listed in Section 9.4.1 between SUI patients exposed to duloxetine versus SUI patients not exposed to duloxetine, a Cox proportional hazard model was used to estimate adjusted hazard ratios along with the corresponding 95% confidence intervals. Estimations were based on models that incrementally included covariates of interest detailed in Table 5.2 of B056 Statistical Analysis Plan (Annex 2).

9.9.2.3. Exploratory analyses

Exposure-adjusted incidence for each suicide-related event, and for all events combined, with corresponding 95% confidence intervals were calculated for the analytic cohorts overall and stratified by depression status with effect for depression status (with a log exposure offset). These estimations were performed separately based on the following analytic cohorts:

- Women with a diagnosis of SUI, accounting for duloxetine exposure status, if applicable
- Women without a diagnosis of urinary incontinence of any type, accounting for duloxetine exposure status, if applicable

- Women with a diagnosis of SUI receiving duloxetine treatment for this indication
- Women with a diagnosis of SUI not receiving duloxetine treatment for any indication

Suicidality incidence rates (unadjusted for amount of follow up time) and corresponding 95% Clopper-Pearson confidence intervals were also calculated for the overall female population in the GPRD dataset and by 5-year age groups.

9.9.3. Missing values

As these analyses/cohorts were selected based on the available data, no data are considered missing. Hence, no methods for addressing missing data are warranted.

9.9.4. Sensitivity analyses

The following subgroup analyses were conducted:

1. In order to assess the impact of the gaps between prescriptions on the exposure duration (especially as-treated analysis), additional analyses were conducted to apply different grace periods other than 30 days, i.e., 60 days and 90 days, and ITT analysis (e.g., intent to treat analysis will follow patients till end of data availability)
2. Due to its low predictability of suicidal outcomes, additional analyses were performed to assess the impact of various definitions of suicidal outcomes. The diagnostic codes were reviewed by two independent Lilly physicians with psychiatric backgrounds, and the final code list was based on consensus.
3. Additional analyses were conducted to assess the impact of proportional hazards. Due to potential imbalance in follow-up time between exposed patients and unexposed patients, additional analyses were conducted to ensure comparable length of follow-up between the cohorts.

9.9.5. Amendments to the statistical analysis plan

After reviewing the baseline characteristics after matching on age, index date, etc., from the main analysis, there were substantial differences between duloxetine-treated and untreated SUI patients in terms of baseline psychiatric conditions (e.g., depression, antidepressant use, etc.). For example, duloxetine-treated patients had a higher proportion of baseline depression (14.44% vs.9.95%), and history of depression (27.06% vs. 19.29%). They were also more likely to be exposed to any psychiatric medication (54.14% vs.38.23%), and, among those prescriptions, more patients were exposed to additional antidepressants (36.10% vs. 23.44%), which may be a sign of increased depression severity.

Two post hoc analyses were proposed to improve the unmeasured confounding between cohorts. Although the additional proposed analyses may not fully adjust for confounding factors, these analyses were intended to help with the interpretation of the study findings in the context of the study design limitations.

9.9.5.1. Post hoc analyses using propensity score stratification methodology

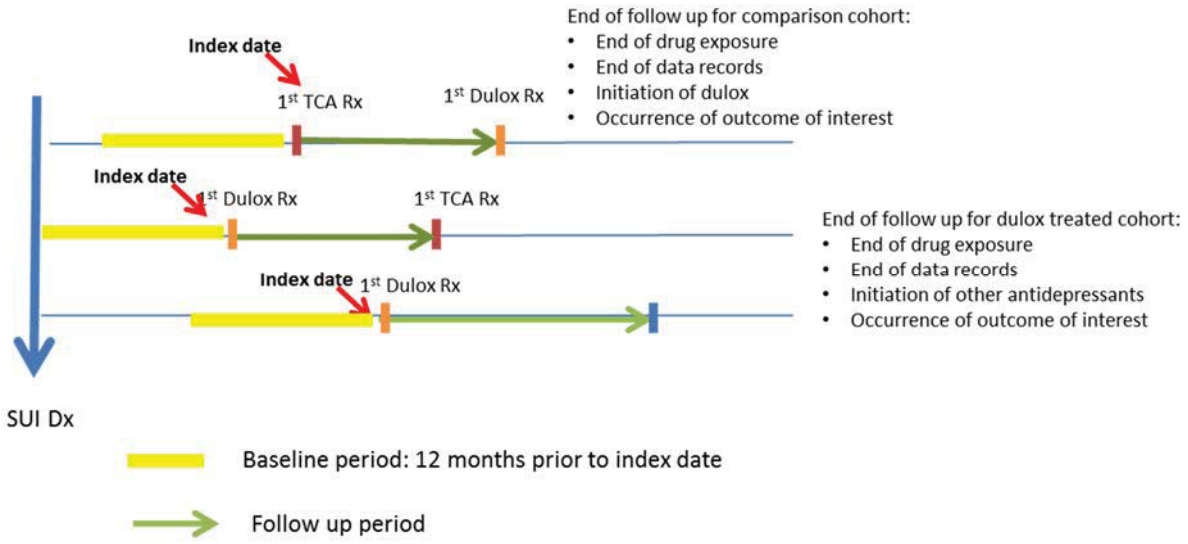
This analysis used propensity score stratification, as it maximizes the use of full sample size compared to propensity score matching. In this method, each subject was classified into a propensity quintile based on the propensity score. The propensity score for each patient was defined by the probability of being in the treated group. The propensity score was estimated using logistic regression, with group (treated versus untreated) as the outcome variable. The logistic regression propensity model included independent variable values collected at baseline. These variables include information such as patient age, history of psychiatric hospitalisations, baseline use of medication known to treat psychiatric conditions, psychiatric disorder comorbidities/history, and various comorbidities captured via the Charleston Comorbidity Index. These propensity scores were used to stratify patients into 5 strata. Due to the limited outcomes observed among the cohorts, 5 strata were considered appropriate. Within each stratum, the effect of treatment on outcomes was estimated by comparing outcomes directly between treated and untreated subjects. The stratum-specific estimates of treatment effect were then pooled across strata to estimate an overall treatment effect (Rosenbaum and Rubin 1984). Thus, stratum-specific differences in means or risk differences were estimated. These were averaged to produce an overall difference in means or risk difference. In general, stratum-specific estimates of effect are weighted by the proportion of subjects who lie within that stratum. Thus, when the sample is stratified into K equal-size strata, stratum-specific weights of 1/K are commonly used when pooling the stratum-specific treatment effects, allowing one to estimate the average treatment effect (Imbens 2004). The use of stratum-specific weights that are equal to that proportion of treated subjects that lie within each stratum allow one to estimate the average treatment effect for treated subjects (Imbens 2004). A pooled estimate of the variance of the estimated treatment effect was obtained by pooling the variances of the stratum-specific treatment effects.

9.9.5.2 Post hoc analyses using additional comparator groups

Confounding by indication and/or severity is very difficult to control when comparing treated with untreated persons. One way to reduce the potential for confounding is to compare with another actively treated cohort of patients with a similar potential for confounding. Given the concerns of underlying depression among patients with SUI treated with duloxetine, the comparator that we proposed was patients with SUI treated with any other antidepressants prescribed after SUI diagnosis (not in SNRI or SSRI class), drug codes are listed in Section 8.2 of B056 Statistical Analysis Plan (Annex 2). The goal of this comparative analysis was to demonstrate the choices for comparator groups and its impact on the association observed from the study. Of note, this approach only controlled for any measured confounding factors, while it was not able to address any unmeasured confounding factors.

Study participants: Among the original SUI-diagnosed patient population, two comparison groups were formed. Like the main analysis, patients with baseline duloxetine exposure were excluded, and patients with other antidepressants exposure (e.g., SSRI class or other SNRI, TCA, etc.) at baseline were presented in a baseline table and considered in the propensity score model. In addition, patients who are co-prescribed with both duloxetine and other antidepressant study drugs (any antidepressants, including SSRI/SNRI except duloxetine) at the index date were

excluded from this analysis. To avoid immortal time bias, all patients had an equal chance to be included in either cohort if they were exposed to study drugs. For example, if a patient was first exposed to other antidepressants (not an SNRI except for duloxetine or SSRI class) after SUI diagnosis, then received duloxetine prescription, the patient was assigned to another antidepressant cohort (not duloxetine group), and censored at the time that she initiated duloxetine or an antidepressant in another class. Patients were not exposed to the study drug at baseline in order to be eligible for the study cohorts. Index date was defined as the initial date of study drug prescription. Patients were followed until the end of data records, or end of drug exposure, or occurrence of outcome of interest, and/or the time of initiation of the other antidepressant drugs in another class other than the study drug in both cohorts. Figure 9.2 demonstrates the formation of both cohorts, index date, baseline period, and follow-up period.



Abbreviations: Dulox = duloxetine; Dx = diagnosis; Rx = prescription; TCA = tricyclic antidepressant.

Figure 9.2. Demonstration of study cohorts (duloxetine vs. any other antidepressant treated), index date, baseline period, follow up period.

Propensity scores were calculated for both cohorts using methods listed in Section 9.9.5.1. Based on the propensity score distribution, patients were stratified into quintiles (the number of strata was determined by the sample size and propensity score distribution). The effect of treatment was evaluated at each stratum, as well as pooled across all strata. The statistical methods used above in Section 9.9.5.1 were repeated here to compare patients treated with duloxetine to patients treated with other antidepressants.

9.10. Quality control

The study utilised an existing database, which was used primarily for research and is fully Health Insurance Portability and Accountability Act (HIPAA) compliant. To ensure their functionality and accuracy, data management and statistical analysis programs that were developed for this

study were validated by internal personnel who were familiar with the study, but were not directly involved in the creation/development of these programs.

- Access to the data was limited to Lilly Research project team members who needed to work with those data for the purposes outlined in this report.
- All statistical programs were reviewed and validated by an individual who was not a team member for accuracy and completeness.
- Results included in this report's text, tables, and/or figures were verified against source documentation by internal personnel who were familiar with the study, but were not directly involved in the development of the report.
- The electronic data were stored at Lilly on a networked computer that is password-protected and is protected from access outside of the network by a firewall.

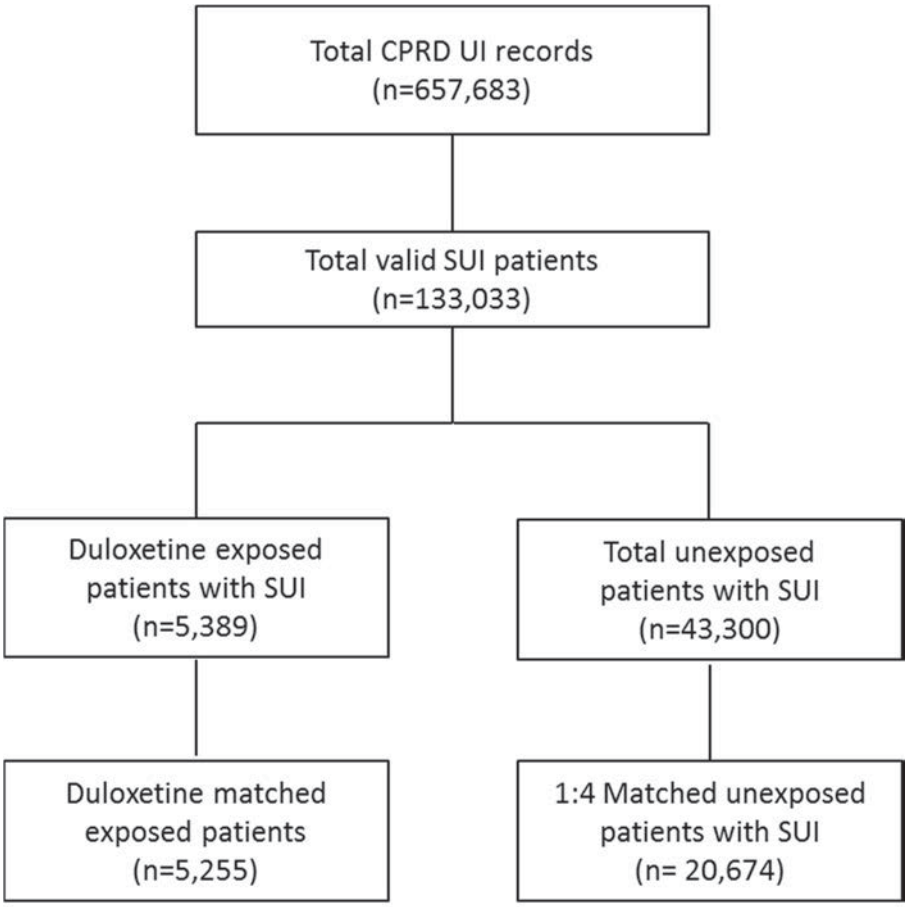
10. Results

10.1. Participants

10.1.1. Patient count for primary analysis population (duloxetine treated vs. untreated cohorts)

In the primary analysis population, there were 5,255 duloxetine-treated patients with SUI and 20,674 untreated patients with SUI. The average duloxetine treatment period for SUI patients was relatively short, therefore using an "as treated" method (patients who were exposed to duloxetine in the analysis), the average follow-up time was 270 days including a 30-day wash-out period. To avoid immortal time bias, a period of cohort follow-up time during which death (or an outcome that determines end of follow-up) cannot occur, the index date of untreated patients was reassigned based on the distribution between SUI diagnosis and the first prescription date. For 24% of patients, the index date was the same as the date of diagnosis; 50% were within 1-2 years after diagnosis, and about 26% of patients were reassigned an index date of greater than 8 years. Although SUI has not been reported to be related to suicidality, it is appropriate to balance the disease duration between the comparison cohorts to avoid comparing incident cases (newly diagnosed patient) to prevalent patients (with multiple years of experience).

Figure 10.1 presents a flow diagram of the patients screened for inclusion and the total number of patients eligible for inclusion in the two cohorts that comprised the primary analysis population (duloxetine-treated versus untreated). Patients were included in the primary analysis population via application of the following CPRD acceptability criteria: index age ≥18, date of birth available, female sex, association with valid practice, 365 days of baseline, no duloxetine exposure at baseline, and valid patient record.



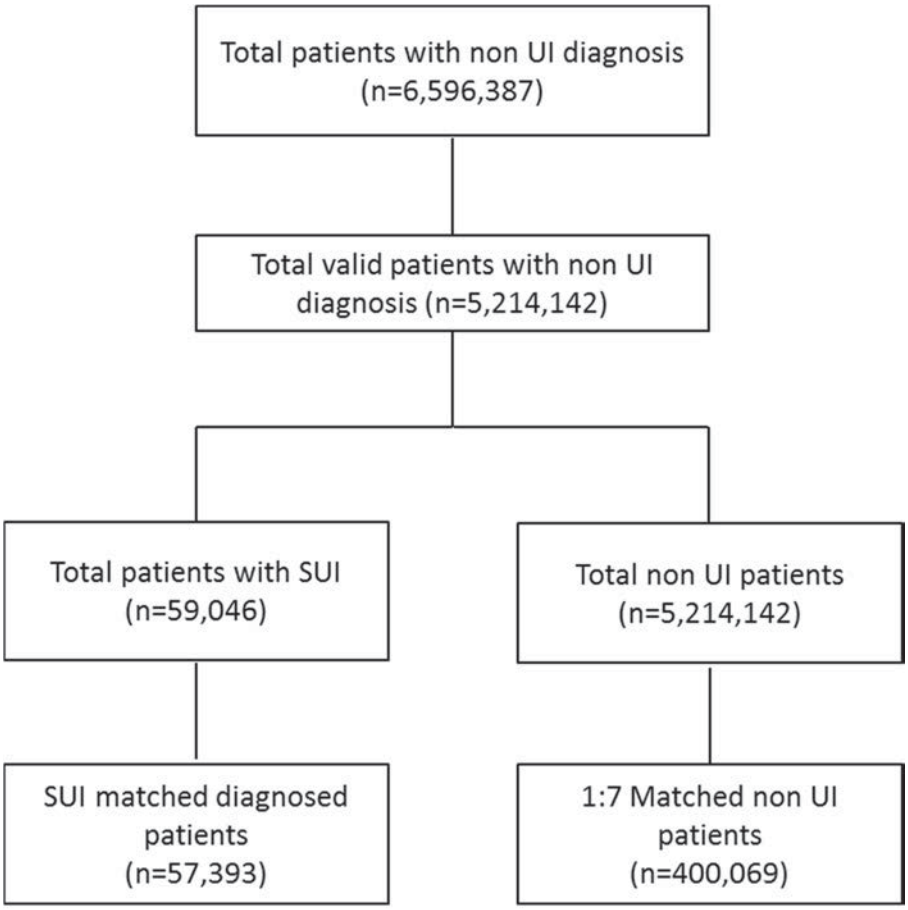
Abbreviations: CPRD = Clinical Practice Research Datalink; SUI = stress urinary incontinence.

Figure 10.1. Selection of patients eligible for inclusion in the primary objective comparison.

10.1.2. Patient count for secondary analysis population (SUI diagnosed vs. non-diagnosed cohorts)

In the secondary analysis population, there were 57,393 patients with SUI and 400,069 non-UI patients. Patients with SUI had a median (minimum to maximum range) follow-up of 1945 (0-7221) days while non-UI patients had a median (minimum to maximum range) follow-up of 1100 (0-7233) days.

Figure 10.2 presents a flow diagram of the patients screened for inclusion, the number of patients excluded for each exclusion criteria, and the total number of patients eligible for inclusion in the two cohorts that comprised the primary analysis population (patients with SUI versus non-SUI patients). Patients were excluded from the secondary analysis population via application of the following CPRD acceptability criteria: index age ≥18, date of birth available, female sex, association with valid practice, 365 days of baseline, no duloxetine exposure at baseline, and valid patient record.



Abbreviations: SUI = stress urinary incontinence; UI = urinary incontinence.

Figure 10.2. Selection of patients eligible for inclusion in the secondary objective comparison.

10.2. Descriptive data

10.2.1. Baseline characteristics: Duloxetine-treated and untreated patients with SUI

Table APP.1 presents baseline demographic characteristics for the primary patient cohort (duloxetine-treated and untreated patients).

Duloxetine-treated patients with SUI had more baseline psychiatric comorbidities compared to untreated patients, which was consistent with the understanding of dual prescription, namely treating patients with both urinary incontinent symptoms and depressive conditions with a single product indicated for both conditions. For both SUI and depression, these diagnoses were counted if they were recorded in the database. Those patients with only symptoms and without a recorded diagnosis were not counted in any adjusted analysis). For example, more duloxetine-treated patients had a higher proportion of baseline depression (14.44% vs.9.95%), and a history of depression (27.06% vs. 19.29%) compared to untreated patients. Furthermore, duloxetine-treated patients were more likely to be exposed to any psychiatric medication (54.14%

vs.38.23%) and additional antidepressants (36.10% vs. 23.44%), possibly due to more severe depression compared to untreated patients.

10.2.2. Baseline characteristics: Patients with and without SUI

Table APP.2 presents baseline demographic characteristics for the secondary patient cohort (patients with SUI and non-UI patients).

In general, patients with SUI and non UI patients were comparable on many baseline characteristics except for baseline depression and use of psychiatric medication. More patients with SUI had a history of depression (13.03% vs. 7.44%) compared to non-UI patients. In addition, patients with SUI were more likely to take baseline medications, including any selected psychiatric therapy (35.54% vs. 24.26%), antidepressants (22.56% vs. 13.65%), and other selected psychiatric therapy (18.05% vs. 13.40%).

10.3. Main results

10.3.1. Incidence rates of suicidal outcomes

Incidence rate was calculated for overall patients in each study cohort, as well as by age group and by depression status; based on different follow-up period estimations. The incidence rate was calculated using 2 as-treated analysis methods: 1) as-treated analysis (patients' follow-up period was censored at end of duloxetine exposure for treated cohort, but not censored for untreated cohort) and 2) as-treated analysis censored (patients follow-up was censored for both cohorts to equalise the follow-up period).

Overall Incidence Rate and Stratification by Age Group (As-treated Analysis, Uncensored): Table APP.3 presents incidence rates of suicide attempt and suicidal ideation across duloxetine-treated and untreated cohorts.

The crude incidence rate of suicide attempt for the **overall** duloxetine-treated cohort was 416.83 per 100,000 person-years compared to a crude incidence rate of 50.66 per 100,000 person-years for the duloxetine-untreated cohort. When stratifying by age group, the majority of patients were between 25 to 64 years of age; no trend analyses were conducted due to lack of patients in other age groups.

In the 25-64 year age group, the crude incidence rate of suicide attempt was 599.70 per 100,000 person-years for the duloxetine-treated cohort and 61.72 per 100,000 person-years for the duloxetine-untreated cohort.

The crude incidence rate of suicide ideation for the **overall** duloxetine-treated cohort was 416.27 per 100,000 person-years compared to a crude incidence rate of 69.87 per 100,000 person-years for the duloxetine-untreated cohort. Similarly, the majority of patients were between 25 to 64 years of age.

In the 25-64 year age group, the crude incidence rate of suicide ideation was 551.29 per 100,000 person-years for the duloxetine-treated cohort and 83.58 per 100,000 person-years for the duloxetine-untreated cohort.

Table APP.4 presents incidence rates of suicide attempt and suicide ideation stratified by age group across duloxetine-treated and untreated cohorts (censored).

The crude incidence rate of suicide attempt for the overall duloxetine-treated cohort was 416.83 per 100,000 person-years compared to a crude incidence rate of 32.59 per 100,000 person-years for the duloxetine untreated cohort. When stratifying by age group, the majority of the patients were between 25 to 64 year of age; no trend analyses were conducted due to lack of patients in other age groups.

- In the 25-64 year age group, the crude incidence rate of suicide attempt was 599.70 per 100,000 person-years for the duloxetine-treated cohort and 46.86 per 100,000 person-years for the duloxetine untreated cohort.

The crude incidence rate of suicidal ideation for the overall duloxetine-treated cohort was 416.27 per 100,000 person-years compared to a crude incidence rate of 56.95 per 100,000 person-years for the duloxetine untreated cohort.

In the 25-64 year age group, it was 551.29 per 100,000 person-years for the duloxetine-treated cohort and 81.68 per 100,000 person-years for the duloxetine-untreated cohort.

10.3.1.1. Stratification by recorded baseline depression (comparison between treated and untreated patients)

Incidence Rate of Depression Stratification by Depression Status (Baseline Depression, Historical Depression and No Recorded Depression) -- As-Treated Analysis – Untreated Population Uncensored: Table APP.5 presents incidence rates of suicide attempt and suicidal ideation stratified by depression status across duloxetine-treated and untreated cohorts.

Patients without recorded depression had the lowest incidence rate for both suicidal attempts and suicidal ideation. Among patients with depression diagnoses, patients who had depression diagnosis 1 year prior to index date had a higher incidence rate of suicidal attempt compared to patients who had baseline depression (within 1 year prior to index date) for both duloxetine-treated and untreated patients.

- For patients with historical depression, the crude incidence rate of **suicide attempt** for the duloxetine-treated cohort was 539.39 per 100,000 person-years compared to a crude incidence rate of 136.77 per 100,000 person-years for the duloxetine untreated cohort; in contrast, for patients with baseline depression, the crude incidence rate of suicide attempt for the duloxetine-treated cohort was 501.71 per 100,000 person-years compared to a crude incidence rate of 123.12 per 100,000 person-years for the duloxetine untreated cohort. For patients with no recorded depression, the crude incidence rate of suicide attempt for the duloxetine-treated cohort was 348.03 per 100,000 person-years compared to a crude incidence rate of 34.44 per 100,000 person-years for the duloxetine-untreated cohort.
- For patients with baseline depression, the crude incidence rate of **suicidal ideation** for the duloxetine-treated cohort was 663.08 per 100,000 person-years compared to a crude incidence rate of 158.50 per 100,000 person-years for the duloxetine-untreated cohort; in

contrast, for patients with historical depression, the crude incidence rate of suicidal ideation for the duloxetine-treated cohort was 537.66 per 100,000 person-years compared to a crude incidence rate of 147.15 per 100,000 person-years for the duloxetine untreated cohort. For patients with no recorded depression, the crude incidence rate of suicidal ideation for the duloxetine-treated cohort was 348.58 per 100,000 person-years compared to a crude incidence rate of 55.80 per 100,000 person-years for the duloxetine-untreated cohort.

Incidence Rate of Depression Stratification by Recorded Baseline Depression (Baseline Depression, Historical Depression and No Recorded Depression) -- As-Treated Analysis – Untreated Population Censored: Table APP.6 presents incidence rates and hazard ratios of suicide attempt and suicide ideation stratified by depression status across duloxetine-treated and untreated cohorts.

Patients without recorded depression had the lowest incidence rate for both suicidal attempts and suicidal ideation. Among patients with depression diagnoses, patients who had depression diagnosis >1 year prior to index date had a higher incidence rate of suicidal ideation compared to patients who had baseline depression (within 1 year prior to index date) for both duloxetine-treated and untreated patients.

- For patients with historical depression, the crude incidence rate of **suicide attempt** for the duloxetine-treated cohort was 539.39 per 100,000 person-years compared to a crude incidence rate of 129.86 per 100,000 person-years for the duloxetine-untreated cohort; in contrast, for patients with baseline depression, the crude incidence rate of suicide attempt for the duloxetine-treated cohort was 501.71 per 100,000 person-years compared to a crude incidence rate of 123.12 per 100,000 person-years for the duloxetine-untreated cohort. For patients with no recorded depression, the crude incidence rate of suicide attempt for the duloxetine-treated cohort was 348.03 per 100,000 person-years compared to a crude incidence rate of 10.52 per 100,000 person-years for the duloxetine-untreated cohort.
- For patients with baseline depression, the crude incidence rate of **suicide ideation** for the duloxetine-treated cohort was 663.08 per 100,000 person-years compared to a crude incidence rate of 300.76 per 100,000 person-years for the duloxetine-untreated cohort; in contrast, for patients with historical depression, the crude incidence rate of suicide ideation for the duloxetine-treated cohort was 537.66 per 100,000 person-years compared to a crude incidence rate of 86.90 per 100,000 person-years for the duloxetine-untreated cohort. For patients with no recorded depression, the crude incidence rate of suicidal ideation for the duloxetine-treated cohort was 348.58 per 100,000 person-years compared to a crude incidence rate of 31.47 per 100,000 person-years for the duloxetine-untreated cohort.

10.3.2. Comparison of suicidal outcomes between duloxetine-treated and untreated: Cox regression models

For the primary objective, outcome analyses were performed using 2 different as-treated methods comparing duloxetine-treated to untreated patients: 1) as-treated analysis (patients' follow-up periods were censored at end of duloxetine exposure for the treated cohort, but not censored for the untreated cohort; 2) as treated analysis censored (patients follow-up was censored for both cohorts to equalise the follow-up period.

As-Treated Analysis – Untreated Population Uncensored: Table APP.7 presents the crude and adjusted associations between duloxetine treatment and the risk of each suicidality outcome within women with a SUI diagnosis.

The crude hazard ratios for suicide attempt and non-fatal suicide attempt were 6.70 (3.36, 13.37, p<0.0001); after adjusting for baseline depression, psychiatric medication use, and other imbalanced covariates (fully adjusted model), the adjusted hazard ratios for suicide attempt and non-fatal suicide attempt were 2.92 (1.44, 5.95, p=0.003), suggesting an approximate three-fold increase in suicide attempt risk.

The crude hazard ratio for suicide ideation was 6.07 (3.03, 12.14, p<0.0001); the adjusted hazard ratio (full model with additional baseline covariates) for suicide ideation was 3.32 (1.63, 6.78, p=0.001), suggesting a an approximate 3 fold increase in suicidal ideation risk.

As-Treated Analysis – Untreated Population Censored: Table APP.8 presents treatment differences in the risk of each suicidality outcome within women with a SUI diagnosis.

- The crude hazard ratios for suicide attempt and non-fatal suicide attempt were 12.79 (4.17, 39.22 p<0.0001); after adjusting for baseline depression, psychiatric medication use, and other imbalanced covariates, the hazard ratios for suicide attempts and non-fatal suicide attempts were 5.06 (1.56, 16.45, p=0.007). There is a significant reduction in point estimation (from 12.8 to 5.1) between the fully adjusted model and crude estimation, which can be attributable to the significance of measured confounding factors, but also raise a concern about the robustness of this finding if residual confounding factors exist.
- The crude hazard ratio for suicide ideation was 7.30 (2.92, 18.30, p<0.0001); the adjusted hazard ratio (full model with additional baseline covariates) for suicide ideation was 3.89 (1.46, 10.43, p=0.007).

10.3.2.1. Exploratory objective: Incidence rates of suicidal outcomes in patients with and without SUI

10.3.2.1.1. Overall incidence rate and stratification by age group

Table APP.9 presents incidence rates of suicide attempt and suicide ideation across patients with and without a SUI diagnosis, irrespective of treatment.

The crude incidence rate of suicide attempt for the overall SUI patient cohort was 61.46 per 100,000 person-years compared to a crude incidence rate of 46.65 per 100,000 person-years for

the non-UI patient cohort. When stratifying by age group, the majority of patients (77.1%) were between 25 to 64 years of age; no trend analyses were conducted due to small numbers of patients in other age groups.

- In the 25-64 year age group, the crude incidence rate of suicide attempt was 70.10 per 100,000 person-years for the SUI patient cohort and 53.76 per 100,000 person-years for the non-UI patient cohort.

The crude incidence rate of suicide ideation for the overall SUI patient cohort was 94.55 per 100,000 person-years compared to a crude incidence rate of 60.46 per 100,000 person-years for the non-UI patient cohort. Similarly, the majority of patients were between 25 to 64 years of age.

- In the 25-64 year age group, the crude incidence rate of suicide ideation was 104.97 per 100,000 person-years for the SUI patient cohort and 70.63 per 100,000 person-years for the non-UI patient cohort.

10.3.2.1.2. Stratification by recorded baseline depression (SUI vs. non UI patients)

Incidence Rate of Depression Stratification by Depression Status (Baseline Depression, Historical Depression and No Recorded Depression): Table APP.10 presents incidence rates and hazard ratios of suicide attempt and suicide ideation stratified by depression status across patients with and without a SUI diagnosis, irrespective of treatment.

Patients without recorded depression had the lowest incidence rate for both suicidal attempts and suicidal ideation. Among patients with depression diagnoses, patients who had depression diagnosis 1 year prior to index date had a higher incidence rate of suicidal attempt and suicidal ideation compared to patients who had baseline depression (within 1 year prior to index date) for both SUI and non-UI patient cohorts.

- For patients with historical depression, the crude incidence rate of suicide attempt for the SUI patient cohort was 164.52 per 100,000 person-years compared to a crude incidence rate of 151.78 per 100,000 person-years for the non-UI patient cohort; in contrast, for patients with baseline depression, the crude incidence rate of suicide attempt for the SUI patient cohort was 137.74 per 100,000 person-years compared to a crude incidence rate of 149.29 per 100,000 person-years for the non-UI patient cohort. For patients with no recorded depression, the crude incidence rate of suicide attempt for the SUI patient cohort was 51.24 per 100,000 person-years compared to a crude incidence rate of 38.34 per 100,000 person-years for the non-UI patient cohort.
- For patients with baseline depression, the crude incidence rate of suicide ideation for the SUI patient cohort was 257.72 per 100,000 person-years compared to a crude incidence rate of 177.67 per 100,000 person-years for the non-UI patient cohort; in contrast, for patients with historical depression, the crude incidence rate of suicide ideation for the SUI patient cohort was 276.47 per 100,000 person-years compared to a crude incidence rate of 240.48 per 100,000 person-years for the non-UI patient cohort. For patients with no recorded depression, the crude incidence rate of suicidal ideation for the SUI patient

cohort was 76.49 per 100,000 person-years compared to a crude incidence rate of 48.12 per 100,000 person-years for the non-UI patient cohort.

10.3.2.2. Exploratory analysis: Cox regression models (SUI vs. non UI patients)

Table APP.11 presents the crude and adjusted associations between SUI diagnosis and the risk of each suicidality outcome.

The crude hazard ratio for suicide attempt was 1.36 (1.18, 1.58, p<0.0001); after adjusting for baseline depression, psychiatric medication use, and other imbalanced covariates (fully adjusted model), the hazard ratio for suicide attempt was 0.90 (0.77, 1.04, p=0.169).

The crude hazard ratio for suicide ideation was 1.60 (1.41, 1.81, p<0.0001); the adjusted hazard ratio (full model with additional baseline covariates) for suicide ideation was 1.07 (0.94, 1.21, p=0.315).

10.3.3. Summary of main results

Depending on the statistical models used, the point estimates suggest a 2.9- to 5.1-fold increased risk for suicide attempt in women with SUI treated with duloxetine when compared with women with SUI not treated with duloxetine, however the results need to be interpreted in the context of study limitations (discussed in following section). For suicidal ideation, the increased risk was 3.3 to 3.9. In the exploratory analysis of suicide-related ideation and behaviour, the analyses overall suggest that women with SUI do not have an increased risk for suicidality compared to women without UI.

10.4. Other analyses

Additional analyses were performed as outlined in the SAP. An ITT analysis was performed to compare the current CPRD data analyses to the previous study analyses, which used an ITT exposure condition for the primary objective analyses. A subgroup analysis was performed to examine the primary and secondary objectives in a subgroup of patients without recorded baseline depression and/or antidepressant use. Analyses were performed with variable "gaps" in duloxetine exposure to simulate real world situations when patients may have a possible break in their duloxetine exposure. Considering the uncertainties as to whether certain CPRD READ codes represent an actual suicide attempt, analyses were performed to include patients with additional "possible" suicide-related events. Finally, post-hoc analyses were performed using propensity score stratification and an analysis using a different comparator group, patients with SUI treated with antidepressants other than duloxetine.

10.4.1. Sensitivity analysis 1: Intent-to-treat analysis

10.4.1.1. Incidence rates of suicidal outcomes and Cox regression (duloxetine treated vs. untreated)

Table APP.12 presents the crude and adjusted associations between duloxetine treatment groups and the risk of each suicidality outcome within women with a SUI diagnosis.

The crude incidence rate of suicide attempt for the **overall** duloxetine-treated cohort was 125.40 per 100,000 person-years compared to a crude incidence rate of 50.66 per 100,000 person-years for the duloxetine-untreated cohort.

The crude hazard ratios for suicide attempt and non-fatal suicide attempt were 2.47 (1.53, 3.98, p=0.0002); after adjusting for baseline depression, psychiatric medication use, and other imbalanced covariates (fully adjusted model), the adjusted hazard ratios for suicide attempt and non-fatal suicide attempt were 1.36 (0.82, 2.26, p=0.238).

The crude hazard ratio for suicide ideation was 3.04 (2.06, 4.4, p<0.0001); the adjusted hazard ratio (full model with additional baseline covariates) for suicide ideation was 2.22 (1.47, 3.34, p=0.0001).

10.4.1.1.1. Stratification by age group

Table APP.13 presents incidence rates and hazard ratios of suicide attempt and suicide ideation across duloxetine-exposed and unexposed cohorts.

When stratifying by age group, the majority of patients (70.4%) were between 25 to 64 years of age; no trend analyses were conducted due to small numbers of patients in other age groups.

- In the 25-64 year age group, the crude incidence rate of suicide attempt was 165.78 per 100,000 person-years for the duloxetine-treated cohort and 61.72 per 100,000 person-years for the duloxetine-untreated cohort.

The crude incidence rate of suicide ideation for the **overall** duloxetine-treated cohort was 210.92 per 100,000 person-years compared to a crude incidence rate of 69.87 per 100,000 person-years for the duloxetine-untreated cohort. Similarly, the majority of patients were between 25 to 64 years of age.

- In the 25-64 year age group, the crude incidence rate of suicide ideation was 254.98 per 100,000 person-years for the duloxetine-treated cohort and 83.58 per 100,000 person-years for the duloxetine-untreated cohort.

10.4.1.1.2. Stratification by recorded baseline depression

Incidence Rate of Suicidality Stratified by Recorded Baseline Depression (Baseline Depression, Historical Depression and No Recorded Depression): Table APP.14 presents incidence rates and hazard ratios of suicide attempt and suicide ideation stratified by depression status across duloxetine-treated and untreated cohorts.

Patients without recorded depression had the lowest incidence rate for both suicidal attempts and suicidal ideation. Among patients with depression diagnoses, patients who had depression diagnosis 1 year prior to index date had a lower incidence rate of suicidal attempt and higher incidence of suicidal ideation compared to patients who had baseline depression (within 1 year prior to index date) for both duloxetine-treated and untreated patients.

For patients with historical depression, the crude incidence rate of **suicide attempt** for the duloxetine-treated cohort was 208.28 per 100,000 person-years compared to a crude incidence rate of 136.77 per 100,000 person-years for the duloxetine-untreated cohort; in contrast, for patients with baseline depression, the crude incidence rate of suicide attempt for the duloxetine-treated cohort was 247.12 per 100,000 person-years compared to a crude incidence rate of 123.12 per 100,000 person-years for the duloxetine-untreated cohort. For patients with no recorded depression, the crude incidence rate of suicide

- attempt for the duloxetine-treated cohort was 89.94 per 100,000 person-years compared to a crude incidence rate of 34.44 per 100,000 person-years for the duloxetine-untreated cohort.
- For patients with baseline depression, the crude incidence rate of **suicide ideation** for the duloxetine-treated cohort was 427.80 per 100,000 person-years compared to a crude incidence rate of 158.50 per 100,000 person-years for the duloxetine-untreated cohort; in contrast, for patients with historical depression, the crude incidence rate of suicide ideation for the duloxetine-treated cohort was 441.71 per 100,000 person-years compared to a crude incidence rate of 147.15 per 100,000 person-years for the duloxetine-untreated cohort. For patients with no recorded depression, the crude incidence rate of suicidal ideation for the duloxetine-treated cohort was 137.65 per 100,000 person-years compared to a crude incidence rate of 55.80 per 100,000 person-years for the duloxetine-untreated cohort.

10.4.2. Sensitivity analysis 2: Subgroup analysis: Restriction to patients without recorded baseline depression and/or antidepressant use (duloxetine vs. non-exposed patients)

A subgroup analysis was conducted excluding patients with baseline depression diagnosis. After adjusting for other covariates, the association between duloxetine and suicidal outcomes was numerically increased. Details of these analyses are presented in Table APP.15, Table APP.16, and Table APP.17.

10.4.3. Sensitivity analysis 3: Varying exposure windows: (duloxetine vs. non-exposed)

In the main analyses, patients were allowed an up to 30-day washout period before they were considered to be no longer exposed. In these sensitivity analyses, the gap variable was extended to 60 and 90 days. Similar to the results of the results of the main analyses, patients with SUI treated with duloxetine had higher risks for suicide attempts and suicidal ideation when compared to patients with SUI not treated with duloxetine. Further details can be found in Table APP.18, Table APP.19, Table APP.20, and Table APP.21.

10.4.4. Sensitivity analysis 4: Possible outcomes

These analyses were performed to include additional events that may have been suicide-related but there was not clear intent of self-harm. Similar to the results of the results of the main analyses, patients with SUI treated with duloxetine had higher risks for possible suicide attempts and suicidal ideation when compared to patients with SUI not treated with duloxetine. Further details can be found in Table APP.22.

10.4.5. Post hoc analysis 1: Propensity score stratification

This post-hoc analysis was performed to investigate assess the robustness of the main analysis results. Propensity scores were calculated for all patients, which was an estimation of the probability of patients being treated by duloxetine given the measured baseline characteristics. These propensity scores were used to stratify patients into 5 strata: 1st quintile (N=734 duloxetine-treated and N=4548 unexposed patients), 2nd quintile (N=778 duloxetine-treated and N=4206 unexposed patients), 3rd quintile (N=910 duloxetine-treated and N=4378 unexposed patients), 4th quintile (N=1132 duloxetine-treated and N=4058 unexposed patients), and 5th quintile (N=1701 duloxetine-treated and N=3484 unexposed patients). Similar to the results of the main analyses, patients with SUI treated with duloxetine had higher risks for suicide attempts when compared to patients with SUI not treated with duloxetine. Further details can be found in Table APP.23, Table APP.24, Figure APP.1, and Figure APP.2.

10.4.6. Post hoc analysis 2: Using a different comparator group

Upon review of the patient characteristics for the main study analyses, it was apparent that many of the patients with SUI (both those treated with duloxetine and those not treated with duloxetine) had depression and had received other psychiatric treatment in the past. This raised a concern that there may be significant differences in baseline characteristics (i.e., more psychiatric comorbidities between duloxetine-treated patients with SUI compared to patients with SUI not treated with duloxetine). If this were true then regression analyses adjusting for diagnosed depression may or may not be able to fully account for the psychiatric comorbidity. Some patients with SUI not treated with duloxetine had received treatment with other antidepressants, so comparisons were made between these 2 groups (e.g., SUI plus duloxetine and SUI plus other antidepressant) as it was hypothesised these 2 groups might be more comparable with respect to recorded depression as an important risk factor for suicidality. Of note, this post hoc analysis suffered from inadequate sample size and statistical power.

10.4.6.1. Baseline characteristics

Table APP.25 presents baseline demographic characteristics stratified by propensity score among duloxetine-treated and other antidepressant-treated women with a SUI diagnosis.

Overall, duloxetine-treated patients were comparable to patients treated with other antidepressants, however, they were younger (mean age of 55.8 vs. 58.5) and were treated with fewer psychiatric therapies (38.1% vs. 47.9% [any selected] and 19.5% vs. 27.1% [other selected]). Baseline depression (10.7% vs. 10.9%) and other comorbidities were comparable between duloxetine-treated and other antidepressant-treated patients. Additionally, the majority of patients treated with duloxetine and other antidepressants did not have a recorded diagnosis of depression; only 20.0% of duloxetine-treated patients and 18.5% of other antidepressant-treated patients had a recorded diagnosis of historical depression. The reasons for this finding are unclear as, even if a diagnosis of depression was made in a hospital setting by a psychiatric specialist, the information would be automatically communicated to the respective general practitioners. It appears however that this important information was simply not thereafter recoded in the database itself in the vast majority of cases where patients were being treated with antidepressants.

10.4.6.2. Cox regression (duloxetine-treated vs. other antidepressant-treated)

Table APP.26 presents the crude and adjusted associations between exposure (duloxetine treated versus other antidepressants treated comparator) and the risk of each suicidality outcome among women with a SUI diagnosis.

The crude hazard ratios for **suicide attempt and non-fatal suicide attempt** were 1.55 (0.52, 4.57, p=0.43); after adjusting for baseline depression, psychiatric medication use, and other imbalanced covariates (fully adjusted model), the adjusted hazard ratios for suicide attempt and non-fatal suicide attempt were 1.94 (0.63, 5.95, p=0.25), demonstrating that treatment with duloxetine presented a numerically but not statistically significant increased risk of suicide attempt and non-fatal suicide attempt compared to another antidepressant.

The crude hazard ratio for **suicidal ideation** was 0.49 (0.15, 1.59, p=0.24); the adjusted hazard ratio (full model with additional baseline covariates) for suicide ideation was 0.51 (0.16, 1.67, p=0.27), suggesting a numerically but not statistically significant decreased risk of suicide ideation with duloxetine versus another antidepressant.

Additional post-hoc analyses, although of inadequate sample size and statistical power, were performed. Overall, these analyses show that there are no differences between the two cohorts. A plot of the propensity scores shows an overlapping distribution for duloxetine treated and treated with another antidepressant. Further details can be found in Table APP.27. Figure APP.3, and Figure APP.4.

10.4.7. Summary of additional analyses

10.4.7.1. Sensitivity analysis 1: Intent-to-treat

This analysis was the follow-up for both treated and untreated until the end of their follow-up time/data availability/occurrence of outcome. After adjusting for baseline depression, psychiatric medication use, and other imbalanced covariates, the association between duloxetine and suicidal outcomes did not reach statistical significance.

10.4.7.2. Sensitivity analysis 2: Subgroup

The subgroup analysis was conducted excluding patient with baseline depression diagnosis recorded in the database, after adjusting for other covariates, the association between duloxetine and suicidal outcomes was numerically increased. The observation could be attributable to unmeasured confounding and unrecorded depression diagnosis (SUI patient were prescribed with duloxetine for dual purpose) (see Annex 2).

10.4.7.3. Sensitivity analysis 3: Variable exposure

When the gap variable was extended from 30 to 60 and 90 days, the results were consistent with the main analyses using 30 days.

10.4.7.4. Sensitivity analysis 4: Possible events

When additional events that may have been suicide-related but there was no clear intent at self-harm were included, the results were consistent with the main analyses using a strict definition for suicidality (Annex 2).

10.4.7.5. Post-hoc analysis1: propensity score stratification

The results of the main analyses using multivariate regression were supported after using propensity score stratification as an additional method to adjust for baseline variables.

10.4.7.6. Post-hoc analysis 2: different comparator group

When duloxetine-treated patients with SUI were compared to patients with SUI who were treated with other antidepressants, the association was not statistically significant.

10.5. Adverse events/adverse reactions

Not applicable because individual case data were not collected/evaluated.

11. Discussion

11.1. Key results

- Using the as-treated analysis described above, the adjusted hazard ratios were 2.92 (1.44, 5.95, p=0.003) and 5.06 (1.56, 16.45, p=0.007), depending on the length of follow-up for untreated patients (either censored as their matches or end of their records), suggesting an approximately three- to five-fold increased risk of suicidal attempt with duloxetine treatment, after adjusting for measured/recorded important risk factors.
- Duloxetine-treated patients with SUI had more baseline psychiatric comorbidities compared to untreated patients; for example, after matching, duloxetine-treated patients still had a higher proportion of baseline depression (14.44% vs.9.95%) and a history of depression (27.06% vs. 19.29%) compared to untreated patients. Furthermore, they were more likely to have been exposed to any psychiatric medication (54.14% vs. 38.23%), which may have been due to the severity of depression compared to untreated patients.
- Among the sensitivity and post hoc analyses, of particular interest is the comparison of duloxetine-treated patients with SUI to patients with SUI treated with other antidepressants, which identified that the baseline characteristics were comparable between the cohorts, e.g., depression (10.7% vs. 10.9% respectively) and other comorbidities.
- A large majority of patients using antidepressants (about 89%) failed to have a recorded diagnosis of baseline depression, a key risk factor of suicidality that is defined by GP's diagnosis codes.

11.2. Limitations

The study findings were likely affected by the potential bias in the study design (see Section 9.6). Furthermore, as with other electronic medical records, the CPRD database has its limitations. Some of the limitations resulted from data structure and others are due to the sample population. Key limitations include the following:

- Data are collected during patient encounters using a system that is designed for individual patient care, not research. The presence or absence of disease may not be accurate, as the diagnostic code may be incorrectly coded or included as rule-out criteria rather than actual disease. The diagnosis of depression and other psychiatric condition were solely based on READ codes without considering clinical symptoms, which were infrequently captured in the database. Thus, these comorbidities were not validated.
- Prescription data documented in the database reflects the behaviour of the prescriber and not the patient, who may or may not fill the prescription at the pharmacy and may not actually take the medication, even if the prescription is filled.
- CPRD contains electronic medical records to capture diagnosis, prescriptions and procedures encountered at a general practitioner (GP)'s office or accessible by GP. For example, we observed that less than 11% of the antidepressant–treated patients had any diagnoses of depression at baseline (see Table APP.25), however, we would expect that the majority of patients should have depression diagnosed prior to the prescription of an

antidepressant, regardless of whether the diagnosis is made by the GP or by another clinician in a hospital setting. The reasons for this finding are unclear but it is a significant limitation to our study.

- The positive predictive value of suicidality from READ or Oxford Medical Information System medical codes within the CPRD database is low. Thomas and colleagues showed that suicidal outcomes have limited positive predictive value (Thomas et al. 2013). The read code algorithms had very low sensitivity (26.1%; 95% CI: 24.3–28.0%) and positive predictive value (55.5%; 95% CI: 52.5–58.5%), and underestimated suicide rates in both sexes for all age groups. However, our study has adapted an algorithm that has been independently reviewed by two Lilly psychiatrists, and the code list was finalised by consensus. Given this concern, we also defined the outcomes in several different ways to assess the impact of using different sets of read codes. A database approach may not be the most reliable resource to define suicidal outcomes, although, at the time the study was initiated, it was the only viable option available.
- As of March 2017, the CPRD database captures information from >24 million patients from >800 GP practices. However, a small sample size may be obtained for certain outcomes and result in a limited subgroup analysis.
- There is always the possibility of residual confounding, although the application of propensity score matching aims to minimise any confounding factors between the cohorts.

11.3. Interpretation

Although the present study found an association between duloxetine use and suicide-related outcomes (non-fatal suicidal attempt and suicidal ideation) in duloxetine-treated patients with SUI compared to untreated patients with SUI, these findings are likely to be influenced by the imbalance of comorbid depression within the duloxetine patient population and inability to accurately measure and adjust for this important risk factor for suicide. Postmarketing experience has demonstrated that duloxetine-treated patients with SUI have a higher rate of comorbid psychiatric conditions than the broader SUI population. This is consistent with the observations from the present study and plausible given that duloxetine is indicated for both MDD and SUI.

The following discussion will address these methodological concerns and their likely impact on interpretation of the findings in more detail.

Confounding in the SUI population

Findings from the current analysis appear to demonstrate that the SUI patient population treated with duloxetine in the CPRD do not constitute an “unconfounded” patient population in which to investigate duloxetine use and suicidality risk. Contrary to our original assumption in 2004 when this study was first proposed, there was no reason to suppose that patients diagnosed with a non-psychiatric condition like SUI would be at a higher risk of suicidality, and the analytical methods using the CPRD database were set up on the basis that the confounder factor (including depression) could be well adjusted.

Due to the nature of the study population, an observational study can be biased by uncontrolled confounding factors. Lacking randomisation, measured and unmeasured confounding factors are major limitations of any observational study. As mentioned in Section 11.2, not all suicidal outcome risk factors are recorded and hence measurable in the CPRD database (e.g., depression symptoms and/or severity, personal and family history of suicidality etc.), therefore, the findings need to be interpreted with the possibility that residual confounding factors for which the analysis was unable to adjust for may have existed in the statistical model. The changes in hazard ratios observed between the crude and fully adjusted models indicated that the association was greatly impacted by baseline comorbidities and raised the concern of residual confounding. For example, when adjusting for risk factors that were imbalanced between the treated vs. untreated cohorts (e.g., depression, other psychiatric conditions, and medication use), the association between duloxetine exposure and suicidality risk changed from crude HR = 6.70, (95% CI: 3.36, 13.37) to adjusted HR= 2.92, (95% CI: 1.44, 5.95). This illustrates the heterogeneity in the baseline risk factors between the cohorts and the impact of these confounding factors on the association between duloxetine and suicidality.

Change in Analytical Methodology

There are some differences in the fifth analysis compared to the previous 4 analyses, mainly the previous analyses used "intent-to-treat" methodology, instead of "as-treated" methodology. The analytical method was amended because it was observed that untreated patients often had significantly greater periods of observation compared to duloxetine-treated patients (270 days vs. 10 years for duloxetine-treated and untreated cohorts, respectively), so an "as-treated (censoring)" analysis was adopted to attempt to equalise the "exposure" intervals. The study used an "as treated" analysis as the primary analysis; and modified the analysis to more appropriately assess the association during a pharmacological temporal window. The intent-to-treat approach, which was used as a primary analysis previously, was repeated in the present study as sensitivity analysis #1. Consistent with previous results, the HR was 1.36 [95%CI 0.82, 2.26; p=0.238]. Additional sensitivity analyses (e.g., subgroup analysis, varying exposure windows and outcome definition) and 2 post hoc analyses (i.e., propensity score stratification to improve measured confounders and comparison to other antidepressant cohort to improve comparability between cohorts) were conducted with the attempt to improve the balance in risk factors between the study cohorts. Although these analyses were designed to enhance our understanding of the association, results of these additional analyses were limited by small sample size, statistical power, and the inability to robustly measure important risk factors, e.g., depression.

Incomplete Recording of Depression Diagnosis in CPRD

Depression as a key risk factor was defined using READ codes (see Annex 2). The findings of this analysis clearly demonstrated that a putative depression diagnosis was not completely recorded in CPRD, which was reflected as a key finding in comparison between duloxetine and other (non-duloxetine) antidepressants users. The post hoc analysis was proposed to evaluate patients with similar baseline psychiatric conditions as duloxetine SUI users to potentially minimize the bias in the study. The findings illustrated that psychiatric comorbidities were

comparable between the duloxetine and other antidepressant users cohorts, indicating that duloxetine-treated patients have more suicidality risk factors (e.g., depression) than the untreated SUI population. The data also showed a poor ascertainment of important risk factors (e.g., depression), as reflected by the low proportion of recorded depression diagnoses within the non-duloxetine antidepressant cohort (11% baseline depression). This number would be expected to be much higher in a population of patients taking antidepressants. This illustrates that depression diagnosis is incompletely captured in the database. Furthermore, the impact of depression on the incidence of suicidality is substantial as shown in Table APP.5. Stratifying by baseline depression, the incidence of suicidal attempt was increased by about 4-fold among untreated patients with SUI with and without recorded baseline depression (123.12 per 100,000 person-years vs. 34.44 per 100,000 person-years). Thus, as this variable is poorly captured in the database and duloxetine has both an indication for MDD and SUI, the statistical models cannot accurately adjust/account for this confounder.

The lack of confounder ascertainment is important because it limits our ability to compare (and adjust for risk factors) duloxetine-treated patients in the primary analysis. This can result in an overestimate of the association, as duloxetine-treated patients with SUI more closely resemble antidepressant users assumed to have underlying depression (though not captured in the database) and the data do not allow for the adjustment.

No Other Viable Data Sources

There are no other viable data sources to study this research question because the patient population is small and highly confounded by comorbid depression (recorded and not recorded).

The present observational study does not have an advantage over other data sources (i.e., RCT) in terms of study design and statistical power. Due to the slow increase in duloxetine dispensing among patients with SUI, the sample size was a challenge for studying the group of duloxetine-treated patients with SUI and suicide-related outcomes. In the present study, the number of duloxetine-treated patients with SUI was 5,255 (3119 person years), which was accumulated over a long time period (286 in 2006, 1020 in 2007, 1346 in 2008, 2398 in 2010). While the primary analysis had a little over 80% power to detect a difference (Annex 2), the power was limited for the subgroup analyses.

Moreover, other observational data sources, e.g., THIN database, will not be able to overcome the limitations mentioned above in the study design, primarily confounding by indication and confounding by severity. Therefore, an observational approach is not feasible to further investigate duloxetine use and suicide-related outcomes among SUI patients due to uncontrolled confounding issues. Observational studies investigating the risk of suicidality among other duloxetine-indicated patients have been conducted by MAH, see details in Section 12.

While duloxetine has been approved since 2004, there is a large amount of well-controlled RCT data available and other observational studies that have been published regarding suicidality risk. A critical review of the duloxetine randomised clinical trial database was made (detailed in Section 12 and Appendix 2) and another observational study among psychiatric patients was discussed (detailed in Section 12) below.

11.3.1. Benefit risk assessment

Duloxetine was approved based on a benefit/risk assessment. There has been no further efficacy data collected to suggest that the benefit has changed. Considering the study findings are inconclusive, there is no new information to suggest a change in risk profile. Based on the data from placebo-controlled clinical and open-label studies (Appendix 3) and spontaneous postmarketing data (Appendix 4), over and above what is already addressed in the SmPC and outlined in the risk management plan, Lilly considers that there is no conclusive evidence of an increased risk of suicidality associated with the use of duloxetine. Therefore, there is no new information to change the benefit/risk of using duloxetine for the treatment of SUI.

11.4. Generalisability

The CPRD database is an ongoing primary care database of anonymised medical records from general practitioners, with approximately 8.0% of the UK population included. Thus, patients are broadly representative of the UK general population in terms of age, sex, and ethnicity and are, in theory, generalisable to larger populations.

12. Other information

12.1. Randomised clinical trials

Accumulated patient exposures from randomised clinical trials (RCT) have grown during the post marketing period, since the initial observational analysis was proposed, and the sample size has grown larger compared to that in the CPRD database, which analyzed 5255 SUI patients treated by duloxetine. Analyses of the integrated clinical trial database of adult patients from placebo-controlled studies of duloxetine were performed in 2006, 2010, 2013, and, most recently, in 2017. All analyses were consistent throughout the years (see Appendix 4).

The most recent analysis conducted was an integrated clinical trial database analysis of adult patients from placebo-controlled studies of duloxetine on studies completed as of 21 FEB 2017. Patients treated for all indications were included and the database contained all placebo-controlled SUI studies. Adverse events were searched for events related to suicide using MedDRA preferred terms including: Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Poisoning deliberate, Self injurious behaviour, Self injurious ideation, Suicidal behaviour, Suicidal ideation, and Suicide attempt. There were 14058 total duloxetine-treated patients (2646.83 PY of exposure) and 10820 placebo-treated patients (2102.35 PY of exposure) and a total of 52 patients with at least one treatment-emergent suicidal related event (duloxetine arm: n = 34, placebo arm:n = 18). The incidence rate of suicide-related risks was not statistically significantly different between treatment groups (12.85 events per 1000 PY for the duloxetine-treated cohort vs. 8.56 events per 1000 PY for the placebo-treated cohort). The relative risk for suicide-related events was 1.50 (0.85, 2.66, p=0.164).

In summary, there was not a statistically significantly higher risk of suicidality events observed with duloxetine treatment versus placebo in duloxetine-treated patients in all indications, consistent with previous analyses of the RCT database.

12.2. Other observational studies

Lilly has been unable to identify any other independent observational studies have been published to investigate suicidality risk among SUI patients .

Given the issue of suicidality and associated use of SSRI since 2004, the MAH has conducted another observational study published by Valuck et al. (2016) to address the association between duloxetine and suicidality risk among MDD patients, who are at a higher risk of suicidal behaviours due to the underlying disease. The Valuck study involved much larger study cohorts (n= 52355 from the incident depression cohort and n=75756 from the general population sample) than has been possible with the current duloxetine-treated SUI study using the CPRD and this study also reported a lack of association among the high risk patient population.

The study findings are detailed below:

The observational study (Valuck et al. 2016) compared the use of antidepressants and the risk of suicidal attempts among depressed adults. The study was a propensity score-matched retrospective cohort study, utilising data from the IMS life link database and multiple comparator

groups, in addition to antidepressant drug class vs. class comparisons, and a general population cohort was included to estimate the association between the underlying illness (depression) and suicide attempt. Among adults (aged 25 to 64 years, n=113,710), the association between SNRI exposure and suicidal attempts varied significantly by comparators groups.

- When comparing patients using SNRIs to the general population, HR=9.0 (95% CI: 3.60, 22.50), or comparing patients using SSRIs to general population, HR= 6.87 (95% CI: 3.10, 15.20), which demonstrated the impact of underlying disease (depression) on the study findings.
- When comparing patients using SNRIs to untreated depressed patients, HR= 0.85 (95% CI: 0.17, 4.19), the association was no longer significant and the SNRI use had no relationship to suicidal attempts. Although confounding by depression severity may exist between SNRI treated and untreated depressive patients (with treated patients likely being more severe than untreated patients), the two study cohorts were more balanced at baseline risk factors. Furthermore, when comparing patients using SNRI to patients using SSRI, HR = 0.76 (0.36, 1.63). Despite this possible limitation (i.e., imbalance in disease severity) an association was not found, providing assurance about lacking adverse drug effect.

Despite the limitations of being an observational study, the Valuck et al. study included more patients, different comparison cohorts to demonstrate the impact of underlying depression on the association between SNRI exposure and suicidality. Due to the large sample size, the Valuck study was able to provide a more precise estimation of lack of the effect of SNRI use, as a class, and suicidality among patients with MDD.

13. Conclusion

Based on the limitations of the current study, as described above, the results neither confirmed nor refuted that there may be an association between duloxetine use and suicidality. There has been a growing body of evidence providing information on duloxetine use (along with other antidepressants) and suicide since the time of this original commitment (in 2005). This larger and more robust body of evidence does not indicate an association between duloxetine and suicidal behaviour. Although an increased incidence was observed in this study, this finding more likely resulted from insurmountable limitations and confounding factors, such as under diagnosis of depression. Results from the present study were inconsistent with the remainder of evidence that does not support this potential association. Therefore, the results from this study do not change the benefit/risk profile for duloxetine.

Given this and concerns with the limitations of any observational or controlled RCT approach, Lilly does not consider that there is any viable option to further study the potential association between duloxetine treatment and suicidality among the SUI patient population. This position importantly takes into account current risk minimisation wording in the SmPC as well as the existing EU risk management provisions for the product (regardless of indication). These clearly classify suicidality as an important identified risk which is and has always been a highly conservative approach in the face of prevailing data. Lilly does not propose to make any changes to modify these provisions on the basis of the findings of this study.

14. References

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Appendix 1

Table APP.1. Baseline Characteristics Between Duloxetine-treated and Untreated Groups

	Duloxetine-treated n= 5,255		Duloxetine Untreated n= 20,674		
	n	%	n	%	Standardized Difference[a]
Age At Index					
Mean_Age At Index (years)	56.42	.	56.40	.	0.00
Std_Age At Index	13.92	.	13.81	.	0.00
Charlson Comorbidities					
Cancer	22	0.42	280	1.35	**-0.10**
Cerebrovascular Disease	28	0.53	115	0.56	-0.00
Chronic Pulmonary Disease	385	7.33	1103	5.34	0.08
Congestive Heart Disease	6	0.11	72	0.35	-0.05
Dementia	15	0.29	60	0.29	-0.00
Diabetes	388	7.38	968	4.68	**0.11**
Diabetes With Complications	73	1.39	93	0.45	**0.10**
Hemiplegia	.	.	4	0.02	0.00
Metastatic Tumour	2	0.04	55	0.27	-0.06
Mild liver Disease	1	0.02	11	0.05	-0.02
Moderate Liver Disease	.	.	5	0.02	0.00
Myocardial Infarction	7	0.13	39	0.19	-0.01
Peptic Ulcer Disease	3	0.06	22	0.11	-0.02
Peripheral Vascular Disease	13	0.25	49	0.24	0.00
Renal Disease	109	2.07	361	1.75	0.02
Rheumatological Disorder	44	0.84	134	0.65	0.02
Charlson Score					
Mean_Charlson Score	0.25	.	0.21	.	0.06
Std_Charlson Score	0.62	.	0.66	.	0.06
Other Baseline Comorbidities[b]					
Alcohol Abuse	100	1.90	326	1.58	0.03
Anxiety	252	4.80	725	3.51	0.07
Bipolar Disorder	82	1.56	161	0.78	0.07
Borderline Personality Disorder	2	0.04	11	0.05	-0.01
Depression	759	14.44	2058	9.95	**0.14**
Family History of Suicide	2	0.04	2	0.01	0.02
Schizophrenia	9	0.17	18	0.09	0.02
Substance Abuse	52	0.99	142	0.69	0.03
Personal History of Suicide	1	0.02	1	0.00	0.01
Historical Conditions (Before Baseline)[b]					

	Duloxetine-treated n= 5,255		Duloxetine Untreated n= 20,674		
	n	%	n	%	Standardized Difference[a]
Depression	1422	27.06	3988	19.29	**0.19**
Alcohol Abuse	493	9.38	1621	7.84	0.06
Substance Abuse	247	4.70	845	4.09	0.03
Personal History of Suicide	4	0.08	8	0.04	0.02
Baseline Medication[b]					
Any Selected Psychiatric Therapy[c]	2845	54.14	7903	38.23	**0.32**
Antidepressant Therapy	1897	36.10	4845	23.44	**0.28**
Psychosis Therapy	170	3.24	498	2.41	0.05
Hypnotics Anxiolytics Therapy	559	10.64	1224	5.92	**0.17**
Other Selected Psychiatric Therapy[d]	1758	33.45	4276	20.68	**0.29**
Pychiatric Hospitalizations					
History of Hospitalizations	3	0.06	6	0.03	0.01

Abbreviations: n = number of patients

[a] Bolded = standardized difference ≥0.1

[b] Baseline defined as 1 year prior to Index Date.

[c] Treated with one of the following: antidepressant, psychosis, hypnotics anxiolytics, or other selected psychiatric therapies.

[d] Any psychiatric medication that is not listed exclusively as just an antidepressant, psychosis or hypnotic anxiolytics therapy.

Table APP.2. Baseline Characteristics Between SUI and Non-SUI Groups

	SUI Cohort n= 57,393		Non UI Cohort n= 400,069		
	n	%	n	%	Standardized Difference[a]
Age At Index					
Mean_Age At Index (years)	52.18	.	52.16	.	0.00
Std_Age At Index	14.83	.	14.82	.	0.00
Charlson Comorbidities					
Aids	.	.	1	0.00	0.00
Cancer	285	0.50	2675	0.67	-0.02
Cerebrovascular Disease	226	0.39	1391	0.35	0.01
Chronic Pulmonary Disease	2949	5.14	11691	2.92	**0.11**
Congestive Heart Disease	118	0.21	891	0.22	-0.00
Dementia	48	0.08	743	0.19	-0.03
Diabetes	1772	3.09	9802	2.45	0.04
Diabetes With Complications	207	0.36	1167	0.29	0.01
Hemiplegia	3	0.01	43	0.01	-0.01
Metastatic Tumour	16	0.03	311	0.08	-0.02
Mild liver Disease	16	0.03	155	0.04	-0.01
Moderate Liver Disease	8	0.01	48	0.01	0.00
Myocardial Infarction	57	0.10	473	0.12	-0.01
Peptic Ulcer Disease	67	0.12	340	0.08	0.01
Peripheral Vascular Disease	113	0.20	577	0.14	0.01
Renal Disease	531	0.93	3311	0.83	0.01
Rheumatological Disorder	334	0.58	1773	0.44	0.02
Charlson Score					
Mean_Charlson Score	0.14	.	0.11	.	0.06
Std_Charlson Score	0.45	.	0.44	.	0.06
Other Baseline Comorbidities[b]					
Alcohol Abuse	718	1.25	4077	1.02	0.02
Anxiety	1979	3.45	8123	2.03	0.09
Bipolar Disorder	571	0.99	2355	0.59	0.05
Borderline Personality Disorder	21	0.04	114	0.03	0.01
Depression	3907	6.81	18916	4.73	0.09
Family History of Suicide	5	0.01	8	0.00	0.01
Schizophrenia	63	0.11	294	0.07	0.01
Substance Abuse	366	0.64	1792	0.45	0.03
Personal History of Suicide	1	0.00	16	0.00	-0.00
Historical Conditions (Before Baseline)[b]					
Depression	7480	13.03	29755	7.44	**0.19**
Alcohol Abuse	3937	6.86	18888	4.72	0.09

	SUI Cohort n= 57,393		Non UI Cohort n= 400,069		
	n	%	n	%	Standardized Difference[a]
Substance Abuse	1764	3.07	7911	1.98	0.07
Personal History of Suicide	27	0.05	81	0.02	0.02
Baseline Medication[b]					
Any Selected Psychiatric Therapy	20397	35.54	97075	24.26	**0.25**
Antidepressant Therapy	12948	22.56	54618	13.65	**0.23**
Psychosis Therapy	1019	1.78	5836	1.46	0.03
Hypnotics Anxiolytics Therapy	3001	5.23	15524	3.88	0.07
Other Selected Psychiatric Therapy	10359	18.05	53626	13.40	**0.13**
Pychiatric Hospitalizations					
History of Hospitalizations	19	0.03	89	0.02	0.01

Abbreviations: n = number of patients; SUI = stress urinary incontinence; UI = urinary incontinence

[a] Bolded = standardized difference ≥0.1

[b] Baseline defined as 1 year prior to Index Date.

[c] Treated with one of the following: antidepressant, psychosis, hypnotics anxiolytics, or other selected psychiatric therapies.

[d] Any psychiatric medication that is not listed exclusively as just an antidepressant, psychosis or hypnotic anxiolytics therapy.

Table APP.3. Incidence Rates Stratified by Age Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis - Untreated Population Uncensored

		Duloxetine-treated n= 5,255					Duloxetine Untreated n= 20,674					
Outcome	Age group	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	p-value
Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	Overall	5,255	13	0.25	3,119	416.83	20,674	37	0.18	73,034	50.66	0.313
	18-24	24	0	0.00	7	0.0000	75	0	0.00	157	0.00	.
	25-64	3,700	13	0.35	2,168	599.70	14,618	34	0.23	55,086	61.72	0.202
	65 +	1,531	0	0.00	944	0.0000	5,981	3	0.05	17,791	16.86	1.000*
Suicidal Ideation	Overall	5,255	13	0.25	3,123	416.27	20,674	51	0.25	72,989	69.87	0.993
	18-24	24	0	0.00	7	0.0000	75	1	1.33	156	639.54	1.000*
	25-64	3,700	12	0.32	2,177	551.29	14,618	46	0.31	55,035	83.58	0.926
	65 +	1,531	1	0.07	940	106.42	5,981	4	0.07	17,798	22.475	1.000*

Abbreviations: IR = incidence rate; n = number; PY = person years; SUI = stress urinary incontinence.

Chi-Square was used to calculate p-values; Fisher's exact test was used to calculate p-values with cell count < 5 (indicated with asterisk [*]).

Table APP.4. Incidence Rates Stratified by Age Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis – Untreated Population Censored)

		Duloxetine-treated n= 5,255					Duloxetine Untreated n= 20,674					
Outcome	Age group	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	p-value
Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	Overall	5,255	13	0.25	3,119	416.83	20,674	4	0.02	12,275	32.59	<.0001*
	18-24	24	0	0.00	7	0.00	75	0	0.00	21	0.00	.
	25-64	3,700	13	0.35	2,168	599.70	14,618	4	0.03	8,535	46.86	<.0001*
	65 +	1,531	0	0.00	944	0.00	5,981	0	0.00	3,719	0.00	.
Suicidal Ideation	Overall	5,255	13	0.25	3,123	416.27	20,674	7	0.03	12,292	56.95	<.0001
	18-24	24	0	0.00	7	0.00	75	0	0.00	21	0.00	.
	25-64	3,700	12	0.32	2,177	551.29	14,618	7	0.05	8,571	81.68	<.0001
	65 +	1,531	1	0.07	940	106.42	5,981	0	0.00	3,700	0.00	0.204*

Abbreviations: IR = incidence rate; n = number; PY = person years; SUI = stress urinary incontinence. Chi-Square was used to calculate p-values; Fisher's exact test was used to calculate p-values with cell count < 5 (indicated with asterisk [*]).

Table APP.5. Incidence Rates Stratified by Depression Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis - Untreated Population Uncensored)

		Duloxetine-treated n= 5,255					Duloxetine Untreated n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	3	0.40	598	501.71	2,058	7	0.34	5,685	123.12	1.163 (0.3 , 4.508)
	Suicide Ideation	759	4	0.53	603	663.08	2,058	9	0.44	5,678	158.50	1.206 (0.37 , 3.928)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	5	0.35	927	539.39	3,988	13	0.33	9,505	136.77	1.079 (0.384 , 3.032)
	Suicide Ideation	1,422	5	0.35	930	537.66	3,988	14	0.35	9,514	147.15	1.002 (0.36 , 2.786)
No Recorded Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	7	0.19	2,011	348.03	15,941	21	0.13	60,975	34.44	1.469 (0.624 , 3.459)
	Suicide Ideation	3,619	7	0.19	2,008	348.58	15,941	34	0.21	60,932	55.80	0.907 (0.402 , 2.047)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.6. Incidence Rates Stratified by Depression Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis - Untreated Population Censored)

		Duloxetine-treated n= 5,255					Duloxetine Untreated n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CI
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	3	0.40	598	501.71	2,058	1	0.05	1,335	74.90	8.163 (0.848, 78.593)
	Suicide Ideation	759	4	0.53	603	663.08	2,058	4	0.19	1,330	300.76	2.721 (0.679, 10.905)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	5	0.35	927	539.39	3,988	3	0.08	2,310	129.86	4.687 (1.119 19.638)
	Suicide Ideation	1,422	5	0.35	930	537.66	3,988	2	0.05	2,302	86.90	7.032 (1.363, 36.288)
Never had Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	7	0.19	2,011	348.03	15,941	1	0.01	9,509	10.52	30.891 (3.8, 251.158)
	Suicide Ideation	3,619	7	0.19	2,008	348.58	15,941	3	0.02	9,532	31.47	10.296 (2.661 , 39.834)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.7. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis – Untreated Population Uncensored)

	Duloxetine-treated n= 5,255		Duloxetine Untreated n= 20674		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort[a]	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	13	3,119	37	73,034	6.70	3.36	13.37	<.0001	5.51	2.73	11.12	<.0001	4.26	2.08	8.71	<.0001	2.92	1.44	5.95	0.003
Non-Fatal Suicide Attempt	13	3,119	37	73,034	6.70	3.36	13.37	<.0001	5.51	2.73	11.12	<.0001	4.26	2.08	8.71	<.0001	2.92	1.44	5.95	0.003
Suicide Ideation	13	3,123	51	72,989	6.07	3.03	12.14	<.0001	5.00	2.48	10.07	<.0001	4.65	2.29	9.44	<.0001	3.32	1.63	6.78	0.001
Suicide, Completed/Attempt/Ideation	24	3,101	84	72,865	5.86	3.53	9.72	<.0001	4.86	2.91	8.11	<.0001	4.10	2.43	6.91	<.0001	2.87	1.70	4.83	<.0001

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

Note n = 0 for completed suicide outcome.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

Table APP.8. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis – Untreated Population Censored)

	Duloxetine Exposed n= 5,255		Duloxetine Unexposed n= 20,674		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort[a]	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	13	3,119	4	12,275	12.79	4.17	39.22	<.0001	11.44	3.69	35.47	<.0001	9.21	2.90	29.26	0.0002	5.06	1.56	16.45	0.007
Non-Fatal Suicide Attempt	13	3,119	4	12,275	12.79	4.17	39.22	<.0001	11.44	3.69	35.47	<.0001	9.21	2.90	29.26	0.0002	5.06	1.56	16.45	0.007
Suicide Ideation	13	3,123	7	12,292	7.30	2.92	18.30	<.0001	6.26	2.46	15.93	0.0001	5.63	2.18	14.53	0.0004	3.89	1.46	10.43	0.007
Suicide, Completed/Attempt/Ideation	24	3,101	11	12,204	8.58	4.20	17.51	<.0001	7.50	3.64	15.46	<.0001	6.42	3.07	13.44	<.0001	4.00	1.87	8.57	0.0004

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

Note n = 0 for completed suicide outcome.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

Table APP.9. Incidence Rates Stratified by Age Within Patients with a SUI Diagnosis vs. Patients without a SUI Diagnosis

		SUI Cohort n= 57,393					Non UI Cohort n= 400,069					
Outcome	Age group	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	p-value[a]
Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	Overall	57,393	220	0.38	357,979	61.46	400,069	816	0.20	1,749,144	46.65	<.0001
	18-24	867	8	0.92	4,068	196.68	6,057	16	0.26	10,574	151.31	0.002
	25-64	44,234	200	0.45	285,308	70.10	308,486	735	0.24	1,367,108	53.76	<.0001
	65 +	12,292	12	0.10	68,604	17.49	85,526	65	0.08	371,462	17.50	0.424
Suicide Ideation	Overall	57,393	338	0.59	357,468	94.55	400,069	1,057	0.26	1,748,339	60.46	<.0001
	18-24	867	19	2.19	4,061	467.86	6,057	19	0.31	10,571	179.74	<.0001
	25-64	44,234	299	0.68	284,849	104.97	308,486	965	0.31	1,366,360	70.63	<.0001
	65 +	12,292	20	0.16	68,558	29.17	85,526	73	0.09	371,409	19.66	0.009

Abbreviations: IR = incidence rate; n = number; PY = person years; SUI = stress urinary incontinence.

[a] Chi-Square was used to calculate p-values.

Table APP.10. Incidence Rates Stratified by Depression Status Within Patients with a SUI Diagnosis vs. Patients without a SUI Diagnosis

		SUI Cohort n= 5,255					Non UI Cohort n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,907	22	0.56	15,973	137.74	18,916	95	0.50	63,634	149.29	1.122 (0.705 , 1.786)
	Suicide Ideation	3,907	41	1.05	15,909	257.72	18,916	113	0.60	63,602	177.67	1.765 (1.232 , 2.527)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	7,480	46	0.61	27,960	164.52	29,755	148	0.50	97,513	151.78	1.238 (0.888 , 1.725)
	Suicide Ideation	7,480	77	1.03	27,851	276.47	29,755	234	0.79	97,306	240.48	1.312 (1.013 , 1.7)
No recorded Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	48,295	165	0.34	322,004	51.242	361,103	621	0.17	1,619,579	38.343	1.99 (1.676 , 2.363)
	Suicide Ideation	48,295	246	0.51	321,632	76.485	361,103	779	0.22	1,618,957	48.117	2.368 (2.051 , 2.734)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.11. Treatment Differences in the Risk of Each Suicidality Outcome Within Patients with a SUI Diagnosis vs. Patients without a SUI Diagnosis

	SUI Cohort n= 57,393		Non UI Cohort n= 400,069		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (with Depression & Anti-Depressant Use)				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	220	357,979	816	1,749,144	1.36	1.18	1.58	<.0001	1.29	1.11	1.50	0.001	1.04	0.89	1.20	0.639	1.02	0.88	1.19	0.799	0.90	0.77	1.04	0.169
Completed Suicide	8	358,941	45	1,752,008	0.94	0.44	2.00	0.881	0.95	0.45	2.03	0.902	0.80	0.37	1.70	0.558	0.78	0.37	1.66	0.521	0.71	0.33	1.52	0.383
Non-Fatal Suicide Attempt	212	358,013	777	1,749,218	1.38	1.18	1.60	<.0001	1.30	1.11	1.51	0.001	1.04	0.89	1.21	0.605	1.02	0.88	1.19	0.758	0.90	0.77	1.05	0.190
Suicide Ideation	338	357,468	1,057	1,748,339	1.60	1.41	1.81	<.0001	1.49	1.32	1.68	<.0001	1.24	1.09	1.40	0.001	1.22	1.07	1.38	0.002	1.07	0.94	1.21	0.315
Suicide, Completed/Attempt/Ideation	526	356,578	1,757	1,745,715	1.51	1.37	1.67	<.0001	1.42	1.29	1.56	<.0001	1.16	1.06	1.28	0.002	1.15	1.04	1.26	0.007	1.01	0.92	1.12	0.821

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

Table APP.12. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; Intent-to treat Analysis)

	Duloxetine-treated n=5255		Duloxetine Untreated n=20674		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	31	24,720	37	73,034	2.47	1.53	3.98	0.0002	2.25	1.39	3.64	0.001	2.21	1.37	3.59	0.001	1.36	0.82	2.26	0.238
Suicide Ideation	52	24,654	51	72,989	3.04	2.06	4.47	<.0001	2.77	1.88	4.09	<.0001	2.70	1.83	3.99	<.0001	2.22	1.47	3.34	0.0001
Suicide, Completed/Attempt/Ideation	76	24,572	84	72,865	2.69	1.97	3.67	<.0001	2.46	1.80	3.37	<.0001	2.41	1.76	3.30	<.0001	1.65	1.07	2.54	0.024

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

Table APP.13. Incidence Rates Stratified by Age Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; Intent-to treat Analysis)

		Duloxetine-treated n=5255					Duloxetine Untreated n=20674					
Outcome	Age group	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	p-value
Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	Overall	5,255	31	0.59	24,720	125.40	20,674	37	0.18	73,034	50.661	<0.0001
	18-24	24	1	4.17	106	946.87	75	0	0.00	157	0.00	0.242*
	25-64	3,700	30	0.81	18,096	165.78	14,618	34	0.23	55,086	61.72	<0.0001
	65 +	1,531	0	0.00	6,518	0.00	5,981	3	0.05	17,791	16.86	1.000*
Suicide Ideation	Overall	5,255	52	0.99	24,654	210.92	20,674	51	0.25	72,989	69.87	<0.0001
	18-24	24	0	0.00	108	0.00	75	1	1.33	156	639.54	1.000*
	25-64	3,700	46	1.24	18,040	254.98	14,618	46	0.31	55,035	83.58	<0.0001
	65 +	1,531	6	0.39	6,506	92.23	5,981	4	0.07	17,798	22.48	0.007*

Abbreviations: IR = incidence rate; n = number; PY = person years; SUI = stress urinary incontinence.

Chi-Square was used to calculate p-values; Fisher's exact test was used to calculate p-values with cell count < 5 (indicated with asterisk [*]).

Table APP.14. Incidence Rates Stratified by Depression Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; Intent-to-treat Analysis

		Duloxetine-treated n=5255					Duloxetine Untreated n=20674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	7	0.92	2,833	247.12	2,058	7	0.34	5,685	123.12	2.727 (0.953 , 7.802)
	Suicide Ideation	759	12	1.58	2,805	427.80	2,058	9	0.44	5,678	158.50	3.657 (1.535 , 8.715)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	10	0.70	4,801	208.28	3,988	13	0.33	9,505	136.77	2.166 (0.947 , 4.95)
	Suicide Ideation	1,422	21	1.48	4,754	441.71	3,988	14	0.35	9,514	147.15	4.255 (2.158 , 8.39)
Never had Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	17	0.47	18,902	89.935	15,941	21	0.13	60,975	34.441	3.578 (1.886 , 6.789)
	Suicide Ideation	3,619	26	0.72	18,889	137.65	15,941	34	0.21	60,932	55.800	3.386 (2.029 , 5.649)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.15. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis – Untreated Population Uncensored [Baseline Depression Excluded])

	Duloxetine-treated n=5,255		Duloxetine Untreated n=20,674		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort[a]	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	10	2,521	30	67,349	6.82	3.09	15.07	<.0001	5.97	2.69	13.25	<.0001	4.61	2.06	10.30	0.0002	3.17	1.40	7.16	0.006
Non-Fatal Suicide Attempt	10	2,521	30	67,349	6.82	3.09	15.07	<.0001	5.97	2.69	13.25	<.0001	4.61	2.06	10.30	0.0002	3.17	1.40	7.16	0.006
Suicide Ideation	9	2,520	42	67,311	7.70	3.41	17.38	<.0001	7.10	3.13	16.07	<.0001	6.75	2.96	15.39	<.0001	4.89	2.13	11.22	0.0002
Suicide, Completed/Attempt/Ideation	17	2,507	69	67,211	6.39	3.53	11.60	<.0001	5.79	3.19	10.54	<.0001	4.94	2.70	9.03	<.0001	3.49	1.90	6.43	<.0001

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

Note n = 0 for completed suicide outcome.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

Table APP.16. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As-Treated Analysis – Untreated Population Censored [Baseline Depression Excluded])

	Duloxetine-treated n=4,,496		Duloxetine Untreated n=18,616		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort[a]	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	10	2,521	3	10,940	14.47	3.98	52.59	<.0001	13.04	3.56	47.79	0.0001	10.26	2.72	38.74	0.0006	6.40	1.65	24.88	0.007
Non-Fatal Suicide Attempt	10	2,521	3	10,940	14.47	3.98	52.59	<.0001	13.04	3.56	47.79	0.0001	10.26	2.72	38.74	0.0006	6.40	1.65	24.88	0.007
Suicide Ideation	9	2,520	3	10,962	13.12	3.55	48.47	0.0001	13.19	3.55	48.97	0.0001	12.61	3.36	47.30	0.0002	9.06	2.34	35.04	0.001
Suicide, Completed/Attempt/Ideation	17	2,507	6	10,883	12.29	4.85	31.18	<.0001	11.77	4.62	30.01	<.0001	10.39	4.01	26.90	<.0001	7.15	2.70	18.93	<.0001

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

Note n = 0 for completed suicide outcome.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

Table APP.17. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; Intent-to-treat Analysis [Baseline Depression Excluded])

	Duloxetine-treated n=4496		Duloxetine Untreated n=18616		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort[a]	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	24	21888	30	67349	2.47	1.45	4.23	0.001	2.30	1.34	3.94	0.003	2.25	1.31	3.86	0.003	1.44	0.82	2.55	0.206
Non-Fatal Suicide Attempt	24	21888	30	67454	2.47	1.45	4.23	0.001	2.30	1.34	3.94	0.003	2.25	1.31	3.86	0.003	1.44	0.82	2.55	0.206
Suicide Ideation	40	21849	42	67311	2.96	1.92	4.56	<.0001	2.78	1.80	4.30	<.0001	2.71	1.75	4.19	<.0001	2.33	1.48	3.68	0.0003
Suicide, Completed/Attempt/Ideation	58	21786	69	67211	2.61	1.84	3.70	<.0001	2.45	1.73	3.48	<.0001	2.39	1.68	3.40	<.0001	2.08	1.24	3.47	0.005

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

Note n = 0 for completed suicide outcome.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt.

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Table APP.18. Incidence Rates Stratified by Depression Status Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; As Treated Analysis -- Untreated Population Uncensored with 60-day Exposure Gap and Extension)

		Duloxetine-treated n= 5,255					Duloxetine Unexposed n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	4	0.53	814	491.20	2,058	7	0.34	5,685	123.12	1.552 (0.453 , 5.318)
	Suicide Ideation	759	5	0.66	820	609.58	2,058	9	0.44	5,678	158.50	1.51 (0.504 , 4.519)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	5	0.35	1,255	398.47	3,988	13	0.33	9,505	136.77	1.079 (0.384 , 3.032)
	Suicide Ideation	1,422	5	0.35	1,264	395.47	3,988	14	0.35	9,514	147.15	1.002 (0.36 , 2.786)
Never had Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	9	0.25	3,002	299.83	15,941	21	0.13	60,975	34.441	1.89 (0.865 , 4.13)
	Suicide Ideation	3,619	8	0.22	3,002	266.52	15,941	34	0.21	60,932	55.800	1.037 (0.479 , 2.241)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.19. Incidence Rates Stratified by Depression Status Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; (As Treated Analysis -- Untreated Population Censored with 60-day Exposure Gap and Extension)

		Duloxetine-treated n= 5,255					Duloxetine Unexposed n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	4	0.53	814	491.20	2,058	2	0.10	1,840	108.72	5.446 (0.996 , 29.796)
	Suicide Ideation	759	5	0.66	820	609.58	2,058	5	0.24	1,840	271.81	2.723 (0.786 , 9.432)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	5	0.35	1,255	398.47	3,988	4	0.10	3,115	128.40	3.514 (0.942 , 13.106)
	Suicide Ideation	1,422	5	0.35	1,264	395.47	3,988	3	0.08	3,121	96.124	4.687 (1.119 , 19.638)
Never had Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	9	0.25	3,002	299.83	15,941	1	0.01	13,910	7.1891	39.74 (5.033 , 313.766)
	Suicide Ideation	3,619	8	0.22	3,002	266.52	15,941	5	0.03	13,953	35.836	7.061 (2.309 , 21.597)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.20. Incidence Rates Stratified by Depression Status Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; (As Treated Analysis -- Untreated Population Uncensored with 90-day Exposure Gap and Extension)

		Duloxetine-treated n= 5,255					Duloxetine Unexposed n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	4	0.53	926	431.86	2,058	7	0.34	5,685	123.12	1.552 (0.453 , 5.318)
	Suicide Ideation	759	5	0.66	933	535.73	2,058	9	0.44	5,678	158.50	1.51 (0.504 , 4.519)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	5	0.35	1,415	353.24	3,988	13	0.33	9,505	136.77	1.079 (0.384 , 3.032)
	Suicide Ideation	1,422	5	0.35	1,426	350.59	3,988	14	0.35	9,514	147.15	1.002 (0.36 , 2.786)
Never had Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	10	0.28	3,572	279.95	15,941	21	0.13	60,975	34.441	2.101 (0.988 , 4.464)
	Suicide Ideation	3,619	9	0.25	3,571	252.05	15,941	34	0.21	60,932	55.800	1.166 (0.559 , 2.434)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.21. Incidence Rates Stratified by Depression Status Within Women with a SUI Diagnosis (Duloxetine-treated vs. Untreated Patients; (As Treated Analysis -- Untreated Population Censored with 90-day Exposure Gap and Extension)

		Duloxetine-treated n= 5,255					Duloxetine Unexposed n= 20,674					Relative Risk
Depression	Outcome	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	RR and CL
Baseline Depression	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	759	4	0.53	926	431.86	2,058	2	0.10	2,142	93.384	5.446 (0.996 , 29.796)
	Suicide Ideation	759	5	0.66	933	535.73	2,058	5	0.24	2,142	233.48	2.723 (0.786 , 9.432)
Historical Depression (Prior to Baseline)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	1,422	5	0.35	1,415	353.24	3,988	4	0.10	3,608	110.86	3.514 (0.942 , 13.106)
	Suicide Ideation	1,422	5	0.35	1,426	350.59	3,988	3	0.08	3,615	82.990	4.687 (1.119 , 19.638)
Never had Depression (Baseline/Historical)	Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	3,619	10	0.28	3,572	279.95	15,941	3	0.02	16,349	18.350	14.721 (4.049 , 53.515)
	Suicide Ideation	3,619	9	0.25	3,571	252.05	15,941	6	0.04	16,389	36.610	6.621 (2.355 , 18.614)

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence.

Table APP.22. Treatment Differences in the Risk of Each Suicidality Outcome Within Patients with a SUI Diagnosis vs. Patients without a SUI Diagnosis (Intent-to-treat Analysis Population with Possible Suicide Attempts Included)

	Duloxetine-treated n=5255		Duloxetine Untreated n= 20674		Hazard Ratio Base Model				Hazard Ratio Adjusted with Depression				Hazard Ratio Adjusted (Full Model)[a]				Hazard Ratio Adjusted (Full Model + Additional Baseline Covariates)[b]			
Cohort	n	Person Yrs	n	Person Yrs	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	71	24,494	100	72,445	2.09	1.54	2.83	<.0001	1.89	1.39	2.56	<.0001	1.66	1.21	2.27	0.002	1.34	0.98	1.84	0.064
Completed Suicide	1	24,741	0	72,799	7.03E7	0.00	0.00	0.997	2.09E8	0.00	0.00	0.998	2.15E8	0.00	.	0.998	3.44E8	0.00	.	0.999
Non-Fatal Suicide Attempt	71	24,494	100	72,445	2.09	1.51	2.83	<.0001	1.89	1.39	2.56	<.0001	1.66	1.21	2.27	0.002	1.34	0.98	1.84	0.064
Suicide Ideation	45	24,597	48	72,632	2.79	1.86	4.19	<.0001	2.55	1.69	3.83	<.0001	2.39	1.58	3.61	<.0001	2.00	1.32	3.03	0.001
Suicide, Completed/Attempt/Ideation	107	24,371	140	72,293	2.26	1.76	2.91	<.0001	2.07	1.61	2.67	<.0001	1.89	1.46	2.45	<.0001	1.55	1.20	2.00	0.001

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; PY = person years; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

[a] Covariates for Full Model - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of depression, History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt.

[b] Covariates for Full Model + Additional Selected Baseline Covariates - Duloxetine Status, Current depression, Psychiatric comorbidities, History of depression History of psych hospitalization, History of family suicide attempt, Age, Charlson Score, Cancer, Diabetes, Any Selected Psychiatric Therapy, Hypnotics Anxiolytics, Other Selected Psychiatric Therapy, History of personal suicide attempt..

Table APP.23. Baseline Demographics and Characteristics Stratified by Propensity Score (1st through 3rd Quintiles) Between Duloxetine-treated and Untreated Groups (ITT population)

	1st Quintile					2nd Quintile					3rd Quintile				
	Duloxetine-treated n=734		Duloxetine Untreated n=4548			Duloxetine-treated n=778		Duloxetine Untreated n=4206			Duloxetine-treated n=910		Duloxetine Untreated n=4378		
	n	%	n	%	SD[a]	n	%	n	%	SD[a]	n	%	n	%	SD[a]
Age At Index															
Mean_Age At Index	60.60	.	60.73	.	-0.01	52.68	.	52.84	.	-0.02	53.50	.	54.28	.	-0.05
Std_Age At Index	11.88	.	11.89	.	-0.01	10.76	.	10.62	.	-0.02	16.36	.	16.39	.	-0.05
Charlson Comorbidities															
Cancer	21	2.86	265	5.83	**-0.15**	**.**	.	6	0.14	0.00	1	0.11	9	0.21	-0.02
Cerebrovascular Disease	4	0.54	47	1.03	-0.06	1	0.13	3	0.07	0.02	3	0.33	28	0.64	-0.05
Chronic Pulmonary Disease	3	0.41	29	0.64	-0.03	3	0.39	16	0.38	0.00	90	9.89	437	9.98	-0.00
Congestive Heart Disease	6	0.82	66	1.45	-0.06	.	.	3	0.07	0.00	.	.	2	0.05	0.00
Dementia	1	0.14	22	0.48	-0.06	.	.	5	0.12	0.00	6	0.66	12	0.27	0.06
Diabetes	2	0.27	45	0.99	-0.09	.	.	5	0.12	0.00	44	4.84	204	4.66	0.01
Diabetes With Complications	1	0.14	8	0.18	-0.01	.	.	1	0.02	0.00	1	0.11	.	.	0.00
Hemiplegia	.	.	4	0.09	0.00	NA		NA			NA		NA		
Metastatic Tumour	2	0.27	55	1.21	**-0.11**	NA		NA			NA		NA		
Mild liver Disease	.	.	10	0.22	0.00	NA		NA			1	0.11	1	0.02	0.03
Moderate Liver Disease	.	.	5	0.11	0.00	NA		NA			NA		NA		
Myocardial Infarction	3	0.41	24	0.53	-0.02	1	0.13	1	0.02	0.04	1	0.11	5	0.11	-0.00
Peptic Ulcer Disease	1	0.14	17	0.37	-0.05	.	.	2	0.05	0.00	2	0.22	2	0.05	0.05

	1st Quintile					2nd Quintile					3rd Quintile				
	Duloxetine-treated n=734		Duloxetine Untreated n=4548			Duloxetine-treated n=778		Duloxetine Untreated n=4206			Duloxetine-treated n=910		Duloxetine Untreated n=4378		
	n	%	n	%	SD[a]	n	%	n	%	SD[a]	n	%	n	%	SD[a]
Peripheral Vascular Disease	2	0.27	15	0.33	-0.01	1	0.13	1	0.02	0.04	3	0.33	9	0.21	0.02
Renal Disease	1	0.14	44	0.97	**-0.11**	.	.	7	0.17	0.00	35	3.85	121	2.76	0.06
Rheumatological Disorder	.	.	12	0.26	0.00	1	0.13	5	0.12	0.00	13	1.43	44	1.01	0.04
Other Baseline Comorbidities															
Alcohol Abuse	10	1.36	86	1.89	-0.04	1	0.13	13	0.31	-0.04	9	0.99	64	1.46	-0.04
Anxiety	15	2.04	92	2.02	0.00	3	0.39	20	0.48	-0.01	23	2.53	118	2.70	-0.01
Bipolar Disorder	.	.	1	0.02	0.00	NA		NA			2	0.22	3	0.07	0.04
Borderline Personality Disorder	.	.	7	0.15	0.00	.	.	1	0.02	0.00	1	0.11	2	0.05	0.02
Depression	5	0.68	104	2.29	**-0.13**	8	1.03	82	1.95	-0.08	90	9.89	447	10.21	-0.01
Schizophrenia	NA		NA			NA		NA			.	.	3	0.07	0.00
Substance Abuse	1	0.14	4	0.09	0.01	2	0.26	7	0.17	0.02	16	1.76	34	0.78	0.09
Charlson Score															
Mean_Charlson Score	0.11	.	0.28	.	**-0.21**	0.01	.	0.02	.	-0.05	0.26	.	0.23	.	0.06
Std_Charlson Score	0.52	.	1.01	.	**-0.21**	0.09	.	0.19	.	-0.05	0.56	.	0.51	.	0.06
Historical Conditions (Before Baseline)															
Depression	8	1.09	125	2.75	**-0.12**	7	0.90	43	1.02	-0.01	236	25.93	1169	26.70	-0.02
Alcohol Abuse	29	3.95	226	4.97	-0.05	56	7.20	253	6.02	0.05	56	6.15	319	7.29	-0.05
Substance Abuse	43	5.86	240	5.28	0.03	9	1.16	43	1.02	0.01	39	4.29	143	3.27	0.05
Personal History of Suicide	NA		NA			NA		NA			.	.	1	0.02	0.00
Baseline Medication															

	1st Quintile					2nd Quintile					3rd Quintile				
	Duloxetine-treated n=734		Duloxetine Untreated n=4548			Duloxetine-treated n=778		Duloxetine Untreated n=4206			Duloxetine-treated n=910		Duloxetine Untreated n=4378		
	n	%	n	%	SD[a]	n	%	n	%	SD[a]	n	%	n	%	SD[a]
Any Selected Psychiatric Therapy	25	3.41	299	6.57	**-0.15**	2	0.26	19	0.45	-0.03	114	12.53	481	10.99	0.05
Antidepressant Therapy	11	1.50	107	2.35	-0.06	1	0.13	12	0.29	-0.04	62	6.81	243	5.55	0.05
Psychosis Therapy	7	0.95	112	2.46	**-0.12**	1	0.13	8	0.19	-0.02	16	1.76	73	1.67	0.01
Hypnotics Anxiolytics Therapy	6	0.82	50	1.10	-0.03	.	.	6	0.14	0.00	47	5.16	193	4.41	0.04
Other Selected Psychiatric Therapy	9	1.23	160	3.52	**-0.15**	.	.	10	0.24	0.00	12	1.32	66	1.51	-0.02
Propensity Score															
Mean_Propensity Score	0.14	.	0.14	.	**0.22**	0.15	.	0.15	.	0.07	0.17	.	0.17	.	**0.10**
Std_Propensity Score	0.02	.	0.03	.	**0.22**	0.002	.	0.002	.	0.07	0.012	.	0.011	.	**0.10**

Abbreviations: n = number of patients; SD = standardized difference

[a] Bolded = standardized difference ≥0.1

[b] Baseline defined as 1 year prior to Index Date.

[c] Treated with one of the following: antidepressant, psychosis, hypnotics anxiolytics, or other selected psychiatric therapies.

[d] Any psychiatric medication that is not listed exclusively as just an antidepressant , psychosis or hypnotic anxiolytics therapy.

Table APP.24. Baseline Demographics and Characteristics Stratified by Propensity Score (4th through 5th Quintiles) Between Duloxetine-treated and Untreated Groups (ITT population)

	4th Quintile					5th Quintile				
	Duloxetine-treated n=1132		Duloxetine Untreated n=4058			Duloxetine-treated n=778		Duloxetine Untreated n=4206		
	n	%	n	%	SD[a]	n	%	n	%	SD[a]
Age At Index										
Mean_Age At Index	57.61	.	56.83	.	0.06	57.08	.	57.19	.	-0.01
Std_Age At Index	13.45	.	13.70	.	0.06	14.20	.	14.46	.	-0.01
Charlson Comorbidities										
Cancer	NA		NA			NA		NA		
Cerebrovascular Disease	.	.	10	0.25	0.00	20	1.18	27	0.77	0.04
Chronic Pulmonary Disease	46	4.06	160	3.94	0.01	243	14.29	461	13.23	0.03
Congestive Heart Disease	.	.	1	0.02	0.00	NA		NA		
Dementia	1	0.09	7	0.17	-0.02	7	0.41	14	0.40	0.00
Diabetes	51	4.51	238	5.86	-0.06	291	17.11	476	13.66	**0.10**
Diabetes With Complications	1	0.09	2	0.05	0.02	70	4.12	82	2.35	**0.10**
Hemiplegia	NA		NA			NA		NA		
Metastatic Tumour	NA		NA			NA		NA		
Mild liver Disease	NA		NA			NA		NA		
Moderate Liver Disease	NA		NA			NA		NA		
Myocardial Infarction	1	0.09	3	0.07	0.01	1	0.06	6	0.17	-0.03
Peptic Ulcer Disease	.	.	1	0.02	0.00	NA		NA		
Peripheral Vascular Disease	3	0.27	7	0.17	0.02	4	0.24	17	0.49	-0.04
Renal Disease	16	1.41	56	1.38	0.00	57	3.35	133	3.82	-0.03
Rheumatological Disorder	8	0.71	17	0.42	0.04	22	1.29	56	1.61	-0.03
Other Baseline Comorbidities										
Alcohol Abuse	17	1.50	51	1.26	0.02	63	3.70	112	3.21	0.03
Anxiety	45	3.98	207	5.10	-0.05	166	9.76	288	8.27	0.05
Bipolar Disorder	3	0.27	18	0.44	-0.03	77	4.53	139	3.99	0.03
Borderline Personality Disorder	1	0.09	.	.	0.00	.	.	1	0.03	0.00

	4th Quintile					5th Quintile				
	Duloxetine-treated n=1132		Duloxetine Untreated n=4058			Duloxetine-treated n=778		Duloxetine Untreated n=4206		
	n	%	n	%	SD[a]	n	%	n	%	SD[a]
Depression	134	11.84	474	11.68	0.01	522	30.69	951	27.30	0.08
Family History of Suicide	NA		NA			2	0.12	2	0.06	0.02
Schizophrenia	.	.	4	0.10	0.00	9	0.53	11	0.32	0.03
Substance Abuse	9	0.80	27	0.67	0.02	24	1.41	70	2.01	-0.05
Personal History of Suicide	NA		NA			1	0.06	1	0.03	0.01
Charlson Score										
Mean_Charlson Score	0.13	.	0.14	.	-0.03	0.50	.	0.43	.	0.09
Std_Charlson Score	0.43	.	0.42	.	-0.03	0.81	.	0.73	.	0.09
Historical Conditions (Before Baseline)										
Depression	260	22.97	948	23.36	-0.01	911	53.56	1703	48.88	0.09
Alcohol Abuse	97	8.57	323	7.96	0.02	255	14.99	500	14.35	0.02
Substance Abuse	42	3.71	173	4.26	-0.03	114	6.70	246	7.06	-0.01
Personal History of Suicide	.	.	1	0.02	0.00	4	0.24	6	0.17	0.01
Baseline Medication										
Any Selected Psychiatric Therapy	1050	92.76	3708	91.38	0.05	1654	97.24	3396	97.47	-0.02
Antidepressant Therapy	556	49.12	2013	49.61	-0.01	1267	74.49	2470	70.90	0.08
Psychosis Therapy	25	2.21	96	2.37	-0.01	121	7.11	209	6.00	0.05
Hypnotics Anxiolytics Therapy	35	3.09	126	3.10	-0.00	471	27.69	849	24.37	0.08
Other Selected Psychiatric Therapy	466	41.17	1580	38.94	0.05	1271	74.72	2460	70.61	0.09
Pychiatric Hospitalizations										
History of Hospitalizations	.	.	2	0.05	0.000	3	0.18	4	0.11	0.02
Propensity Score										
Mean_Propensity Score	0.22	.	0.22	.	0.04	0.34	.	0.32	.	**0.30**
Std_Propensity Score	0.01	.	0.01	.	0.04	0.08	.	0.06	.	**0.30**

Abbreviations: n = number of patients; SD = standardized difference.

[a] Bolded = standardized difference ≥0.1.

[b] Baseline defined as 1 year prior to Index Date.

[c] Treated with one of the following: antidepressant, psychosis, hypnotics anxiolytics, or other selected psychiatric therapies.

[d] Any psychiatric medication that is not listed exclusively as just an antidepressant , psychosis or hypnotic anxiolytics therapy.

Table APP.25. Baseline Demographics and Characteristics Stratified by Propensity Score Within Women with a SUI Diagnosis (Duloxetine-treated vs. Antidepressant Comparator; As-Treated Analysis – Untreated Population Uncensored)

	Duloxetine-treated n= 3,700		Anti Depressant Treated n= 23,777		
	n	%	n	%	Standardized Difference
Age At Index					
Maximum_Age At Index	92	.	101	.	-0.1907
Mean_Age At Index	55.76	.	58.47	.	-0.1907
Median_Age At Index	55	.	58	.	-0.1907
Minimum_Age At Index	18	.	18	.	-0.1907
Std_Age At Index	14.08	.	14.32	.	-0.1907
Age					
18-29	70	1.89	388	1.63	0.0198
30-39	360	9.73	1653	6.95	0.1006
40-49	951	25.70	4825	20.29	0.1288
50-59	871	23.54	6091	25.62	-0.0482
60-69	755	20.41	5106	21.47	-0.0263
70-79	496	13.41	3785	15.92	-0.0711
>=80	197	5.32	1929	8.11	-0.1116
Index Year					
Maximum_Index Year	2015	.	2015	.	0.3087
Mean_Index Year	2008	.	2007	.	0.3087
Median_Index Year	2008	.	2008	.	0.3087
Minimum_Index Year	2004	.	1995	.	0.3087
Std_Index Year	3.05	.	5.07	.	0.3087
Follow Up					
Maximum_Follow Up Duration (Days)	3718	.	6640	.	-0.1211
Mean_Follow Up Duration (Days)	178	.	225	.	-0.1211
Median_Follow Up Duration (Days)	65	.	86	.	-0.1211

	Duloxetine-treated n= 3,700		Anti Depressant Treated n= 23,777		
	n	%	n	%	Standardized Difference
Minimum_Follow Up Duration (Days)	0	.	0	.	-0.1211
Std_Follow Up Duration (Days)	323	.	436	.	-0.1211
Charlson Comorbidities					
Cancer	16	0.43	325	1.37	-0.0991
Cerebrovascular Disease	16	0.43	209	0.88	-0.0554
Chronic Pulmonary Disease	239	6.46	1635	6.88	-0.0167
Congestive Heart Disease	5	0.14	75	0.32	-0.0380
Dementia	6	0.16	82	0.34	-0.0363
Diabetes	205	5.54	1274	5.36	0.0080
Diabetes With Complications	46	1.24	168	0.71	0.0546
Hemiplegia	.	.	4	0.02	0.0000
Metastatic Tumour	2	0.05	30	0.13	-0.0240
Mild liver Disease	1	0.03	15	0.06	-0.0170
Moderate Liver Disease	.	.	2	0.01	0.0000
Myocardial Infarction	7	0.19	55	0.23	-0.0092
Peptic Ulcer Disease	2	0.05	45	0.19	-0.0388
Peripheral Vascular Disease	7	0.19	81	0.34	-0.0295
Renal Disease	74	2.00	381	1.60	0.0299
Rheumatological Disorder	30	0.81	303	1.27	-0.0456
Other Baseline Comorbidities					
Alcohol Abuse	57	1.54	405	1.70	-0.0129
Anxiety	120	3.24	1142	4.80	-0.0794
Bipolar Disorder	38	1.03	280	1.18	-0.0144
Borderline Personality Disorder	2	0.05	14	0.06	-0.0020
Depression	397	10.73	2584	10.87	-0.0044
Family History of Suicide	1	0.03	3	0.01	0.0102
Schizophrenia	2	0.05	35	0.15	-0.0294

	Duloxetine-treated n= 3,700		Anti Depressant Treated n= 23,777		
	n	%	n	%	Standardized Difference
Substance Abuse	33	0.89	170	0.71	0.0198
Charlson Score					
Maximum_Charlson Score	6	.	9	.	-0.0385
Mean_Charlson Score	0.22	.	0.24	.	-0.0385
Median_Charlson Score	0	.	0	.	-0.0385
Minimum_Charlson Score	0	.	0	.	-0.0385
Std_Charlson Score	0.60	.	0.63	.	-0.0385
Charlson Range Zero	3142	84.92	19680	82.77	0.0584
Charlson Range 1-2	503	13.59	3787	15.93	-0.0658
Charlson Range 3-5	53	1.43	276	1.16	0.0240
Charlson Range 6-7	2	0.05	22	0.09	-0.0142
Charlson Range 8+	.	.	12	0.05	0.0000
Historical Conditions (Before Baseline)					
Depression	741	20.03	4399	18.50	0.0387
Alcohol Abuse	279	7.54	2100	8.83	-0.0471
Substance Abuse	141	3.81	893	3.76	0.0029
Personal History of Suicide	1	0.03	15	0.06	-0.0170
Baseline Medication					
Any Selected Psychiatric Therapy	1408	38.05	11398	47.94	-0.2006
Antidepressant Therapy	929	25.11	6272	26.38	-0.0291
Psychosis Therapy	51	1.38	423	1.78	-0.0321
Hypnotics Anxiolytics Therapy	242	6.54	2139	9.00	-0.0918
Other Selected Psychiatric Therapy	721	19.49	6435	27.06	-0.1800
Pychiatric Hospitalizations					
Hx of Hospitalizations	1	0.03	3	0.01	0.0102
Propensity Score					
Maximum_Propensity Score	0.47	.	0.44	.	0.3926

	Duloxetine-treated n= 3,700		Anti Depressant Treated n= 23,777		
	n	%	n	%	Standardized Difference
Mean_Propensity Score	0.15	.	0.13	.	0.3926
Median_Propensity Score	0.15	.	0.13	.	0.3926
Minimum_Propensity Score	0.017	.	98E-13	.	0.3926
Std_Propensity Score	0.045	.	0.044	.	0.3926

Abbreviations: n = number of patients.

Table APP.26. Treatment Differences in the Risk of Each Suicidality Outcome Within Women with a SUI Diagnosis (Duloxetine-treated vs. Antidepressant Comparator; As-Treated Analysis – Untreated Population Uncensored)

	Duloxetine Exposed n= 3,700				Anti-Depressant Comparator n= 23,777				Hazard Ratio Base Model				Hazard Ratio Adjusted (Full Model)[a]			
Cohort	n Outcome	% Outcome	Person Yrs	Crude IR	n Outcome	% Outcome	Person Yrs	Crude IR	Ratio	LCL	UCL	p-value	Ratio	LCL	UCL	p-value
Suicide attempt (Completed/Non-Fatal)	4	0.11	1,813	220.58	18	0.08	14,690	122.53	1.55	0.52	4.57	0.43	1.94	0.63	5.95	0.25
Completed Suicide	0	0.00	1,814	0.00	1	0.00	14,695	6.81	0.00	0.00	0.00	1.00	0.00	0.00	.	1.00
Non-Fatal Suicide Attempt	4	0.11	1,813	220.58	17	0.07	14,690	115.73	1.64	0.55	4.88	0.37	1.98	0.64	6.12	0.23
Suicide Ideation	3	0.08	1,809	165.81	43	0.18	14,654	293.43	0.49	0.15	1.59	0.24	0.51	0.16	1.67	0.27
Suicide, Completed/Attempt/Ideation	7	0.19	1,808	387.10	61	0.26	14,649	416.41	0.81	0.37	1.77	0.59	0.88	0.40	1.94	0.74

Abbreviations: IR = incidence rate; LCL = lower confidence level; n = number; RR = relative risk; SUI = stress urinary incontinence; UCL = upper confidence level.

[a] Covariates for Full Model -Current depression, Psychiatric comorbidities, History of depression History of psychiatric hospitalization, History of family suicide attempt, History of personal suicide attempt, Index Year , Age at Index, Propensity Score Strata, Any Selected Psychiatric Therapy, Other Selected Psychiatric Therapy.

Table APP.27. Incidence Rates Stratified by Age Within Women with a SUI Diagnosis (Duloxetine-treated vs. Antidepressant Comparator; As-Treated Analysis – Untreated Population Uncensored)

		Duloxetine-treated n= 3,700					Anti-Depressant Treated n= 23,777					
Outcome	Age group	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	n Patients	n Outcome	% Outcome	Person Yrs	Crude IR /100,000 PY	p-value
Suicide Attempt (Completed Suicide/Non-Fatal Suicide)	Overall	3,700	4	0.11	1,813	220.58	23,777	18	0.08	14,690	122.53	0.5268*
	18-24	17	0	0.00	5	0.0000	133	2	1.50	40	5048.4	1.0000*
	25-64	2,635	4	0.15	1,224	326.81	15,521	15	0.10	9,538	157.27	0.3444*
	65 +	1,048	0	0.00	585	0.0000	8,123	1	0.01	5,112	19.561	1.0000*
Suicide Ideation	Overall	3,700	3	0.08	1,809	165.81	23,777	43	0.18	14,654	293.43	0.1988*
	18-24	17	0	0.00	5	0.0000	133	0	0.00	40	0.0000	.
	25-64	2,635	2	0.08	1,225	163.33	15,521	37	0.24	9,503	389.36	0.1115*
	65 +	1,048	1	0.10	580	172.43	8,123	6	0.07	5,111	117.38	0.5725*

Abbreviations: CL = confidence level; IR = incidence rate; n = number; PY = person years

Note Chi-Square was used to calculate p-values; Fisher's exact was used to calculate p-values with cell count < 5 (indicated with asterisk(*))

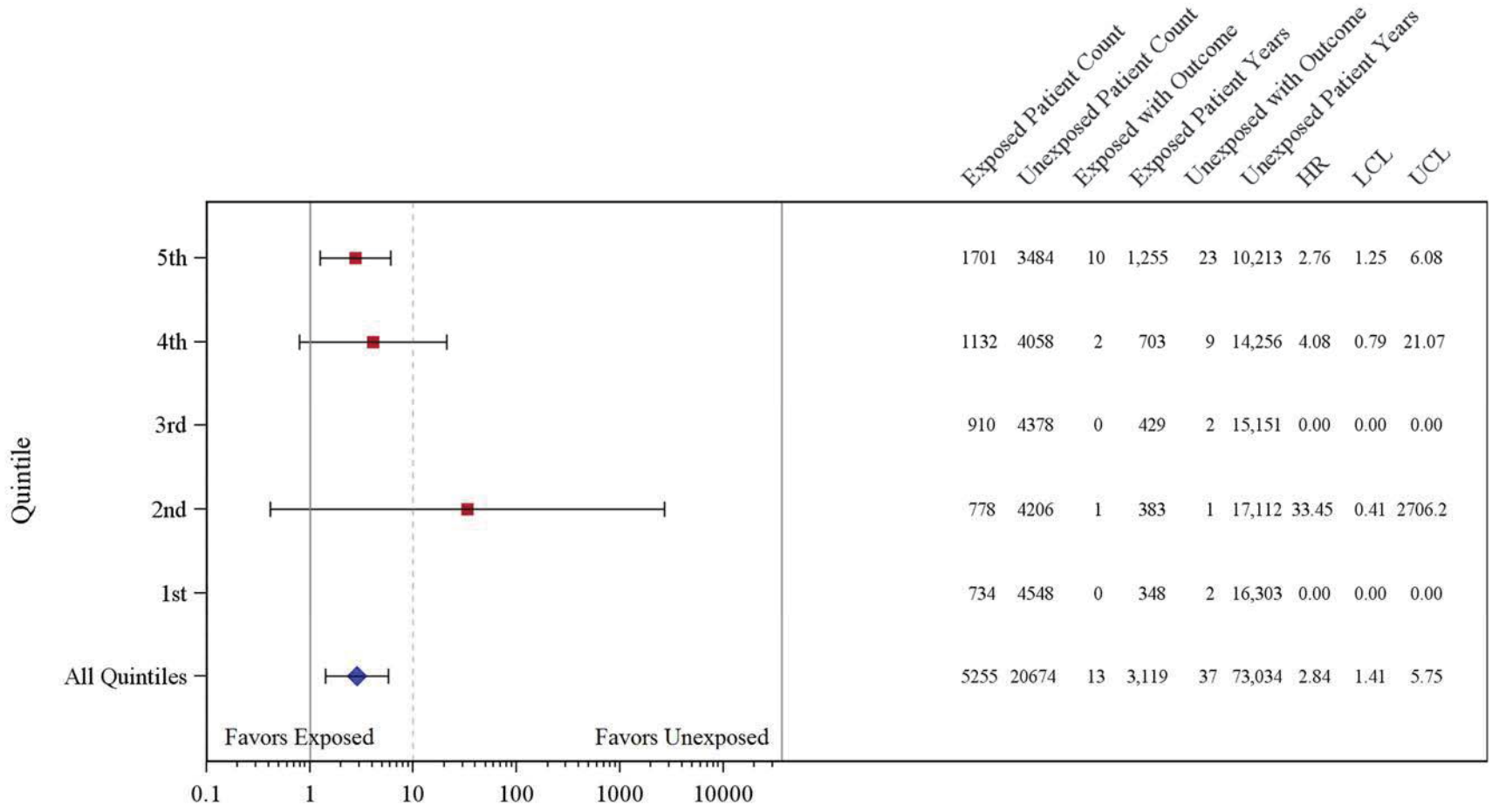

Figure APP.1. **Forest plot for suicide attempt/completed within women with a SUI diagnosis in duloxetine-treated vs.untreated patients (as-treated analysis – untreated population uncensored).**

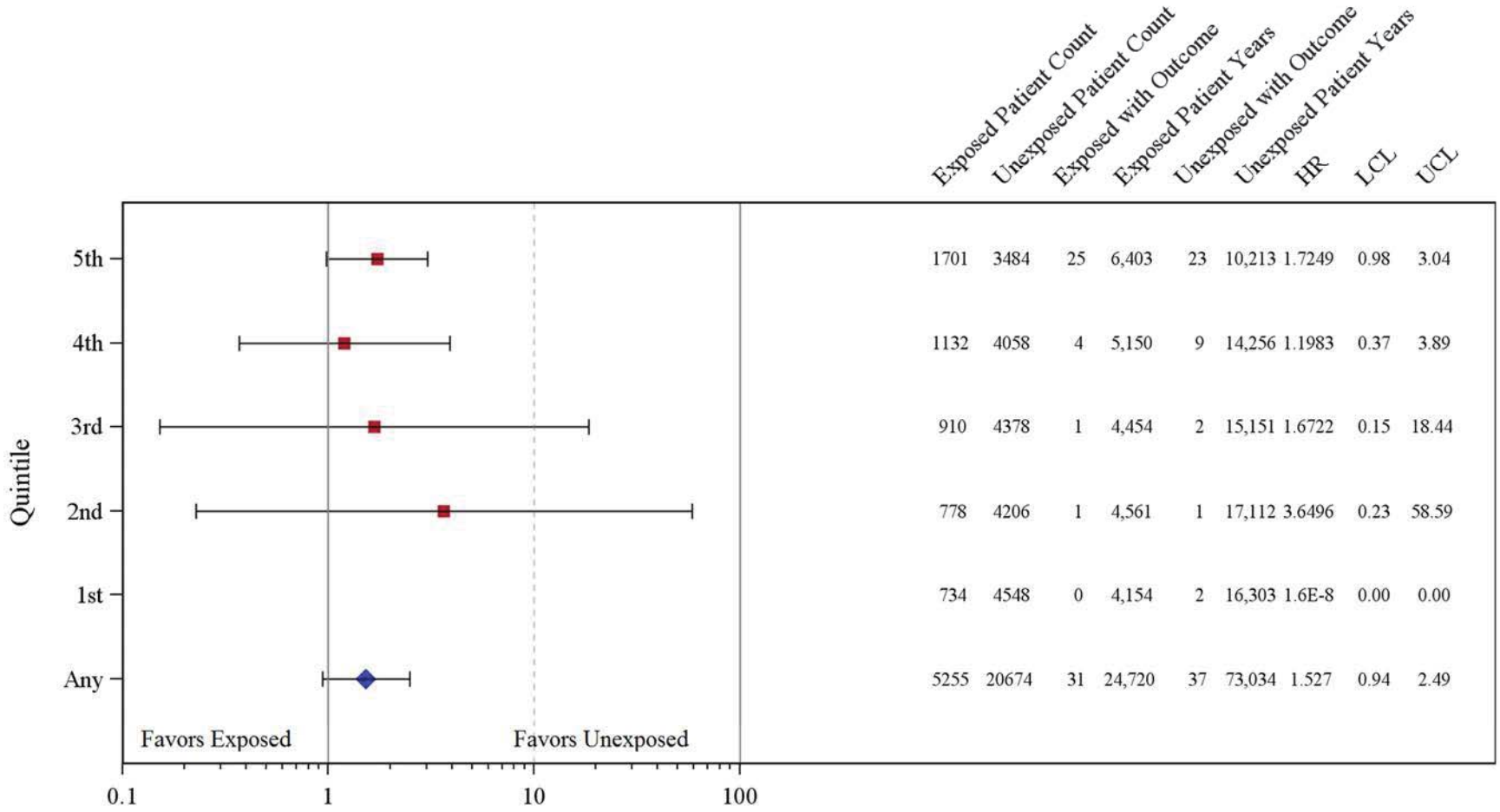

Figure APP.2. **Forest plot for suicide attempt/completed within women with a SUI diagnosis in duloxetine-treated vs. untreated patients (intent-to-treat analysis).**

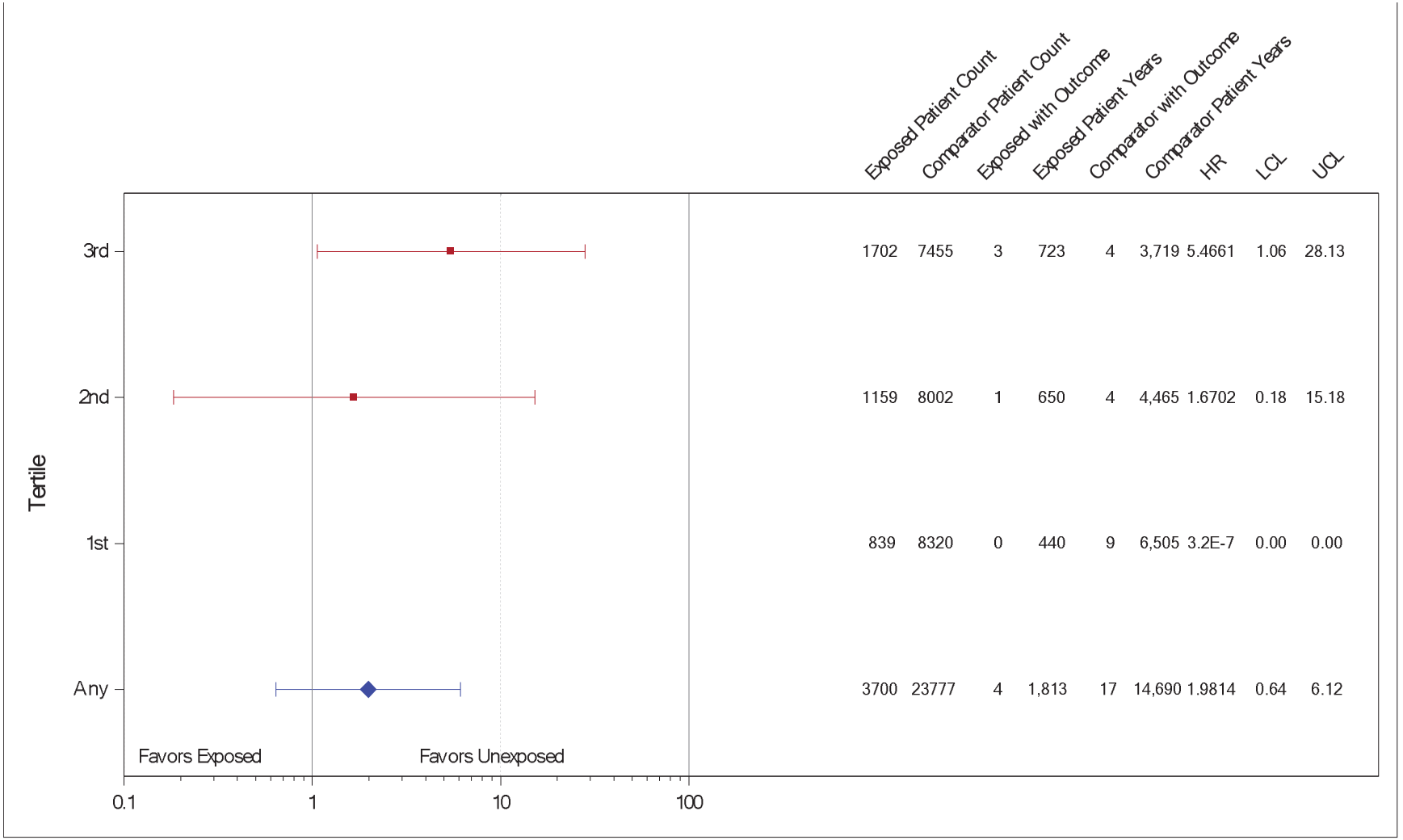

Figure APP.3. **Forest plot for suicide attempt/completed within women with a SUI Diagnosis (Duloxetine-treated vs. Antidepressant Comparator; As-Treated Analysis – Untreated Population Uncensored).**

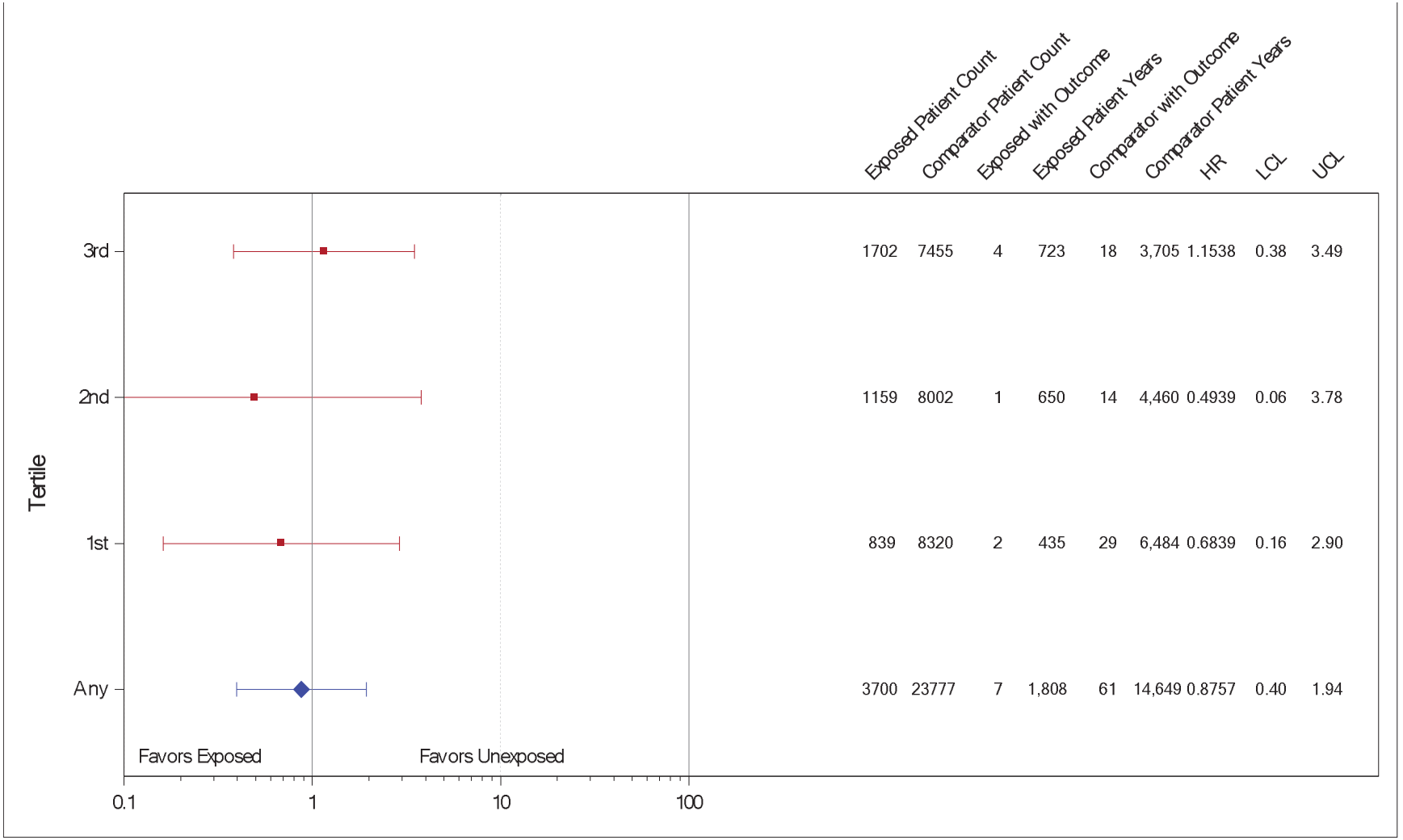

Figure APP.4. **Forest plot for suicide attempt/completed/ideation within women with a SUI Diagnosis (Duloxetine-treated vs. Antidepressant Comparator; As-Treated Analysis – Untreated Population Uncensored).**

Appendix 2

Summary of Previous Analyses

Lilly conducted four previous analyses of the GPRD database to investigate whether there is an association between duloxetine and suicidality among SUI patients. Although no evidence of an association between duloxetine exposure and non-fatal suicide attempts or suicidal ideation in women with SUI has been observed, thus far, Lilly acknowledges that the results may have been limited by small sample size.

The agreement between Lilly and the EMA's Committee for Medicinal Products for Human Use was that the analysis will be conducted again when the number of accrued exposed patients in the United Kingdom General Practice Research Database (CPRD) enables a study that is sufficiently powered in order to be able to rule out a pre-specified limit for non-fatal suicide attempts. Lilly proposed to perform a new analysis with additional exposures upon accrual of a sufficient number of exposed patients to achieve 80% power to rule out a hazard ratio of 2.5 for non-fatal suicide attempts, based on the upper confidence limit of a 2-sided 95% confidence interval for the hazard ratio. Based on preliminary calculations, sufficient accrual in the CPRD database would be observed approximately in 2014 if the event rate persisted, and 74,243 patient years of follow-up would be needed to accrue 49 events. Therefore, the present analysis was initiated. A summary of the four previous analyses is provided:

- The first analysis (2006) did not have sufficient patient exposure numbers, as no suicide-related outcomes were observed among the 286 women exposed to duloxetine or their matches (n=1,663).
- The second analysis (2007) compared 1,020 women with SUI exposed to duloxetine to 4,080 women with SUI who were not exposed to duloxetine. Hazard ratios for non-fatal suicide attempts and suicidal ideation after adjusting for age, morbidity, and psychiatric disorders (including ongoing depression, ongoing anxiety disorder, history of suicidal ideation, recent antidepressant initiation, and number of different antidepressants ever prescribed) showed no statistical significant difference between duloxetine-exposed patients with SUI and their non-exposed comparators . There were no completed suicidality cases in this analysis.
- The third analysis (2008) involved 1,346 duloxetine-exposed women with SUI and 5,383 unexposed women with SUI. This analysis found no statistically significant association between duloxetine exposure and non-fatal suicide attempts, or with suicidal ideation. There were no completed suicidality cases in this analysis.
- The fourth analysis (2010) included 2,398 duloxetine-exposed women with SUI and 9,592 unexposed women with SUI. Duloxetine exposure was not statistically significantly associated with non-fatal suicide attempts or associated with suicidal ideation in women with SUI in analyses stratifying for depression, as well as in the Cox Proportional Hazards analyses performed (sequentially controlling for age, somatic comorbidity, psychiatric comorbidity, history of suicidal ideation and non-fatal attempts, and number of different antidepressant, hypnotic/anxiolytic, and antipsychotic/antimanic

medications ever prescribed), including the fully adjusted model. There were no completed suicidality cases in this analysis.

Appendix 3

Postmarketing Surveillance

Data from spontaneously reported postmarketing surveillance events were also reviewed for suicidality events in patients taking duloxetine for SUI. Cumulatively through 31 July 2016, the worldwide exposure to duloxetine is estimated to be 84 378 000 patients (including 83 063 000 patients receiving Cymbalta and 1 315 000 receiving Yentreve). A query using the Suicide/Self-Injury Standardised Medical Dictionary for Regulatory Authorities Query (SMQ) version 19.1) was performed. The time frame was cumulative through 28 February 2017. The resulting cases were then sorted by indication into 4 groups: psychiatric, pain, bladder-related disorders, and unknown uses. The proportion of cases in each group and the frequency of suicidality events (number of cases divided by cumulative patients exposure) are summarized in Table APP.28.

Table APP.28. Frequency of Reported Suicide/Self-Injury Adverse Events Based on Indication Grouping

Grouping	Percent of All Indications[a]	Percent of Total Exposure[b]
Psychiatric	45.941%	0.0037%
Pain	19.307%	0.0016%
Bladder-Related	0.336%	0.00003%
Unknown or Other	34.416%	0.0028%
Total	100%	0.0081%

[a] Percentage of all indications was calculated by dividing the number of cases in each indication group by the total number of cases with adverse events from the Suicide/Self-Harm SMQ.

[b] Percentage of total exposure was calculated by dividing the number of cases in each indication by the cumulative patient exposure for duloxetine.

When compared to patient exposure, terms in this SMQ are considered very rarely reported (≤0.01%) for all indications. Although the spontaneous cases often do not provide useful information regarding causality, a review of the post marketing cases indicated that among patients using duloxetine for bladder-related issues, 30.43% reported a history of mental illness (i.e. depression, anxiety, bipolar disorder, etc). This was consistent with other data supporting the fact that SUI patients treated with duloxetine have high rates of baseline psychiatric comorbidity.

Examining the events reported in the bladder-related disorders group, 78.26% of the events were suicidal ideation. The remaining 21.74% consisted of suicide-related behavior, of which, there was 1 completed suicide. Thus, suicidality events are very rarely reported in association with duloxetine use in the patient population with bladder-related disorders.

Appendix 4

Randomized Controlled Trials and Duloxetine Utilization Studies

A summary of analyses of the duloxetine randomized clinical trial (RCT) database is shown in Table APP.29. Details regarding the clinical trial population, methodology used, and findings are provided.

A meta-analysis of all completed duloxetine trials in MDD was performed with a data lock of 02 February 2004. Overall, 27 trials including 4956 patients (mean age, 43.0; 64.3% female) who were exposed to duloxetine for an average of 130 days (range, 1–473 days), with a total of 1770 person-years. The observed rate of completed suicide in duloxetine-treated patients (5 cases) was 2.83/1,000 patient-years (PY) and of nonfatal suicide attempts (26 cases), 14.61/1,000 patient-years. Of note, there were no significant differences in the incidence of suicide-related events with duloxetine versus placebo in the 12 placebo-controlled trials (duloxetine, 1812; placebo, 1184 patients). The Mantel-Haenszel incidence difference (MHID) for suicide-related behaviours was -0.03% (95% CI -0.48 to 0.42) and Mantel-Haenszel time-adjusted rate difference method (MHRD) -0.002 (95% CI -0.02 to 0.02). Changes in 17-item Hamilton Rating Scale for Depression ($HAMD_{17}$) Item-3 suicidality scores showed more improvement with duloxetine (MHID, 9.56%; 95% CI, 4.50 to 14.6; $P < 0.001$) and less worsening of suicidal ideation with duloxetine (MHID, -4.25%; 95% CI -6.55 to 1.95; $P < 0.001$). Of the 27 duloxetine trials, no evidence of an increased risk of suicidal behaviour or ideation during treatment with duloxetine compared with placebo in patients with MDD (Acharya et al. 2006).

In 2010, another meta-analysis of all completed placebo-controlled duloxetine trials in all duloxetine indications was submitted as part of a marketing authorisation application in the EU. The data set included all placebo-controlled clinical trials with data lock as of 23 April 2010. Overall, data from 54 trials including 11224 patients exposed to duloxetine (2429.49 patient-years) were compared with 8164 placebo-treated patients (1660.4 patient-years). In the "all indications" data set for the combined outcome of "suicidal behaviour or ideation," the exposure-adjusted rate was 20.17 events per 1000 patient years for duloxetine-treated patients compared with 18.67 events per 1000 patient-years for placebo-treated patients (MHRR 1.01, p-value= .989). In the "psychiatric indication" subset (MDD and GAD) for the combined outcome of "suicidal behaviour or ideation" the exposure-adjusted rate was 38.82 events per 1000 patient years for duloxetine-treated patients compared with 47.35 events per 1000 patient-years for placebo-treated patients (MHRR 0.87, p-value .609). In the "non-psychiatric indication" subset (SUI/LUTD, DPNP, FMS, Chronic Pain) for the combined outcome of "suicidal behaviour or ideation" the exposure-adjusted rate was 8.13 events per 1000 patient years for duloxetine-treated patients compared with 6.81 events per 1000 patient-years for placebo-treated patients (MHRR 1.41, p-value .425). Thus for the 54 placebo-controlled duloxetine trials in this meta-analysis, there was no evidence of an increased risk of suicidal behaviour or ideation during treatment with duloxetine compared with placebo in patients exposed to duloxetine in all indications.

A more recent, larger integrated clinical trial database analysis of adult patients from placebo-controlled studies of duloxetine was performed on studies completed as of 13 DEC 2013. Patients treated for all indications were included and the database contained all placebo-controlled SUI studies. Adverse events were searched for events related to suicide using MedDRA preferred terms including: Completed suicide, Depression suicidal, Intentional overdose, Intentional self-injury, Poisoning deliberate, Self-injurious behaviour, Self-injurious ideation, Suicidal behaviour, Suicidal ideation, and Suicide attempt. There were 13076 total duloxetine-treated patients (2413.34 PY of exposure) and 9855 placebo-treated patients (1871.07PY of exposure). The incidence rate of suicide-related ideation and behaviours was not statistically significantly different between treatment groups (13.67 per 1000 PY for the duloxetine-treated cohort vs. 9.62 per 1000 PY for the placebo-treated cohort). The relative risk for suicide-related events was 1.42 (0.80, 2.52, p=0.230). In summary, there was not a statistically significantly higher risk of suicidality events observed with duloxetine treatment versus placebo in patients treated with duloxetine for all indications.

Another analysis using the same methodology described above was performed using an integrated database with randomised placebo-controlled trials completed as of 21 FEB 2017. No additional SUI studies were added since the prior database described above. In the most recent integrated database there were 14058 total duloxetine-treated patients (2646.83 PY of exposure) and 10820 placebo-treated patients (2102.35 PY of exposure). The incidence rate of suicide-related risks was not statistically significantly different between treatment groups (12.85 per 1000 PY for the duloxetine-treated cohort vs. 8.56 per 1000 PY for the placebo-treated cohort). The relative risk for suicide-related events was 1.50 (0.85, 2.66, p=0.164). In summary, there was not a statistically significantly higher risk of suicidality events observed with duloxetine treatment versus placebo in duloxetine-treated patients in all indications.

While it is understood that clinical trial patients may have different characteristics than patients from the B056 observational study, these data from clinical trials represent substantially more patients than those observed in the B056 study and patients with likely more closely matched characteristics due to randomization of study patients. It appears that the relative risk for suicidal ideation and behaviours is stable over time in the clinical trial population.

Table APP.29. Summary of Analyses of the Duloxetine Randomized Clinical Trial Database

Date of Review	Clinical Trial Population	N (DLX/PBO)	Method	Finding	Note
2005	SUI patients in 4 pivotal Placebo-controlled SUI clinical trials	958/955	Manual Review of TEAEs	0 Suicide attempts	Published in Hurley 2006
2006	All completed duloxetine MDD clinical trials	1812/1184	Text-string search of searchable text fields in integrated database, adjudication of outcomes by company physicians.	DLX: 16 events of suicidal ideation or behavior per 1,000 PY; PBO: 11 events per 1,000 PY. RR[a] 0.97 [0.25, 3.785]; p=.968	Acharya 2006
2010	Patients from Placebo-controlled clinical trials, all indications	11224/8164	Text-string search of searchable text fields in integrated database, adjudication of outcomes by company physicians.	DLX: 20.17 events of suicidal ideation or behavior per 1,000 PY; PBO: 18.67 events per 1,000 PY. RR[a] 1.01 [0.65, 1.56]; p=.967	Meta-analysis for EU chronic pain submission
	Psychiatric indications	3917/2548		DLX: 38.82 events of suicidal ideation or behavior per 1,000 PY; PBO: 47.35 events per	

Date of Review	Clinical Trial Population	N (DLX/PBO)	Method	Finding	Note
				1,000 PY. RR[a] 0.90 [0.54, 1.51] ; p=.692	
	Non-psychiatric indications	7307/5616		DLX: 8.13 events of suicidal ideation or behavior per 1,000 PY; PBO: 6.81 events per 1,000 PY. RR[a] 1.37 [0.58, 3.20] ; p=.470	
2014	Patients from Placebo-controlled clinical trials, all indications	13076/9855	Search for specific adverse event terms (Poisson regression)	DLX: 13.67 events of suicidal ideation or behavior per 1,000 PY; PBO: 9.62 events per 1,000 PY. RR 1.42 [0.80, 2.52]; p=0.230	Routine analysis for RMP
2017	Patients from Placebo-controlled clinical trials, *all indications*	14058/10820	Search for specific adverse event terms (Poisson regression)	52 suicidal outcomes cases (n=18 PBO and n=34 DLX) DLX: 12.85 events per 1,000 PY PBO: 8.56 per 1,000	Routine analysis for RMP

Date of Review	Clinical Trial Population	N (DLX/PBO)	Method	Finding	Note
				PY; RR 1.50 [0.85, 2.66]; p=0.164	
	Psychiatric indications	4948/3443		DLX: 36.10 events per 1,000 PY PBO: 26.25 per 1,000 PY RR 1.38 [0.72, 2.61]; p=.330	
	Non-psychiatric indications	9110/1377		DLX: 3.21 events per 1,000 PY PBO: 2.55 events per 1,000 PY RR 1.26 [0.35, 4.46]; p=.722	

Abbreviations: DLX = duloxetine; PBO = placebo; PY = patient-year.
[a] Mantel-Haenszel Risk Ratio.

A Prescription-Event Monitoring (PEM) analysis was also completed which provided duloxetine drug utilization information from a non-interventional, prospective, observational post-marketing, surveillance study that monitored the safety of 19485 patients during the introduction of duloxetine into general practice in England. In it, data from two PEM studies were pooled and the data stratified into subgroups defined by indication. Of note, 13.0% of patients in the urologic cohort had been treated with antidepressants in the three months prior to duloxetine treatment; the majority of suicidal attempts were reported among patients with psychiatric conditions.

- Within the Psychiatric, Urologic and Miscellaneous subgroups, 779 (7.1% of subgroup total), 25 (0.3% of subgroup total), and 10 (1.2% of subgroup total) patients, respectively, were reported to have had an event of suicidal ideation after starting duloxetine treatment.
- The number of patients reported to have had an event of suicide attempt was 345 (3.1% of the Psychiatric subgroup total), 6 (0.1% of the Urologic subgroup total) and 5 (0.6% of the Miscellaneous subgroup total), respectively. The incidence of suicidal behavior appeared to be higher in this PEM study compared with incidences in clinical trials, likely due to the fact that patients with a previous history of suicidal behavior were not excluded from this PEM study as they were in the clinical trials.

Furthermore, Michel and colleagues (2013) published results from an observational study (DUROSA study), which evaluated the safety and tolerability of duloxetine during routine clinical care in women with SUI in Germany. A high depression score at baseline was found in 26.6% and 15.6% of SUI-treated patients being classified as a probable or most likely case of depressive disorder, respectively, prior to duloxetine exposure. Thoughts of self-harm, suicidal thinking, and a history of suicide attempts were also frequent at baseline in these patients. However, despite reporting on a total of 8923 duloxetine-treated patients yielding a total exposure of 3233 patient-years, the study did not report any suicide-related events.

Annex 1. List of standalone documents

Not applicable.

Annex 2. B056 statistical analysis plan

Statistical Analysis Plan:

F1J-MC-B056: **Stress Urinary Incontinence and Suicidality**

Seen in the United Kingdom General Practice Research Database

Version 2.0

Generic Name (LY248686)

This is an observational study, retrospective cohort study design, using UK general practical data base. The study is designed to investigate whether women with stress urinary incontinence (SUI) who were exposed to duloxetine are at an increased risk of suicidality relative to matched comparable women with SUI who were not exposed to duloxetine in a real-world electronic medical records database CPRD.

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol F1J-MC-B056

Approval Date: 03-May-2017 GMT

1. Background

This statistical analysis plan (SAP) documents the fifth analysis in which Eli Lilly and Company (Lilly) investigates whether women with stress urinary incontinence (SUI) who were exposed to duloxetine are at an increased risk of suicidality relative to matched comparable women with SUI who were not exposed to duloxetine in a real-world electronic medical records database CPRD.

Four previously conducted analyses have been documented and the study reports have been submitted to regulatory agencies (i.e. CHMA) in 2006, 2007, 2008 and 2010. The findings are:

The first analysis (2006) did not have enough exposure numbers to investigate the association;

The second analysis (2007) compared 1,020 SUI women exposed to duloxetine to 4,080 SUI women unexposed patients. Hazard ratios for non-fatal suicide attempts and suicidal ideation after adjusting for age, morbidity, and psychiatric disorders (including ongoing depression, ongoing anxiety disorder, history of suicidal ideation, recent antidepressant initiation, and number of different antidepressants ever prescribed) showed no statistically significant difference between duloxetine exposed SUI patients and their non-exposed comparators. There were no completed suicides in this analysis.

The third analysis (2008) involved 1,346 duloxetine exposed SUI women and 5,383 unexposed SUI patients. This analysis found no statistically significant association between duloxetine exposure and non-fatal suicide attempts, or with suicidal ideation. There were no completed suicides in this analysis.

The fourth analysis (2010) included 2,398 duloxetine-exposed SUI women and 9,592 unexposed SUI patients. Duloxetine exposure was not statistically significantly associated with non-fatal suicide attempts or associated with suicidal ideation in women with SUI in analyses stratifying for depression, as well as in the Cox Proportional Hazards analyses performed (sequentially controlling for age, somatic comorbidity, psychiatric comorbidity, history of suicidal ideation and non-fatal attempts, and number of different antidepressant, hypnotic/anxiolytic, and antipsychotic/antimanic medications ever prescribed), including the fully adjusted model. There were no completed suicides in this analysis.

While the above four thus-far conducted analyses have shown no evidence of an association between duloxetine exposure and non-fatal suicide attempts or suicidal ideation, CHMP has requested the analysis to be conducted again when the accrued exposed patients in GPRD is sufficient for a powered study that is able to rule out a pre-specified limit for non-fatal suicide attempts. Therefore, the database was accessed in Q4 2013 where it was determined that the necessary follow-up had not been attained; and in Q4 2014 when the sample size estimation reached the pre-specified total follow-up time (details see Appendix 8.1).

2. Revision History

Version 2.0: major changes are made to version 2.0, including the sensitivity analysis in section 5.3.3 and post hoc analysis in section 5.3.4

3. Study Objectives

The study will be performed to evaluate the following safety objectives included in the study protocol, using the United Kingdom Clinical Practice Research Datalink (CPRD) covering data from 2004 to 2014. All analyses will be performed accounting for demographics and clustering by medical practice. The overall purposes of the study include the followings:

- To estimate the incidence rate of completed suicide, non-fatal suicide attempts, suicidal ideation, suicidal behaviors (completed suicide in combination with non-fatal suicide attempts), and all combined outcomes in community-based general medical practices, with stratification for a documented diagnosis of depression, in:
  - Women with a diagnosis of SUI
  - Comparable women without a diagnosis of urinary incontinence of any type
  - A subset of women with a diagnosis of SUI receiving duloxetine treatment for this indication
  - A subset of women with a diagnosis of SUI not receiving duloxetine treatment for any indication
- To evaluate the association between suicidality-related outcomes and SUI case status or not, accounting for important demographic and medical history covariates.
- To assess, if feasible given the data, the association between suicidality-related outcomes and receipt of duloxetine treatment in the subpopulation of women with SUI, accounting for important demographic and medical history covariates.
- To describe the observed age group-specific rates of suicidality in females in a general practitioners' dataset.

With the increased number of SUI women exposed to duloxetine over time, the objectives that were not feasible to evaluate during the early stage of this study now became feasible, for example to assess the association between duloxetine treatment and suicidality related outcomes. Therefore, the study objectives are reprioritized based on the newly updated data. Specifically,

3.1. Primary Objective

The primary objective of the study is to assess the association between suicide attempts (both non-fatal and completed) and receipt of duloxetine treatment in women with SUI compared to SUI women without duloxetine treatment, accounting for important demographic and medical history covariates.

3.2. Secondary Objectives

Secondly, the study is aimed to examine the association between suicidal ideation and receipt of duloxetine treatment in women with SUI compared to SUI women without duloxetine treatment, accounting for important demographic and medical history covariates.

3.3. Exploratory Objectives

The proposed study will carry out the following descriptive analyses including estimating the incidence rate of completed suicide, non-fatal suicide attempts, suicidal ideation, suicidal

behaviors (completed suicide in combination with non-fatal suicide attempts) among women with SUI diagnosis stratifying by receiving duloxetine treatment or not;

- To describe the observed age group-specific rates of suicidality in females in a general practitioners' dataset.
- To evaluate the association between suicidality-related outcomes and SUI case status or not, accounting for important demographic and medical history covariates, and duloxetine status, if applicable.

4. Study Design

4.1. Summary of Study Design

This is a retrospective cohort study

4.2. Determination of Sample Size

The calculation of sample size/patient years was completed (for details see Appendix 8.1).

Consistent with the protocol specifications, the follow-up for duloxetine-treated SUI patients started from the first duloxetine prescription, until the outcome (i.e. non-fatal suicide attempts or completed suicide) or the end of the data availability. The **total duloxetine-treated SUI patients' follow-up time is 17,349** patient years, which indicates that the overall follow up time is approximately 86,745 patient years. This exposure exceeds the requisite patient-years (i.e.74,243 patient-years).

4.3. Determination of the Study Population

Eligible women will be those registered in active medical practices with GPRD quality-verified records, aged 18 and older, and with a minimum follow up-time of 1 year.

Study population in the primary and secondary study objectives:

All eligible women with a first diagnostic code for SUI identified in the GPRD dataset will be included in the SUI cohort. (Read codes K586.00, K198.00, 1A24.00, 1A24.11, 1593.00, 7B33800, and 7B33C00).

- **Duloxetine treated SUI cohort:** Among these SUI patients, women prescribed duloxetine for SUI were identified and considered "exposed". The pool of eligible controls is restricted to those unexposed patients in a practice that had a minimum of one case. Patients with baseline exposure to duloxetine will be excluded from the analysis.
- **Non duloxetine treated SUI cohort** (comparison cohort): The comparison cohort of women with SUI who did not receive a duloxetine prescription, was constituted through an approximately 4:1 random sample of eligible patients with SUI who matched duloxetine-exposed patients on the basis of **year of birth, clinical practice, index date (± 30 days) (definition see below) and diagnosis of SUI (± 90 days).** The matching variables were selected to account for the age distribution of SUI, as well as for the clustering of women within a practice to account for unobserved practice variation. To further adjust for immortal time bias, the index date of SUI unexposed patients will be re-assigned to match the duloxetine prescription date of SUI exposed patients.

Study population in the exploratory study objectives:

- **SUI diagnosed cohort**: All eligible women with a first diagnostic code for SUI identified in the GPRD dataset will be included in the SUI cohort.
- **Non-UI cohort** (comparison cohort): Women without urinary incontinence of any type will be eligible as participants in the comparison non-UI cohort. This analytic

comparison cohort will be constituted through a 7:1 matching of non-UI to SUI diagnosed women by **year of birth**, **clinical practice, and duloxetine prescription**. Among non-UI patients, the corresponding index date will be re-assigned to match the date of SUI diagnosis date.

Relevant medical information for women included in the analysis, as available in the GPRD dataset, will be summarized and used for characterizing the women by covariates of interest.

4.4. Determination of Observation Period/Drug Exposure

Baseline period is defined as no drug exposure during 1 year prior to index date.

Index date is defined as the following:

Primary and secondary study objectives:

- Index date of duloxetine treated SUI cohort is the first prescription date of duloxetine;
- Index date of non-duloxetine treated SUI cohort will be randomly assigned, and derived from the distribution of the number of days from the initial SUI diagnosis to the prescription date of initial duloxetine use among treated patients. The index date was selected at random and assigned to the nonusers according to the distribution of time between diagnosis and prescription derived from the treated cohort. Therefore, the overall distribution of the index date of the non-users matches that of the users' time for the first duloxetine prescription. This matched prescription time between duloxetine users and non-users at cohort entry approach is considered reasonable given SUI is a chronic condition and has been reported as a way to control for time-related bias (Zhou et al. 2005).

Exploratory study objectives:

- Index date of SUI diagnosed cohort is the first SUI diagnosis date;
- Index date of non-UI cohort will be reassigned based on the SUI diagnosis date of the matched SUI cases.

End of duloxetine exposure is defined as last prescription plus duration of the prescription and wash out period (30 days). The duloxetine exposure of interest is at any time from marketing approval date of August 4, 2004 through June 30, 2014.

End of the follow up is defined as the incidence of the analyzed suicidality events, or until a first date of the following events: death or loss to follow-up is observable in the data, or end of duloxetine exposure, or end of study period. For patients with multiple outcomes of interest, the first outcome will be considered.

Study observation period is defined as the following:

Primary and secondary study objectives:

Study observation period for the comparison between SUI exposed patients and the SUI non-exposed patients will begin with index date (duloxetine initiation for women exposed and the randomly assigned index date for the unexposed SUI patients) until end of the study follow-up (end of duloxetine exposure for women exposed, and end of the follow up date for the untreated SUI patients). The study observation periods of both comparisons see Figure 5.1.

Exploratory study objectives:

Similarity, for the comparison between SUI patients and non-UI patients, study observation period will begin with index date (SUI diagnosis date for SUI patients, and corresponding date for non-UI patients) until end of the follow-up.

Figure 1: Study observation period

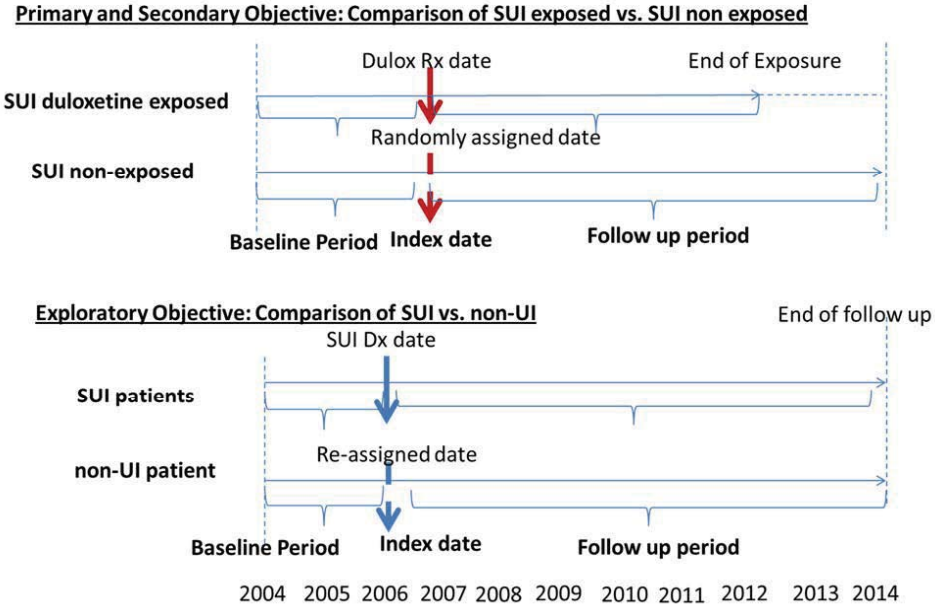

Figure 5.1. Study observation period

4.5. Determination of the Study Outcome of Interest

The following outcomes of interest will be assessed in this study:

- Suicide attempt (includes completed suicide and non-fatal suicide attempts)
- Completed suicide
- Non-fatal suicide attempt
- Suicide ideation

- Combined outcome of completed suicide, non-fatal suicide attempt, or suicide ideation.

Please refer to the Appendix Sections 8.2- 8.14 for suicidality-related Read codes. The relevant medical information will be reviewed by a GPS clinician to confirm the status of the outcome.

In a sensitivity analysis, the nonfatal suicidal attempts will be defined broadly to include additional "possible suicidal attempt" using an intent-to-treat analysis.

4.6. Other study Variables

Covariates of interest are known predictors of suicidality, such as a diagnosis of depression and other psychiatric conditions, past history of non-fatal suicide attempts, a diagnosis of other psychiatric conditions, history of psychiatric hospitalizations, and use of antidepressants as documented in the available medical records (pertinent Read or OXMIS Medical Codes specified in the Appendix Sections 8.3 – 8.9).

Independent variables of interest are baseline depressive diagnosis, other comorbid psychiatric conditions (bipolar, anxiety disorder, schizophrenia and borderline personality), history of psychiatric hospitalizations, number of previous non-fatal suicide attempts, and number and type of anti-depressants used, if any (please refer to the appendix for related codes). Other non-psychiatric comorbidities captured via the Charlson comorbidity index (CCI) will be considered as confounders of the association between SUI and suicidality as well as between duloxetine use and suicidality and used, if appropriate.

Additionally, lifestyle factors, such as alcoholism/alcohol abuse and drug dependence/drug abuse will also be considered as independent variables, if appropriate.

5. Statistical Methods

5.1. General Aspects for Statistical Analysis

5.1.1. Data Sources

The CPRD database (formally GPRD) is an anonymized, longitudinal, primary care medical record database in the United Kingdom (UK). It contains information on all medical care including diagnoses and treatments provided by general practitioners (GP) in the United Kingdom. The CPRD also captures information on diagnoses and treatments from specialists through GP's electronic medical records. In the UK, more than 99% of patients are registered with a GP through the National Health Service. Currently the database captures information from 685 practices, representing approximately 8% of the UK population. Data from CPRD is subjected to checks for continuity and completeness, and data from individual practices are flagged to ensure that researchers are aware of any data quality issues.

Diseases are classified in the CPRD using Read Codes. Read Codes are diagnostic codes used by the general practitioners as part of the patient's electronic medical record. The quality of the data is monitored and patients are labelled as 'acceptable' for use in research by a process that identifies and excludes patients with non-contiguous follow-up or patients with poor data recording. The overall quality of data from individual practices is mediated by use of an "up to standard" date, which is the date at which audits demonstrate that at least 95% of relevant patient encounters are recorded and data are determined to be suitable for epidemiologic research.

5.1.2. Coding

The coding for the study variables refers to the following Appendix Sections:

Appendix 8.2: Read or OXMIS Medical Codes of Study outcomes – Completed suicide, Suicidal attempt and Suicidal ideation, updated through June 30th 2014

Appendix 8.3: Read or OXMIS Medical Codes and corresponding text for **depression**

Appendix 8.4: Read or OXMIS Medical Codes and corresponding text for **history of depression**

Appendix 8.5: Codes in the 'outcome' field and corresponding text description indicating hospitalization

Appendix 8.6: Read or OXMIS Medical Codes and corresponding text in the diagnosis field indicating hospitalization

Appendix 8.7: Read or OXMIS Medical Codes and corresponding text for **bipolar disorder**

Appendix 8.8: Read or OXMIS Medical Codes and medical description for **anxiety**

Appendix 8.9: Read or OXMIS Medical Codes and corresponding text for **schizophrenia** and related thought disorders

Appendix 8.10: Read or OXMIS Medical Codes and corresponding text for **Borderline personality disorders**

Appendix 8.11: Read or OXMIS Medical Codes and corresponding text for **Substance Abuse**

Appendix 8.12 Read or OXMIS Medical Codes and corresponding text for **Alcohol Abuse**

Appendix 8.13 Read or OXMIS Medical Codes and corresponding text for **Charlson Comorbidity Index**

Appendix 8.14 Read or OXMIS Medical Codes and corresponding text for family history of suicidality

5.2. Demographics other Baseline Characteristics

Important demographic and baseline characteristics will be summarized for each of the comparison populations (Duloxetine SUI versus Non-Duloxetine SUI and SUI versus Non-SUI). Continuous factors summarized will include mean index age, mean follow-up time, and Charlson Comorbidity Index (summarized via means and standard deviations). Categorical factors will be summarized via percentages and include psychiatric comorbidities, suicidal history (history of attempts, history of ideation, family history of suicidality), hospitalization history, and psychiatric medication use (by class of medication).

5.3. Analysis Methods

Unless otherwise stated, all formal comparisons of SUI duloxetine-exposed patients to SUI unexposed patients and of SUI women to non-SUI women will be based on the corresponding matched populations detailed in Section 4.3.

Exposure-adjusted incidence for each suicide-related study outcome, and for all outcomes combined, with corresponding 95% confidence intervals will be calculated for the analytic cohorts overall and stratifying by depression status.

5.3.1. Primary Endpoint Analysis

For the primary comparison of suicide attempt (non-fatal attempt and complete suicide) rates between SUI patients exposed to duloxetine versus SUI patients not exposed to duloxetine, a Cox proportional hazard model will be used to estimate adjust hazard ratios along with the corresponding 95% confidence intervals. Estimations will be based on models that will incrementally include the covariates of interest (as detailed below in Table 5.1).

Table 5.1 Cox Regression Models for each suicidality outcome within women with an SUI diagnosis, contrasting women taking duloxetine with those that did not take duloxetine

Covariates	Base model	Base model + Depression	Full model
Duloxetine Status	X	X	X
Current depression		X	X
Psych comorbidities			X
Hx of depression		X	X
Hx of psych hospitalization			X
Hx of suicide attempt			X

5.3.2. Secondary Analyses

Cox Proportional Hazards models will also be used to assess the association between each of the other suicidality-related outcomes listed in Section 4.5 and receipt of duloxetine treatment in the subpopulation of women with SUI, following the same procedure used for the primary comparisons.

For comparison of each suicidality-related outcome listed in Section 4.5 between subjects with and without an SUI diagnosis, a Cox proportional hazard model will be used to estimate adjusted hazard ratios along with the corresponding 95% confidence intervals. Estimations will be based on models that will incrementally include the covariates of interest as detailed in Table 5.2.

Table 5.2 Cox Regression Models for each suicidality outcome, contrasting SUI women versus population sample with no SUI diagnoses

Covariates	Base model	Base model + Depression	Base model + Depression + AD use	Full model
SUI status	X	X	X	X
Current depression		X	X	X
Antidepressant use			X	X
Psych comorbidities				X
Hx of depression		X	X	X
Hx of psych hospitalization				X
Hx of suicide attempt				X

5.3.3. Exploratory and Sensitivity Analyses

Exposure-adjusted incidence for each suicide-related event, and for all events combined, with corresponding 95% confidence intervals will be calculated for the analytic cohorts overall and stratifying by depression status using a Poisson regression model with effect for depression status (with a log exposure offset). These estimations will be performed separately based on the following analytic cohorts:

- Women with a diagnosis of SUI, accounting for duloxetine exposure status, if applicable
- Women without a diagnosis of urinary incontinence of any type, accounting for duloxetine exposure status, if applicable
- Women with a diagnosis of SUI receiving duloxetine treatment for this indication
- Women with a diagnosis of SUI not receiving duloxetine treatment for any indication

Suicidality incidence rates (unadjusted for amount of follow up time) and corresponding 95% Clopper-Pearson confidence intervals will also be calculated for the overall female population in the GPRD dataset and by 5-year age groups.

Additionally, as sensitivity analyses to assess possible confounding of association within the SUI exposed and non-exposed populations, the Cox proportional hazard model analyses of each of the different suicidality-outcomes may be repeated adding the non-psychiatric comorbidities listed in Section 4.6 to the “full models” detailed above in Table 5.1.

Sensitivity analysis 1: In order to assess the impact of the gaps between prescriptions on exposure duration (especially as-treated analysis), additional analyses will be conducted to apply different grace periods other than 30 days, i.e. 60 days and 90 days, and intent-to-treat analysis (e.g. intent-to-treat analysis will follow patients until the end of data availability).

Sensitivity analysis 2: Due to its low predictability of suicidal outcomes, the additional analyses will be performed to assess the impact of various definitions of suicidal outcomes. The diagnostic codes will be reviewed by two independent Lilly physicians with psychiatric clinical experience, and the final code list is based on consensus.

Sensitivity analysis 3: Additional analyses may be conducted to assess the impact of proportional hazard. Due to potential imbalance in follow-up time between treated patients and untreated patients, additional analyses may be conducted to ensure comparable length of follow-up between the cohorts.

5.3.4. Post hoc Analyses

After reviewing the baseline characteristics from the main analysis, there are substantial differences between duloxetine-treated and untreated SUI patients in terms of baseline psychiatric conditions (e.g. depression, antidepressant use, etc.). For example, duloxetine-treated patients had a higher proportion of baseline depression (14.44% vs.9.95%), and history of depression (27.06% vs. 19.29%), furthermore, they were more likely to exposed to any psychiatric medication (54.14% vs.38.23%), among those prescriptions more patients exposed to additional antidepressants (36.10% vs. 23.44%), which may be due to the depression severity. In terms of other comorbidities, duloxetine-treated patients had higher baseline diabetes (7.4% vs. 4.7%) and diabetes with complications (1.4% vs. 0.5%), compared to duloxetine-untreated patients.

Given that depression (and other psychiatric conditions) is a known risk factor of suicidal outcomes, the residual confounding factors are the concerns to bias the association. Although the additional proposed analyses may not fully adjust for confounding, these analyses will help interpret the study findings in the context of the study design limitations.

5.3.4.1. Post Hoc Analyses Using Propensity Score Stratification Methodology

This analysis will use propensity score stratification, as it maximizes the use of full sample size comparing to some other methods, i.e. propensity score matching. In this method, observation for each subject is classified into a propensity quintile based on the propensity score. The propensity score for each patient will be defined by the probability of being in the treated group. The propensity score will be estimated using logistic regression, with group (treated versus untreated) as the outcome variable. The logistic regression propensity model will include independent variable values collected at baseline. These propensity scores will be used to stratify patients into 5 strata. Due to the limited outcomes observed among the cohorts, 5 strata are considered appropriate. Within each stratum, the effect of treatment on outcomes can be estimated by comparing outcomes directly between treated and untreated subjects. The stratum-specific estimates of treatment effect can then be pooled across stratum to estimate an overall treatment effect (Rosenbaum & Rubin, 1984). Thus, stratum-specific differences in means or risk

differences can be estimated. These can be averaged to produce an overall difference in means or risk difference. In general, stratum-specific estimates of effect are weighted by the proportion of subjects who lie within that stratum. Thus, when the sample is stratified into K equal-size strata, stratum-specific weights of 1/K are commonly used when pooling the stratum-specific treatment effects, allowing one to estimate the average treatment effect (Imbens, 2004). The use of stratum-specific weights that are equal to that proportion of treated subjects that lie within each stratum allow one to estimate the average treatment effect for treated subjects (Imbens, 2004). A pooled estimate of the variance of the estimated treatment effect can be obtained by pooling the variances of the stratum-specific treatment effects.

5.3.4.2. Post Hoc Analyses Using Additional Comparator Groups

Confounding by indication and/or severity is very difficult to control when comparing treated with untreated persons. One way to reduce the potential for confounding is to compare with another actively treated cohort of patients with a similar potential for confounding. Given the concerns of underlying depression among SUI patients treated with duloxetine, the comparator that we propose will be SUI patients treated with any other anti-depressants (not in serotonin and norepinephrine reuptake inhibitor [SNRI] or selective serotonin reuptake inhibitor [SSRI] class), drug codes are listed in Appendix 8.15. The goal of this comparative analysis is to demonstrate the choices for comparator groups and its impact on the association observed from the study. Of note, this approach will only control for any measured confounding factors, while it will not be able to address any concerns of unmeasured confounding factors.

Study participants: Among original SUI-diagnosed patient population, two comparison groups will be formed. Like the main analysis, patients with baseline duloxetine exposure will be excluded, and patients with other antidepressants exposure (e.g. SSRI class or other SNRI, TCA, etc.) at baseline will be presented at baseline table and considered in the propensity score model. In addition, patients who are co-prescribed with both duloxetine and other antidepressant study drugs (any antidepressants, including SSRI/SNRI except duloxetine) at the index date will be excluded from this analysis. To avoid immortal time bias, all patients have an equal chance to be included in either cohort if they were exposed to study drugs. For example, if a patient is first exposed to other antidepressants (not an SNRI except for Duloxetine or SSRI class) after SUI diagnosis, then receive duloxetine prescription, the patient will be assigned to another antidepressant cohort (not duloxetine group), and censored at the time that she initiates duloxetine or an antidepressant in another class. Patients will not be exposed to the study drug at baseline in order to be eligible for the study cohorts. Index date is defined as the initial date of study drug prescription. Patients will be followed until the end of data records, or end of drug exposure, or occurrence of outcome of interest, and/or the time of initiation of the other antidepressant drugs in another class other than the study drug in both cohorts. Figure 5.2 demonstrates the formation of both cohorts, index date, baseline period, and follow-up period.

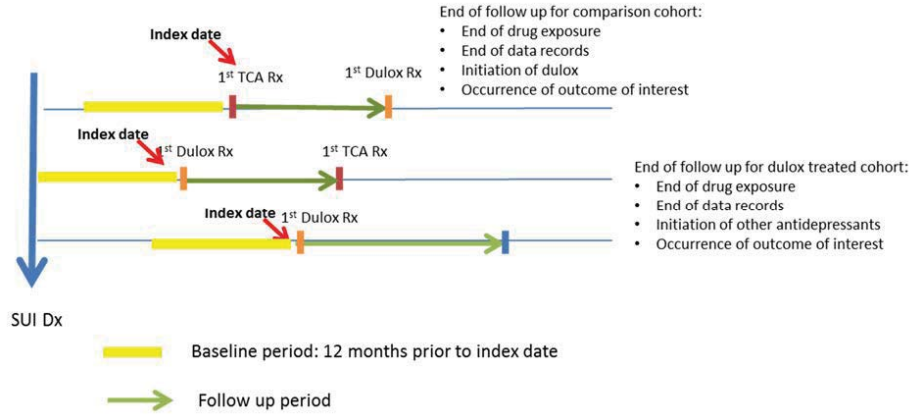

Figure 5.2. **Demonstration of study cohorts (duloxetine vs. any other antidepressant treated), index date, baseline period, follow up period**

Propensity score will be calculated for both cohorts using methods listed in Section 5.3.4.1. Based on the propensity score distribution, patients will be stratified into quintiles (the number of strata may be determined by number of sample size and propensity score distribution). The effect of treatment will be evaluated at each stratum, as well as pooled across all strata. The statistical methods used above in Section 5.3.4.1 will be repeated here to compare patients treated with duloxetine to patients treated with other antidepressants.

6. Updates in the Analysis Plan since B035

Highlights of the additional analyses that weren't previously clarified or planned due to limited sample size:

1. **Baseline period:** Baseline period is defined as 1 year prior to the index date to assess characteristics that patients have prior to treatment or diagnosis. This requirement may reduce the number of patients. If a significant portion of patients is excluded due to less than 1 year baseline, a shorter duration of baseline will be proposed alternatively.

2. **Index date:** the index date for matching the comparison cohorts will be either the date diagnosed or treated with duloxetine, in order to avoid time related bias or immortal time bias.

   Primary and secondary study objectives:
   - Index date of duloxetine treated SUI patients is the first prescription date of duloxetine;
   - Index date of non-duloxetine treated SUI patients will be selected at random and assigned to the nonusers according to the distribution of time between diagnosis and prescription derived from the treated cohort. Therefore, the overall distribution of the index date of the non-users matches that of the users' time for the first duloxetine prescription.

   Exploratory study objectives:
   - Index date of SUI diagnosed patients is the first SUI diagnosis date;
   - Index date of non-UI patients will be reassigned based on the SUI diagnosis date of the matched SUI cases.

3. **Matching criteria**: matching criteria for the both comparisons are proposed to be more restricted, and can be adjusted if sample size is impacted significantly.

   Primary and secondary study objectives:
   - In the comparison between duloxetine exposed SUI vs. unexposed SUI patients, SUI unexposed patients be matched to SUI exposed based on year of birth, clinical practice, SUI diagnosis date ± 90 days, and index date ± 30 days (randomly assigned index date for untreated patients). The consideration of adding diagnosis date as a requirement is to control for changes in the standard of care, and will be adjusted based on the sample size restriction.

   Exploratory study objectives:
   - In the comparison between SUI and non- UI to assess the association between SUI and suicidality, non-UI patient will be matched to SUI patients based on year of birth, clinical practice and duloxetine prescription. The consideration of adding duloxetine prescription is to preclude evaluation of the drug effect. This addition should not significantly impact the sample size.

4. For patients with multiple outcomes of interest, the **first outcome** will be considered, not the most severe condition, because the primary study outcome defined as suicide attempts, which includes non-fatal suicidal attempt and complete suicide. Of note, no completed suicide cases have been reported in any of the previous analyses.

5. **As-treated analysis:** To provide better clarity for the as-treated analysis, the exposure period of treated patients will count a wash out period after the last prescription ends, and the wash-out period is considered to be 30days.

6. Coding: Study variable coding has been updated.

7. References

Imbens, Guido W. "Nonparametric estimation of average treatment effects under exogeneity: A review." Review of Economics and statistics 86.1 (2004): 4-29.

Khan N, Perera R, et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Family Practice*. 2010;11:1.

Rosenbaum P and Rubin D. Reducing bias in observational studies using subclassification on the propensity score. J*ournal of the American Statistical Association.* 1984;79(387): 516-524.

Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol.* 2005;162:1016-1023.

8. Appendix

8.1. Sample size and Power Calculation – Duloxetine and Suicidality Study: Stress Urinary Incontinence and Suicide-Related Behaviors: General Practice Research Database (GPRD) Analysis

8.1.1. Purpose of the document

1. To document the methodology and results of Q42014 in sample size/power calculation for non-fatal suicide attempts, fulfilling the feasibility commitment in the Risk Management Plan (RMP).
2. To make a recommendation to the Duloxetine team in terms of sample size/power calculation for suicidality study and whether to initiate a new analysis for the study outcome.

8.1.2. Background

In 2004, Stress Urinary Incontinence (SUI) was a new non-psychiatric indication for duloxetine. Due to limited epidemiological data on baseline psychiatric comorbidities potentially associated with suicidality, and reports of suicidality events in this indication, the Duloxetine Risk Management Plan (rv1; April 2006) specified that the General Practice Research Database (GPRD) would be used to compare the rate of suicide-related events among women with SUI who were administered duloxetine compared with continent matched women, as well as with duloxetine unexposed women with SUI.

- "GPRD analysis of suicidality in SUI patients: The 4 analyses conducted thus far by Lilly, do not suggest an association between duloxetine treatment and suicidality in women with SUI. However, as Lilly has been requested by regulators that this analysis be conducted again, the following represents Lilly's plan."
- "The analysis will be conducted when accrual of exposed patients in GPRD is sufficient for a powered study that is able to rule out a pre-specified limit for the hazard ratio for the most serious outcome under study thus far, non-fatal suicide attempts. Lilly proposes to perform a new analysis with additional exposures upon accrual of a sufficient number of exposed patients to achieve 80% power to rule out a hazard ratio (hazard treated / hazard untreated) of 2.5 for non-fatal suicide attempts, based on the upper confidence limit of a 2-sided 95% confidence interval for the hazard ratio. Based on preliminary calculations, sufficient accrual in the GPRD database should be observed approximately in 2013 or 2014. Lilly proposes to evaluate the database in Q4 2013 to see if we have achieved the necessary patient-years' follow-up required by our estimate."

The database was evaluated in Q4 2013 and it was determined that the necessary patient-years' follow-up had not been attained. This document details of the feasibility assessment of Q4 2014 and the plan going forward.

8.1.3. Methodology

The sample size is computed based on a two-sample noninferiority log-rank test, using the methodology of Jung, Kang [1]. The constants input to the sample size calculation are: 80% power, two-sided alpha = 0.05, null hypothesis: hazard ratio >= 2.5, ratio of untreated to duloxetine is 4:1. Formula (1) of Jung et al. (see below) was used to determine that **49 events** are needed in order to achieve the specified power with these constants Jung, Kang [1].

$$D = \frac{\{\sqrt{\Delta_0} z_{1-\alpha} + (p_1 + p_2\Delta_0) z_{1-\beta}\}^2}{p_1 p_2 (\Delta_0 - 1)^2}.$$

In order to convert the events needed into the approximate number of patient-years follow-up, we estimated the event rate based on the 2010 report. In that report, there were 22 events with 33,315 years follow-up, which is an **event rate of 0.00066 per patient-year**. If that event rate persists, we would need ***74,243 patient years*** follow-up to have accrued 49 events. The program of this calculation was saved at: lillyce / prd / multi_compound / gps / general_safety / programs_nonsdd / noninferiority_logrank_samplesize.R; and the outputs of the test were saved at: 1) lillyce / prd / multi_compound / gps / general_safety / programs_nonsdd / tfl_output / Jung_testing.pdf; 2) lillyce / prd / multi_compound / gps / general_safety / programs_nonsdd / tfl_output / dulox_samp_size.csv.

It is more efficient to determine patient-years follow-up in the database than to check the number of events.

8.1.4. Calculate the patient-years (treated cohort)

Calculate the number of patient years follow-up for treated patients and multiply it by five (because of the 4:1 matching of untreated to treated) to estimate the total follow-up time. If we have not achieved the required patient-years follow-up (74,243 patient years), we will recheck the patient-years in the database once per year until the database includes the necessary patient-years follow-up.

8.1.5. Results

The calculation of patient years was completed and the patient-year follow up was updated to Q2 2013. Consistent with the protocol specifications, the follow-up for duloxetine-treated SUI patients started from the first duloxetine prescription, until the outcome (i.e. non-fatal suicide attempts) or the end of the data availability. The **total duloxetine-treated SUI patients follow-up time is 17,349** patient years, which indicates that the overall follow up time is approximated 86,745 patient years. The number exceeded the required patient-years (i.e.74,243 patient-years). This is a data-driven approach, and the estimation is based on the assumption that the event rate continues to reach the required number of events (i.e. 49 events, which cannot be confirmed till

the analysis is completed). Since a discrepancy between the follow up time and the number of events is possible, additional data may also be helpful.

8.1.6. Recommendations

Using above data-driven approach, the sample size estimation reached the pre-specified observed total follow-up time. The team was advised to initiate the study using the next available data cut (e.g. Q4 2013).

8.1.7. References

1. Jung SH, Kang SJ, McCall LM, Blumenstein B. Sample size computation for two-sample noninferiority log-rank test. J Biopharm Stat 2005;15:969-79.

8.2. Read or OXMIS Medical Codes of Study outcomes – Completed suicide, Suicidal attempt and Suicidal ideation, updated through June 30th 2014

- Completed Suicide

TK05.00	Suicide + selfinflicted poisoning by drug or medicine NOS
U2...13	[X]Suicide
TK3y.00	Suicide + selfinflicted inj oth mean hang/strangle/suffocate
TK30.00	Suicide and selfinflicted injury by hanging
TK00.00	Suicide + selfinflicted poisoning by analgesic/antipyretic
TK60.00	Suicide and selfinflicted injury by cutting
TK01.00	Suicide + selfinflicted poisoning by barbiturates
TK...14	Suicide and self harm
TK...00	Suicide and selfinflicted injury
TK04.00	Suicide + selfinflicted poisoning by other drugs/medicines
TK3..00	Suicide + selfinflicted injury by hang/strangulate/suffocate
TK7..00	Suicide and selfinflicted injury by jumping from high place
TK61.00	Suicide and selfinflicted injury by stabbing
TK03.00	Suicide + selfinflicted poisoning tranquilliser/psychotropic
TK07.00	Suicide + selfinflicted poisoning by corrosive/caustic subst
TK51.00	Suicide and selfinflicted injury by shotgun
TK0..00	Suicide + selfinflicted poisoning by solid/liquid substances
TK4..00	Suicide and selfinflicted injury by drowning
TK02.00	Suicide + selfinflicted poisoning by oth sedatives/hypnotics
TKx2.00	Suicide and selfinflicted injury by scald
TK6..00	Suicide and selfinflicted injury by cutting and stabbing
TKz..00	Suicide and selfinflicted injury NOS
TK71.00	Suicide+selfinflicted injury-jump from oth manmade structure
TKx1.00	Suicide and selfinflicted injury by burns or fire
TKx..00	Suicide and selfinflicted injury by other means
TK20.00	Suicide + selfinflicted poisoning by motor veh exhaust gas
TK1y.00	Suicide and selfinflicted poisoning by other utility gas
TK21.00	Suicide and selfinflicted poisoning by other carbon monoxide
TK31.00	Suicide + selfinflicted injury by suffocation by plastic bag
TK06.00	Suicide + selfinflicted poisoning by agricultural chemical
TK52.00	Suicide and selfinflicted injury by hunting rifle
TK7z.00	Suicide+selfinflicted injury-jump from high place NOS
TKx0000	Suicide + selfinflicted injury-jumping before moving object
TK3z.00	Suicide + selfinflicted inj by hang/strangle/suffocate NOS
TK72.00	Suicide+selfinflicted injury-jump from natural sites
TK70.00	Suicide+selfinflicted injury-jump from residential premises
TK2..00	Suicide + selfinflicted poisoning by other gases and vapours

TKx5.00	Suicide and selfinflicted injury by crashing motor vehicle
TK54.00	Suicide and selfinflicted injury by other firearm
TK6z.00	Suicide and selfinflicted injury by cutting and stabbing NOS
TKxy.00	Suicide and selfinflicted injury by other specified means
TK01000	Suicide and self inflicted injury by Amylobarbitone
TK0z.00	Suicide + selfinflicted poisoning by solid/liquid subst NOS
TK5..00	Suicide and selfinflicted injury by firearms and explosives
TK10.00	Suicide + selfinflicted poisoning by gas via pipeline
TK1..00	Suicide + selfinflicted poisoning by gases in domestic use
TKx0.00	Suicide + selfinflicted injury-jump/lie before moving object
TKx4.00	Suicide and selfinflicted injury by electrocution
TK11.00	Suicide + selfinflicted poisoning by liquified petrol gas
TKxz.00	Suicide and selfinflicted injury by other means NOS
TK2z.00	Suicide + selfinflicted poisoning by gases and vapours NOS
TK1z.00	Suicide + selfinflicted poisoning by domestic gases NOS
TK01400	Suicide and self inflicted injury by Phenobarbitone
TKx7.00	Suicide and selfinflicted injury caustic subst, excl poison
TKx3.00	Suicide and selfinflicted injury by extremes of cold
TK01100	Suicide and self inflicted injury by Barbitone
TKx7.00	Suicide and selfinflicted injury caustic subst, excl poison
TKx3.00	Suicide and selfinflicted injury by extremes of cold
TK01100	Suicide and self inflicted injury by Barbitone
TK5z.00	Suicide and selfinflicted injury by firearms/explosives NOS
TKx6.00	Suicide and selfinflicted injury by crashing of aircraft
TK2y.00	Suicide + selfinflicted poisoning by other gases and vapours
TK01z00	Suicide and self inflicted injury by barbiturates
TKx0z00	Suicide + selfinflicted inj-jump/lie before moving obj NOS
TK53.00	Suicide and selfinflicted injury by military firearms

- Suicide Attempts (primary outcome, not including possible attempts)

U20..11	[X]Deliberate drug overdose / other poisoning
TK...15	Attempted suicide
TK...11	Cause of overdose - deliberate
U209.00	[X]Intent self poison/exposure to alcohol
TK...13	Poisoning - self-inflicted
U30..11	[X]Deliberate drug poisoning
U2...14	[X]Attempted suicide
U200z00	[X]Intent self poison nonopioid analgesic unspecif place
U200.00	[X]Intent self poison/exposure to nonopioid analgesic
U20A.11	[X]Self poisoning from glue solvent
U20B.11	[X]Self carbon monoxide poisoning

U20..00	[X]Intentional self poisoning/exposure to noxious substances
U208.00	[X]Int self poison/exposure to other/unspec drug/medicament
U204.00	[X]Intent self poison/exposure to psychotropic drug
U20B200	[X]Int self poison other gas/vapour school/pub admin area
U209000	[X]Int self poison/exposure to alcohol at home
U20yz00	[X]Intent self poison unspecif chemical unspecif place
U20A.00	[X]Intentional self poison organ solvent,halogen hydrocarb
U204000	[X]Int self poison/exposure to psychotropic drug at home
U202000	[X]Int self poison/exposure to sedative hypnotic at home
U205.00	[X]Intent self poison/exposure to narcotic drug
U200000	[X]Int self poison/exposure to nonopioid analgesic at home
U202.00	[X]Intent self poison/exposure to sedative hypnotic
U20B.00	[X]Intent self poison/exposure to other gas/vapour
U20y000	[X]Int self poison/exposure to unspecif chemical at home
U205000	[X]Int self poison/exposure to narcotic drug at home
U20B000	[X]Int self poison/exposure to other gas/vapour at home
U201000	[X]Int self poison/exposure to antiepileptic at home
U20By00	[X]Int self poison other gas/vapour other spec place
U20y.00	[X]Intent self poison/exposure to unspecif chemical
U209z00	[X]Intent self poison alcohol unspecif place
U20y200	[X]Int self poison unspecif chemical school/pub admin area
U208000	[X]Int self poison/exposure to oth/unsp drug/medicam home
U20Bz00	[X]Intent self poison other gas/vapour unspecif place
U201.00	[X]Intent self poison/exposure to antiepileptic
U201z00	[X]Intent self poison antiepileptic unspecif place
U204z00	[X]Intent self poison psychotropic drug unspecif place
U207z00	[X]Intent self poison oth autonomic drug unspecif place
U20C.12	[X]Self poisoning with paraquat
U208z00	[X]Intent self poison oth/unsp drug/medic unspecif place
U205z00	[X]Intent self poison narcotic drug unspecif place
U202z00	[X]Intent self poison sedative hypnotic unspecif place
U207.00	[X]Intent self poison/exposure to oth autonomic drug
U20C.00	[X]Intent self poison/exposure to pesticide
U202y00	[X]Int self poison sedative hypnotic other spec place
U205y00	[X]Int self poison narcotic drug other spec place
U20A400	[X]Int self poison org solvent,halogen hydrocarb,in highway
U207000	[X]Int self poison/exposure to oth autonomic drug at home
U20C.11	[X]Self poisoning with weedkiller
U20Cy00	[X]Int self poison pesticide other spec place
U206.00	[X]Intent self poison/exposure to hallucinogen
U200y00	[X]Int self poison nonopioid analgesic other spec place
U204y00	[X]Int self poison psychotropic drug other spec place

U200100	[X]Intent self poison nonopioid analgesic at res institut
U20C000	[X]Int self poison/exposure to pesticide at home
U208y00	[X]Int self poison oth/unsp drug/medic other spec place
U209y00	[X]Int self poison alcohol other spec place
U204100	[X]Intent self poison psychotropic drug at res institut
ZX1..13	Deliberate self-harm
ZX...00	Self-harm
U2...00	[X]Intentional self-harm
U72..00	[X]Sequel intentn self-harm assault+event of undeterm intent
U720.00	[X]Sequelae of intentional self-harm
U200y00	[X]Int self poison nonopioid analgesic other spec place
U204y00	[X]Int self poison psychotropic drug other spec place
U200100	[X]Intent self poison nonopioid analgesic at res institut
U20C000	[X]Int self poison/exposure to pesticide at home
U208y00	[X]Int self poison oth/unsp drug/medic other spec place
U209y00	[X]Int self poison alcohol other spec place
U2Az.00	[X]Intentional self harm by blunt object occ unspecif place
TK...11	Cause of overdose - deliberate
U20..11	[X]Deliberate drug overdose / other poisoning
14K1.00	Intentional overdose of prescription only medication

- Possible Suicide Attempts (used in a secondary ITT analysis)

Tz...00	Causes of injury and poisoning NOS
U40..00	[X]Poisoning/expos to noxious substance,undetermined intent
TN...11	Poisoning undetermined - accidentally or purposely inflicted
U40y.00	[X]Poisoning/exposure, ? intent, to unspecif chemical
U409.00	[X]Poisoning/exposure, ? intent, to alcohol
U40C.00	[X]Poisoning/exposure, ? intent, to pesticide
U408.00	[X]Poison/exposure, ?intent, to other/unspec drug/medicament
U405.00	[X]Poisoning/exposure, ? intent, to narcotic drug
U400.00	[X]Poisoning/exposure, ? intent, to nonopioid analgesic
U402.00	[X]Poisoning/exposure, ? intent, to sedative hypnotic
U40B.00	[X]Poisoning/exposure, ? intent, to other gas/vapour
U409000	[X]Poison/exposure ?intent, to alcohol at home
U40y600	[X]Poison/expos ?intent unspec chemic indust/construct area
U408000	[X]Poison/exposure ?intent, to oth/unsp drug/medicam home
U404.00	[X]Poisoning/exposure, ? intent, to psychotropic drug
SyuFM00	[X]Poisoning by other psychotropic drugs, NEC
U408000	[X]Poison/exposure ?intent, to oth/unsp drug/medicam home
U404.00	[X]Poisoning/exposure, ? intent, to psychotropic drug
SL95.00	Other tranquilliser poisoning

SL70z00	Barbiturate poisoning NOS
SL96z00	Hallucinogen poisoning NOS
SL35100	Vitamin D poisoning
SL74.00	Methaqualone compound poisoning
SLH4.00	Pharmaceutical excipient poisoning
SyuFB00	[X]Poisoning by other opioids
TN3y.00	Injury ?accidental, other means of hang/strangle/suffocate
SL...15	Overdose of drug
U200.11	[X]Overdose - paracetamol
U200.13	[X]Overdose - aspirin
U202.12	[X]Overdose - diazepam
U204.11	[X]Overdose - antidepressant
U200.12	[X]Overdose - ibuprofen
U202.13	[X]Overdose - temazepam
U204.12	[X]Overdose - amitriptyline
U202.16	[X]Overdose - benzodiazepine
U202.11	[X]Overdose - sleeping tabs
U202.17	[X]Overdose - barbiturate
U202.15	[X]Overdose - nitrazepam
U204.13	[X]Overdose - SSRI
U202.18	[X]Overdose - amobarbital

- Suicide Ideation

1BD1.00	Suicidal ideation
1BD3.00	Suicidal plans
1BD4.00	Suicide risk
1B19.11	Suicidal - symptom
1B19.00	Suicidal
1BD7.00	Low suicide risk
1BD5.00	High suicide risk
1BD6.00	Moderate suicide risk
8G6Z.00	Anti-suicide psychotherapy NOS
8G6..00	Anti-suicide psychotherapy
1BDC.00	Intent of deliberate self harm with detailed plans
1BDA.00	Thoughts of deliberate self harm
1BD8.00	At risk of DSH - deliberate self harm
1BD..00	Harmful thoughts
1BDD.00	Unknown risk of deliberate self harm
1BD2.00	Morbid thoughts
1BDB.00	Plans for deliberate self harm without intent
Z9K3.00	Suicide prevention

ZRn6.11	SRS - Suicide risk scale
8G61.00	Potential suicide care
1BDE.00	Suicide risk increased from previous level
1BDF.00	Suicide risk unchanged from previous level

8.3. Read or OXMIS Medical Codes and corresponding text for depression

1B17.00	Depressed
2257	O/E - depressed
62T1.00	Puerperal depression
8BK0.00	Depression management programme
9HA0.00	On depression register
9kQ..00	On full dose long term treatment depression - enh serv admin
E11..12	Depressive psychoses
E112.00	Single major depressive episode
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E112000	Single major depressive episode, unspecified
E112100	Single major depressive episode, mild
E112200	Single major depressive episode, moderate
E112300	Single major depressive episode, severe, without psychosis
E112400	Single major depressive episode, severe, with psychosis
E112500	Single major depressive episode, partial or unspec remission
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
E113.11	Endogenous depression - recurrent
E113000	Recurrent major depressive episodes, unspecified
E113100	Recurrent major depressive episodes, mild
E113200	Recurrent major depressive episodes, moderate
E113300	Recurrent major depressive episodes, severe, no psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis
E113500	Recurrent major depressive episodes,partial/unspec remission
E113700	Recurrent depression
E113z00	Recurrent major depressive episode NOS
E118.00	Seasonal affective disorder
E11y200	Atypical depressive disorder
E11z200	Masked depression
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
E135.00	Agitated depression

E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E204.11	Postnatal depression
E290.00	Brief depressive reaction
E290z00	Brief depressive reaction NOS
E291.00	Prolonged depressive reaction
E2B..00	Depressive disorder NEC
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu32.00	[X]Depressive episode
Eu32.11	[X]Single episode of depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms
Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32314	[X]Single episode of reactive depressive psychosis
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32y12	[X]Single episode of masked depression NOS
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS
Eu32z12	[X]Depressive disorder NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33.15	[X]SAD - Seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild

Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu34100	[X]Dysthymia
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu3y111	[X]Recurrent brief depressive episodes
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
Eu53011	[X]Postnatal depression NOS
Eu53012	[X]Postpartum depression NOS
R007z13	[D]Postoperative depression
1B17.11	C/O - feeling depressed
1B1U.00	Symptoms of depression
1B1U.11	Depressive symptoms
1BT..00	Depressed mood
1BT..12	Sad mood
1JJ..00	Suspected depression
212S.00	Depression resolved
6G00.00	Postnatal depression counselling
8CAa.00	Patient given advice about management of depression
8HHq.00	Referral for guided self-help for depression
9H90.00	Depression annual review
9H91.00	Depression medication review
9H92.00	Depression interim review
9k4..00	Depression - enhanced services administration
9k40.00	Depression - enhanced service completed
9Ov..00	Depression monitoring administration
9Ov0.00	Depression monitoring first letter
9Ov1.00	Depression monitoring second letter
9Ov2.00	Depression monitoring third letter
9Ov3.00	Depression monitoring verbal invite
9Ov4.00	Depression monitoring telephone invite

E001300	Presenile dementia with depression
E002100	Senile dementia with depression
E004300	Arteriosclerotic dementia with depression
Eu02z16	[X] Senile dementia, depressed or paranoid type
Eu20400	[X]Post-schizophrenic depression
Eu32B00	[X]Antenatal depression
Q018.00	Fetus or neonate affected by maternal postnatal depression

8.4. Read or OXMIS Medical Codes and corresponding text for history of depression (events occurred at baseline prior to index date)

1465	H/O: depression
1B17.00	Depressed
2257	O/E - depressed
62T1.00	Puerperal depression
8BK0.00	Depression management programme
9HA0.00	On depression register
9HA1.00	Removed from depression register
9kQ..00	On full dose long term treatment depression - enh serv admin
E11..12	Depressive psychoses
E112.00	Single major depressive episode
E112.11	Agitated depression
E112.12	Endogenous depression first episode
E112.13	Endogenous depression first episode
E112.14	Endogenous depression
E112000	Single major depressive episode, unspecified
E112100	Single major depressive episode, mild
E112200	Single major depressive episode, moderate
E112300	Single major depressive episode, severe, without psychosis
E112400	Single major depressive episode, severe, with psychosis
E112500	Single major depressive episode, partial or unspec remission
E112600	Single major depressive episode, in full remission
E112z00	Single major depressive episode NOS
E113.00	Recurrent major depressive episode
E113.11	Endogenous depression - recurrent
E113000	Recurrent major depressive episodes, unspecified
E113100	Recurrent major depressive episodes, mild
E113200	Recurrent major depressive episodes, moderate
E113300	Recurrent major depressive episodes, severe, no psychosis
E113400	Recurrent major depressive episodes, severe, with psychosis

E113500	Recurrent major depressive episodes,partial/unspec remission
E113600	Recurrent major depressive episodes, in full remission
E113700	Recurrent depression
E113z00	Recurrent major depressive episode NOS
E118.00	Seasonal affective disorder
E11y200	Atypical depressive disorder
E11z200	Masked depression
E130.00	Reactive depressive psychosis
E130.11	Psychotic reactive depression
E135.00	Agitated depression
E200300	Anxiety with depression
E204.00	Neurotic depression reactive type
E204.11	Postnatal depression
E290.00	Brief depressive reaction
E290z00	Brief depressive reaction NOS
E291.00	Prolonged depressive reaction
E2B..00	Depressive disorder NEC
E2B0.00	Postviral depression
E2B1.00	Chronic depression
Eu32.00	[X]Depressive episode
Eu32.11	[X]Single episode of depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu32.13	[X]Single episode of reactive depression
Eu32000	[X]Mild depressive episode
Eu32100	[X]Moderate depressive episode
Eu32200	[X]Severe depressive episode without psychotic symptoms
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms
Eu32212	[X]Single episode major depression w'out psychotic symptoms
Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu32311	[X]Single episode of major depression and psychotic symptoms
Eu32312	[X]Single episode of psychogenic depressive psychosis
Eu32313	[X]Single episode of psychotic depression
Eu32314	[X]Single episode of reactive depressive psychosis
Eu32400	[X]Mild depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32y00	[X]Other depressive episodes
Eu32y11	[X]Atypical depression
Eu32y12	[X]Single episode of masked depression NOS
Eu32z00	[X]Depressive episode, unspecified
Eu32z11	[X]Depression NOS

Eu32z12	[X]Depressive disorder NOS
Eu32z13	[X]Prolonged single episode of reactive depression
Eu32z14	[X] Reactive depression NOS
Eu33.00	[X]Recurrent depressive disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33.13	[X]Recurrent episodes of reactive depression
Eu33.14	[X]Seasonal depressive disorder
Eu33.15	[X]SAD - Seasonal affective disorder
Eu33000	[X]Recurrent depressive disorder, current episode mild
Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
Eu33300	[X]Recurrent depress disorder cur epi severe with psyc symp
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu33y00	[X]Other recurrent depressive disorders
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33z11	[X]Monopolar depression NOS
Eu34100	[X]Dysthymia
Eu34113	[X]Neurotic depression
Eu34114	[X]Persistant anxiety depression
Eu3y111	[X]Recurrent brief depressive episodes
Eu41200	[X]Mixed anxiety and depressive disorder
Eu41211	[X]Mild anxiety depression
Eu53011	[X]Postnatal depression NOS
Eu53012	[X]Postpartum depression NOS
R007z13	[D]Postoperative depression
1B17.11	C/O - feeling depressed
1B1U.00	Symptoms of depression
1B1U.11	Depressive symptoms
1BT..00	Depressed mood
1BT..12	Sad mood
1JJ..00	Suspected depression
212S.00	Depression resolved
6G00.00	Postnatal depression counselling
8CAa.00	Patient given advice about management of depression
8HHq.00	Referral for guided self-help for depression

9H90.00	Depression annual review
9H91.00	Depression medication review
9H92.00	Depression interim review
9k4..00	Depression - enhanced services administration
9k40.00	Depression - enhanced service completed
9Ov..00	Depression monitoring administration
9Ov0.00	Depression monitoring first letter
9Ov1.00	Depression monitoring second letter
9Ov2.00	Depression monitoring third letter
9Ov3.00	Depression monitoring verbal invite
9Ov4.00	Depression monitoring telephone invite
E001300	Presenile dementia with depression
E002100	Senile dementia with depression
E004300	Arteriosclerotic dementia with depression
Eu02z16	[X] Senile dementia, depressed or paranoid type
Eu20400	[X]Post-schizophrenic depression
Eu32B00	[X]Antenatal depression
Q018.00	Fetus or neonate affected by maternal postnatal depression

8.5. Codes in the ‘outcome’ field and corresponding text description indicating hospitalization

A	Inpatient, doctor referral to accident and emergency
D	Inpatient, hospital discharge summary
H	Inpatient, hospital admission
S	Inpatient, self-referral to accident and emergency

8.6. Read or OXMIS Medical Codes and corresponding text in the diagnosis field indicating hospitalization

T927	Admission hospital
T927 aa	Hospital inpatient
T927 mt	Admitted mental hospital
T9270ac	Compulsory admission to hospital
T932	Discharged from hospital

Y1190ac	Hospital admission mental health act
13f8.11	Hospital inpatient
8h2..00	Emergency hospital admission
8he..00	Discharged from hospital

8.7. Read or OXMIS Medical Codes and corresponding text for bipolar disorder

212V.00	Bipolar affective disorder resolved
E11..00	Affective psychoses
E11..11	Bipolar psychoses
E11..13	Manic psychoses
E110.00	Manic disorder, single episode
E110000	Single manic episode, unspecified
E110100	Single manic episode, mild
E110200	Single manic episode, moderate
E110300	Single manic episode, severe without mention of psychosis
E110400	Single manic episode, severe, with psychosis
E110600	Single manic episode in full remission
E110z00	Manic disorder, single episode NOS
E111.00	Recurrent manic episodes
E111000	Recurrent manic episodes, unspecified
E111100	Recurrent manic episodes, mild
E111200	Recurrent manic episodes, moderate
E111300	Recurrent manic episodes, severe without mention psychosis
E111400	Recurrent manic episodes, severe, with psychosis
E111500	Recurrent manic episodes, partial or unspecified remission
E111600	Recurrent manic episodes, in full remission
E111z00	Recurrent manic episode NOS
E114.00	Bipolar affective disorder, currently manic
E114.11	Manic-depressive - now manic
E114000	Bipolar affective disorder, currently manic, unspecified
E114100	Bipolar affective disorder, currently manic, mild
E114200	Bipolar affective disorder, currently manic, moderate
E114300	Bipolar affect disord, currently manic, severe, no psychosis
E114400	Bipolar affect disord, currently manic,severe with psychosis
E114500	Bipolar affect disord,currently manic, part/unspec remission
E114600	Bipolar affective disorder, currently manic, full remission
E114z00	Bipolar affective disorder, currently manic, NOS
E115.00	Bipolar affective disorder, currently depressed
E115.11	Manic-depressive - now depressed

E115000	Bipolar affective disorder, currently depressed, unspecified
E115100	Bipolar affective disorder, currently depressed, mild
E115200	Bipolar affective disorder, currently depressed, moderate
E115300	Bipolar affect disord, now depressed, severe, no psychosis
E115400	Bipolar affect disord, now depressed, severe with psychosis
E115500	Bipolar affect disord, now depressed, part/unspec remission
E115600	Bipolar affective disorder, now depressed, in full remission
E115z00	Bipolar affective disorder, currently depressed, NOS
E116.00	Mixed bipolar affective disorder
E116000	Mixed bipolar affective disorder, unspecified
E116100	Mixed bipolar affective disorder, mild
E116200	Mixed bipolar affective disorder, moderate
E116300	Mixed bipolar affective disorder, severe, without psychosis
E116400	Mixed bipolar affective disorder, severe, with psychosis
E116500	Mixed bipolar affective disorder, partial/unspec remission
E116600	Mixed bipolar affective disorder, in full remission
E116z00	Mixed bipolar affective disorder, NOS
E117.00	Unspecified bipolar affective disorder
E117000	Unspecified bipolar affective disorder, unspecified
E117100	Unspecified bipolar affective disorder, mild
E117200	Unspecified bipolar affective disorder, moderate
E117300	Unspecified bipolar affective disorder, severe, no psychosis
E117400	Unspecified bipolar affective disorder,severe with psychosis
E117500	Unspecified bipolar affect disord, partial/unspec remission
E117600	Unspecified bipolar affective disorder, in full remission
E117z00	Unspecified bipolar affective disorder, NOS
E11y.00	Other and unspecified manic-depressive psychoses
E11y000	Unspecified manic-depressive psychoses
E11y100	Atypical manic disorder
E11y300	Other mixed manic-depressive psychoses
E11yz00	Other and unspecified manic-depressive psychoses NOS
Eu30.00	[X]Manic episode
Eu30.11	[X]Bipolar disorder, single manic episode
Eu30y00	[X]Other manic episodes
Eu30z00	[X]Manic episode, unspecified
Eu31.00	[X]Bipolar affective disorder
Eu31.11	[X]Manic-depressive illness
Eu31.12	[X]Manic-depressive psychosis
Eu31000	[X]Bipolar affective disorder, current episode hypomanic
Eu31100	[X]Bipolar affect disorder cur epi manic wout psychotic symp
Eu31200	[X]Bipolar affect disorder cur epi manic with psychotic symp
Eu31300	[X]Bipolar affect disorder cur epi mild or moderate depressn
Eu31500	[X]Bipolar affect dis cur epi severe depres with psyc symp
Eu31600	[X]Bipolar affective disorder, current episode mixed

Eu31700	[X]Bipolar affective disorder, currently in remission
Eu31y00	[X]Other bipolar affective disorders
Eu31y11	[X]Bipolar II disorder
Eu31y12	[X]Recurrent manic episodes
Eu31z00	[X]Bipolar affective disorder, unspecified
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
ZV11111	[V]Personal history of manic-depressive psychosis
ZV11112	[V]Personal history of manic-depressive psychosis
146D.00	H/O: manic depressive disorder
E110.11	Hypomanic psychoses
E11z.00	Other and unspecified affective psychoses
E11z000	Unspecified affective psychoses NOS
E11zz00	Other affective psychosis NOS
Eu3..00	[X]Mood - affective disorders
Eu30211	[X]Mania with mood-congruent psychotic symptoms
Eu31.13	[X]Manic-depressive reaction
Eu31800	[X]Bipolar affective disorder type I
Eu31900	[X]Bipolar affective disorder type II
Eu31911	[X]Bipolar II disorder
Eu3y000	[X]Other single mood affective disorders
Eu3yy00	[X]Other specified mood affective disorders
Eu3z.00	[X]Unspecified mood affective disorder

8.8. Read or OXMIS Medical Codes and medical description for anxiety

E200.00	Anxiety states
E200111	Panic attack
E200100	Panic disorder
E200z00	Anxiety state NOS
1B1V.00	C/O - panic attack
E200400	Chronic anxiety
1466	H/O: anxiety state
E200200	Generalised anxiety disorder
E200000	Anxiety state unspecified
E202100	Agoraphobia with panic attacks
E202000	Phobia unspecified
Eu41100	[X]Generalized anxiety disorder
Eu40000	[X]Agoraphobia
Eu40.00	[X]Phobic anxiety disorders

Eu41z11	[X]Anxiety NOS
Eu41.00	[X]Other anxiety disorders
E202.00	Phobic disorders
E200500	Recurrent anxiety
E202200	Agoraphobia without mention of panic attacks
Eu41011	[X]Panic attack
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]
Eu41111	[X]Anxiety neurosis
Eu40z11	[X]Phobia NOS
Eu41z00	[X]Anxiety disorder, unspecified
E202.12	Phobic anxiety
Eu40100	[X]Social phobias
E202z00	Phobic disorder NOS
Eu41012	[X]Panic state
Eu41113	[X]Anxiety state
Z4L1.00	Anxiety counselling
Eu40012	[X]Panic disorder with agoraphobia
E280.00	Acute panic state due to acute stress reaction
Eu41112	[X]Anxiety reaction
Eu40z00	[X]Phobic anxiety disorder, unspecified
E2D0.00	Disturbance of anxiety and fearfulness childhood/adolescent
225J.00	O/E - panic attack
Z481.00	Phobia counselling
Eu40011	[X]Agoraphobia without history of panic disorder
E2D0z00	Disturbance anxiety and fearfulness childhood/adolescent NOS
Eu93100	[X]Phobic anxiety disorder of childhood
Eu41300	[X]Other mixed anxiety disorders
Eu41y00	[X]Other specified anxiety disorders
Eu40y00	[X]Other phobic anxiety disorders
Eu40z12	[X]Phobic state NOS
8G52.00	Antiphobic therapy
13WB.11	Anxious mother
173f.00	Anxiety about breathlessness
1B13.00	Anxiousness
1B13.11	Anxiousness - symptom
1B13.12	Anxious
8G94.00	Anxiety management training
8HHp.00	Referral for guided self-help for anxiety
E202.11	Social phobic disorders
E202300	Social phobia, fear of eating in public
E202400	Social phobia, fear of public speaking
E202500	Social phobia, fear of public washing
E202600	Acrophobia

E202700	Animal phobia
E202800	Claustrophobia
E202900	Fear of crowds
E202A00	Fear of flying
E202B00	Cancer phobia
E202C00	Dental phobia
E203.00	Obsessive-compulsive disorders
E203.11	Anancastic neurosis
E203000	Compulsive neurosis
E203100	Obsessional neurosis
E203z00	Obsessive-compulsive disorder NOS
E205.00	Neurasthenia - nervous debility
E205.11	Nervous exhaustion
E20y300	Psychasthenic neurosis
E292000	Separation anxiety disorder
Eu05400	[X]Organic anxiety disorder
Eu41y11	[X]Anxiety hysteria
Eu51511	[X]Dream anxiety disorder
Eu93000	[X]Separation anxiety disorder of childhood
Eu93200	[X]Social anxiety disorder of childhood

8.9. Read or OXMIS Medical Codes and corresponding text for schizophrenia and related thought disorders

13L3.12	Schizophrenic child
1464	H/O: schizophrenia
212W.00	Schizophrenia resolved
212X.00	Psychosis resolved
285..11	Psychotic condition, insight present
E1...00	Non-organic psychoses
E10..00	Schizophrenic disorders
E100.00	Simple schizophrenia
E100.11	Schizophrenia simplex
E100000	Unspecified schizophrenia
E100100	Subchronic schizophrenia
E100200	Chronic schizophrenic
E100300	Acute exacerbation of subchronic schizophrenia
E100400	Acute exacerbation of chronic schizophrenia
E100500	Schizophrenia in remission
E100z00	Simple schizophrenia NOS
E101.00	Hebephrenic schizophrenia

E101000	Unspecified hebephrenic schizophrenia
E101400	Acute exacerbation of chronic hebephrenic schizophrenia
E101500	Hebephrenic schizophrenia in remission
E101z00	Hebephrenic schizophrenia NOS
E102.00	Catatonic schizophrenia
E102000	Unspecified catatonic schizophrenia
E102100	Subchronic catatonic schizophrenia
E102z00	Catatonic schizophrenia NOS
E103.00	Paranoid schizophrenia
E103000	Unspecified paranoid schizophrenia
E103200	Chronic paranoid schizophrenia
E103300	Acute exacerbation of subchronic paranoid schizophrenia
E103400	Acute exacerbation of chronic paranoid schizophrenia
E103500	Paranoid schizophrenia in remission
E103z00	Paranoid schizophrenia NOS
E104.00	Acute schizophrenic episode
E105.00	Latent schizophrenia
E105200	Chronic latent schizophrenia
E105500	Latent schizophrenia in remission
E106.00	Residual schizophrenia
E107.00	Schizo-affective schizophrenia
E107.11	Cyclic schizophrenia
E107000	Unspecified schizo-affective schizophrenia
E107100	Subchronic schizo-affective schizophrenia
E107200	Chronic schizo-affective schizophrenia
E107300	Acute exacerbation subchronic schizo-affective schizophrenia
E107400	Acute exacerbation of chronic schizo-affective schizophrenia
E107500	Schizo-affective schizophrenia in remission
E107z00	Schizo-affective schizophrenia NOS
E10y.00	Other schizophrenia
E10y.11	Cenesthopathic schizophrenia
E10y000	Atypical schizophrenia
E10y100	Coenesthopathic schizophrenia
E10yz00	Other schizophrenia NOS
E10z.00	Schizophrenia NOS
E121.00	Chronic paranoid psychosis
E12z.00	Paranoid psychosis NOS
E13y.00	Other reactive psychoses
E13y100	Brief reactive psychosis
E13z.00	Nonorganic psychosis NOS
E13z.11	Psychotic episode NOS
E14z.11	Childhood schizophrenia NOS
E1z..00	Non-organic psychosis NOS

Eu05200	[X]Organic delusional [schizophrenia-like] disorder
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
Eu20.00	[X]Schizophrenia
Eu20000	[X]Paranoid schizophrenia
Eu20011	[X]Paraphrenic schizophrenia
Eu20100	[X]Hebephrenic schizophrenia
Eu20111	[X]Disorganised schizophrenia
Eu20200	[X]Catatonic schizophrenia
Eu20212	[X]Schizophrenic catalepsy
Eu20213	[X]Schizophrenic catatonia
Eu20214	[X]Schizophrenic flexibilatis cerea
Eu20300	[X]Undifferentiated schizophrenia
Eu20311	[X]Atypical schizophrenia
Eu20500	[X]Residual schizophrenia
Eu20511	[X]Chronic undifferentiated schizophrenia
Eu20600	[X]Simple schizophrenia
Eu20y00	[X]Other schizophrenia
Eu20y12	[X]Schizophreniform disord NOS
Eu20y13	[X]Schizophrenifrm psychos NOS
Eu20z00	[X]Schizophrenia, unspecified
Eu21.11	[X]Latent schizophrenic reaction
Eu21.12	[X]Borderline schizophrenia
Eu21.13	[X]Latent schizophrenia
Eu21.14	[X]Prepsychotic schizophrenia
Eu21.15	[X]Prodromal schizophrenia
Eu21.16	[X]Pseudoneurotic schizophrenia
Eu21.17	[X]Pseudopsychopathic schizophrenia
Eu22011	[X]Paranoid psychosis
Eu22200	[X]Cotard syndrome
Eu23000	[X]Acute polymorphic psychot disord without symp of schizoph
Eu23100	[X]Acute polymorphic psychot disord with symp of schizophren
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
Eu23200	[X]Acute schizophrenia-like psychotic disorder
Eu23214	[X]Schizophrenic reaction
Eu23z12	[X]Reactive psychosis
Eu25.00	[X]Schizoaffective disorders
Eu25000	[X]Schizoaffective disorder, manic type
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25012	[X]Schizophreniform psychosis, manic type
Eu25100	[X]Schizoaffective disorder, depressive type
Eu25111	[X]Schizoaffective psychosis, depressive type
Eu25112	[X]Schizophreniform psychosis, depressive type

Eu25200	[X]Schizoaffective disorder, mixed type
Eu25212	[X]Mixed schizophrenic and affective psychosis
Eu25y00	[X]Other schizoaffective disorders
Eu25z00	[X]Schizoaffective disorder, unspecified
Eu25z11	[X]Schizoaffective psychosis NOS
Eu2z.11	[X]Psychosis NOS
ZS7C611	Schizophrenic language
ZV11000	[V]Personal history of schizophrenia
146H.00	H/O: psychosis
212T.00	Psychosis, schizophrenia + bipolar affective disord resolved
286..11	Poor insight into psychotic condition
8BM0100	Antipsychotic medication review
8HHs.00	Referral to psychosis early intervention service
E0...00	Organic psychotic conditions
E00..00	Senile and presenile organic psychotic conditions
E00y.11	Presbyophrenic psychosis
E02z.00	Drug psychosis NOS
E03y300	Unspecified puerperal psychosis
E040.11	Korsakoff's non-alcoholic psychosis
E04z.00	Chronic organic psychosis NOS
E102400	Acute exacerbation of chronic catatonic schizophrenia
E102500	Catatonic schizophrenia in remission
E103100	Subchronic paranoid schizophrenia
E105000	Unspecified latent schizophrenia
E105z00	Latent schizophrenia NOS
E131.00	Acute hysterical psychosis
E134.00	Psychogenic paranoid psychosis
E141.00	Disintegrative psychosis
E14y100	Borderline psychosis of childhood
E14z.00	Child psychosis NOS
Eu02z12	[X] Presenile psychosis NOS
Eu02z15	[X] Senile psychosis NOS
Eu03.11	[X]Korsakov's psychosis, nonalcoholic
Eu04.13	[X]Acute / subacute infective psychosis
Eu05y11	[X]Epileptic psychosis NOS
Eu0z.11	[X]Organic psychosis NOS
Eu0z.12	[X]Symptomatic psychosis NOS
Eu10500	[X]Mental & behav dis due to use alcohol: psychotic disorder
Eu11500	[X]Mental & behav dis due to use opioids: psychotic disorder
Eu12500	[X]Mental & behav dis due to cannabinoids: psychotic disordr
Eu13500	[X]Mental & behav dis due to seds/hypntcs: psychotic disordr
Eu14500	[X]Mental & behav dis due to use cocaine: psychotic disorder
Eu15500	[X]Mental/behav dis oth stims inc caffeine: psychotic dis

Eu16500	[X]Mental & behav dis due to hallucinogens: psychotic disord
Eu18500	[X]Mental & behav dis due to vol solvents: psychotic disordr
Eu1A500	[X]Mental behav disord due crack cocaine: psychotic disorder
Eu23.00	[X]Acute and transient psychotic disorders
Eu23012	[X]Cycloid psychosis
Eu23300	[X]Other acute predominantly delusional psychotic disorders
Eu23312	[X]Psychogenic paranoid psychosis
Eu23y00	[X]Other acute and transient psychotic disorders
Eu23z00	[X]Acute and transient psychotic disorder, unspecified
Eu23z11	[X]Brief reactive psychosis NOS
Eu24.13	[X]Induced psychotic disorder
Eu25211	[X]Cyclic schizophrenia
Eu26.00	[X]Nonorganic psychosis in remission
Eu2y.00	[X]Other nonorganic psychotic disorders
Eu2y.11	[X]Chronic hallucinatory psychosis
Eu2z.00	[X]Unspecified nonorganic psychosis
Eu44.14	[X]Hysterical psychosis
Eu53111	[X]Puerperal psychosis NOS
Eu84013	[X]Infantile psychosis
Eu84111	[X]Atypical childhood psychosis
Eu84312	[X]Disintegrative psychosis
Eu84314	[X]Symbiotic psychosis

8.10. Read or OXMIS Medical Codes and corresponding text for Borderline personality disorders

Eu60312	[X]Borderline personality disorder
Eu60300	[X]Emotionally unstable personality disorder
E21y200	Borderline personality disorder

8.11. Read or OXMIS Medical Codes and corresponding text for Substance Abuse

13c5.00	Substance misuse increased
13c6.00	Substance misuse decreased
13c8.00	Reduced drugs misuse
13cB.00	Misuses drugs orally
13cF.00	Preoccupied with substance misuse

13cH.00	Persistent substance misuse
146F.00	H/O: drug abuse
1J1..00	Suspected drug abuse
1T...00	History of substance misuse
1T0..00	H/O heroin misuse
1T02.00	Previous history of heroin misuse
1T2..00	H/O ecstasy misuse
1T3..00	H/O benzodiazepine misuse
1T4..00	H/O amphetamine misuse
1T41.00	H/O weekly amphetamine misuse
1T43.00	Previous history of amphetamine misuse
1T5..00	H/O cocaine misuse
1T50.00	H/O daily cocaine misuse
1T51.00	H/O weekly cocaine misuse
1T6..00	H/O crack cocaine misuse
1T7..00	H/O hallucinogen misuse
1T8..00	H/O cannabis misuse
1T80.00	H/O daily cannabis misuse
1T83.00	Previous history of cannabis misuse
1T90.00	H/O daily solvent misuse
1T91.00	H/O weekly solvent misuse
1TD..00	H/O opiate misuse
1V...00	Drug misuse behaviour
1V0..00	Misuses drugs
1V00.00	Occasional drug user
1V01.00	Long-term drug misuser
1V02.00	Poly-drug misuser
1V0C.00	Drug addict
1V3..00	Drug injection behaviour
1V38.00	Sharing of drug injecting equipment
1V5..00	Routine of drug-related activities
1V6..00	Drug-related offending behaviour
1V64.00	Illicit drug use
1V65.00	Heroin misuse
1V66.00	Ecstasy misuse
677T.00	Substance misuse structured counselling
7P22000	Delivery of rehabilitation for drug addiction
8B23.00	Drug addiction therapy
8B23.13	Drug dependence therapy
8B2N.00	Drug addiction detoxification therapy - methadone
8B2P.00	Drug addiction maintenance therapy - methadone
8B2Q.00	Drug addiction maintenance therapy - buprenorphine
8B2R.00	Drug addiction detoxification therapy - buprenorphine

8BA9.00	Detoxification dependence drug
8BAc.00	Substance misuse management stopped - self withdrawal
8BAd.00	Opiate dependence detoxification
8BAW.00	Drug dependence self detoxification
8BAX.00	Drug dependence home detoxification
8H7x.00	Referral to drug abuse counsellor
8Hh1.00	Self referral to substance misuse service
8I2N.00	Drug dependence home detoxification contraindicated
9G2..00	Drug addiction notification
9G2Z.00	Drug addiction notif NOS
9HC..00	Substance misuse monitoring
9HC2.00	Substance misuse clinical management plan agreed
9HC3.00	Substance misuse clinical management plan reviewed
9HC4.00	Substance misuse treatment withdrawn
9HC6.00	Substance misuse treatment declined
9k5..00	Drug misuse - enhanced services administration
9k50.00	Drug misuse - enhanced service completed
9k52.00	Drug misuse treatment primary care - enhanced services admin
9No5.00	Seen in substance misuse clinic
E24..00	Drug dependence
E24..11	Drug addiction
E240.00	Opioid type drug dependence
E240.11	Heroin dependence
E240.12	Methadone dependence
E240.13	Morphine dependence
E240.14	Opium dependence
E240000	Unspecified opioid dependence
E240100	Continuous opioid dependence
E240200	Episodic opioid dependence
E240300	Opioid dependence in remission
E240z00	Opioid drug dependence NOS
E241.00	Hypnotic or anxiolytic dependence
E241.11	Anxiolytic dependence
E241.12	Barbiturate dependence
E241.13	Benzodiazepine dependence
E241.14	Diazepam dependence
E241.15	Librium dependence
E241.16	Sedative dependence
E241.17	Valium dependence
E241000	Hypnotic or anxiolytic dependence, unspecified
E241100	Hypnotic or anxiolytic dependence, continuous
E241200	Hypnotic or anxiolytic dependence, episodic
E241z00	Hypnotic or anxiolytic dependence NOS

E242.00	Cocaine type drug dependence
E242000	Cocaine dependence, unspecified
E242100	Cocaine dependence, continuous
E242200	Cocaine dependence, episodic
E242z00	Cocaine drug dependence NOS
E243.00	Cannabis type drug dependence
E243.11	Hashish dependence
E243.12	Hemp dependence
E243.13	Marihuana dependence
E243000	Cannabis dependence, unspecified
E243100	Cannabis dependence, continuous
E243200	Cannabis dependence, episodic
E243z00	Cannabis drug dependence NOS
E244.00	Amphetamine or other psychostimulant dependence
E244.11	Psychostimulant dependence
E244.12	Stimulant dependence
E244000	Amphetamine or psychostimulant dependence, unspecified
E244100	Amphetamine or psychostimulant dependence, continuous
E244200	Amphetamine or psychostimulant dependence, episodic
E244z00	Amphetamine or psychostimulant dependence NOS
E245.00	Hallucinogen dependence
E245.11	LSD dependence
E245.12	Lysergic acid diethylamide dependence
E245000	Hallucinogen dependence, unspecified
E245100	Hallucinogen dependence, continuous
E245200	Hallucinogen dependence, episodic
E245z00	Hallucinogen dependence NOS
E247.00	Other specified drug dependence
E247.11	Absinthe addiction
E247000	Other specified drug dependence, unspecified
E247100	Other specified drug dependence, continuous
E247200	Other specified drug dependence, episodic
E247z00	Other specified drug dependence NOS
E248.00	Combined opioid with other drug dependence
E248000	Combined opioid with other drug dependence, unspecified
E248100	Combined opioid with other drug dependence, continuous
E248200	Combined opioid with other drug dependence, episodic
E248z00	Combined opioid with other drug dependence NOS
E249.00	Combined drug dependence, excluding opioids
E249000	Combined drug dependence, excluding opioid, unspecified
E249100	Combined drug dependence, excluding opioid, continuous
E249200	Combined drug dependence, excluding opioid, episodic
E249z00	Combined drug dependence, excluding opioid, NOS

E24A.00	Ecstasy type drug dependence
E24z.00	Drug dependence NOS
E258.00	Nondependent antidepressant type drug abuse
E258z00	Nondependent antidepressant type drug abuse NOS
E259.00	Nondependent mixed drug abuse
E259000	Nondependent mixed drug abuse, unspecified
E259100	Nondependent mixed drug abuse, continuous
E259200	Nondependent mixed drug abuse, episodic
E259300	Nondependent mixed drug abuse in remission
E259400	Misuse of prescription only drugs
E259z00	Nondependent mixed drug abuse NOS
E25y.00	Nondependent other drug abuse
E25y000	Nondependent other drug abuse, unspecified
E25y100	Nondependent other drug abuse, continuous
E25y200	Nondependent other drug abuse, episodic
E25yz00	Nondependent other drug abuse NOS
E25z.00	Misuse of drugs NOS
Eu11200	[X]Mental and behav dis due to use opioids: dependence syndr
Eu11211	[X]Drug addiction - opioids
Eu11212	[X]Heroin addiction
Eu12200	[X]Mental and behav dis due to cannabinoids: dependence synd
Eu12211	[X]Drug addiction - cannabis
Eu13200	[X]Mental and behav dis due to seds/hypntcs: dependence synd
Eu13211	[X]Drug addiction- sedative / hypnotics
Eu14200	[X]Mental and behav dis due to use cocaine: dependence syndr
Eu14211	[X]Drug addiction - cocaine
Eu15211	[X]Drug addiction-other stimul
Eu16200	[X]Mental and behav dis due to hallucinogens: dependence syn
Eu16211	[X]Drug addiction - hallucinogen
Eu18200	[X]Mental and behav dis due to vol solvents: dependence synd
Eu18211	[X]Drug addiction - solvent
Eu19200	[X]Mental and behav dis mlti/oth psych sbs: dependence syndr
Eu19211	[X]Drug addiction NOS
Eu55.00	[X]Abuse of non-dependence-producing substances
L183.00	Drug dependence in pregnancy, childbirth and the puerperium
L183.11	Pregnancy and drug dependence
L183100	Drug dependence during pregnancy - baby delivered
L183300	Drug dependence during pregnancy - baby not yet delivered
L183z00	Drug dependence during pregnancy/childbirth/puerperium NOS
Z1Q6214	Heroin maintenance
ZV11500	[V]Personal history of drug abuse by injection
ZV6D700	[V]Drug abuse counselling and surveillance
1365	Heavy drinker - 7-9u/day

1366	Very heavy drinker - >9u/day
136a.00	Increasing risk drinking
136b.00	Feels should cut down drinking
136c.00	Higher risk drinking
136P.00	Heavy drinker
136Q.00	Very heavy drinker
136Y.00	Drinks in morning to get rid of hangover
13cA.00	Smokes drugs
13cM.00	Substance misuse
1J10.00	Suspected abuse soft drugs
1J11.00	Suspected abuse hard drugs
1T00.00	H/O daily heroin misuse
1T01.00	H/O weekly heroin misuse
1T03.00	H/O infrequent heroin misuse
1T1..00	H/O methadone misuse
1T10.00	H/O daily methadone misuse
1T11.00	H/O weekly methadone misuse
1T12.00	H/O infrequent methadone misuse
1T13.00	Previous history of methadone misuse
1T20.00	H/O daily ecstasy misuse
1T21.00	H/O weekly ecstasy misuse
1T22.00	H/O infrequent ecstasy misuse
1T23.00	Previous history of ecstasy misuse
1T30.00	H/O daily benzodiazepine misuse
1T31.00	H/O weekly benzodiazepine misuse
1T32.00	H/O infrequent benzodiazepine misuse
1T33.00	Previous history of benzodiazepine misuse
1T40.00	H/O daily amphetamine misuse
1T42.00	H/O infrequent amphetamine misuse
1T52.00	H/O infrequent cocaine misuse
1T53.00	Previous history of cocaine misuse
1T60.00	H/O daily crack cocaine misuse
1T61.00	H/O weekly crack cocaine misuse
1T62.00	H/O infrequent crack cocaine misuse
1T63.00	Previous history of crack cocaine misuse
1T73.00	Previous history of hallucinogen misuse
1T81.00	H/O weekly cannabis misuse
1T82.00	H/O infrequent cannabis misuse
1T9..00	H/O solvent misuse
1T93.00	Previous history of solvent misuse
1TA..00	H/O barbiturate misuse
1TB..00	H/O major tranquilliser misuse
1TB0.00	H/O daily major tranquilliser misuse

1TC..00	H/O anti-depressant misuse
1TC0.00	H/O daily anti-depressant misuse
1TC3.00	Previous history of anti-depressant misuse
1TD0.00	H/O daily opiate misuse
1TD1.00	H/O weekly opiate misuse
1TD2.00	H/O infrequent opiate misuse
1TD3.00	Previous history of opiate misuse
1V07.00	Notified addict
1V08.00	Smokes drugs in cigarette form
1V09.00	Smokes drugs through a pipe
1V0A.00	Chases the dragon
1V0B.00	Sniffs drugs
1V0E.00	Health problem secondary to drug misuse
1V26.00	Misused drugs in past
1V32.00	Neck injector
1V35.00	Shares drug equipment
1V3A.00	Does not share drug injection equipment
1V4..00	Priority of drug-related activities
1V62.00	Buying drugs
1V63.00	Possession of drugs
63C6.11	Maternal drug misuse
67H3.00	Lifestyle advice regarding drug misuse
8HkF.00	Referral to substance misuse service
8Hq..00	Admission to substance misuse detoxification centre
9HC5.00	Substance misuse treatment programme completed
9k51.00	Shared care drug misuse treatment - enhanced services admin
9k51.11	Shared care drug misuse treatment
9k53.00	Pharmacy attended for drug misuse - enhanced services admin
9N1yJ00	Seen in drug misuse clinic
9NdN.00	Declined consent for notification of drug misuse
9s...00	Drug misuse clinic administration
E244011	Amfetamine or psychostimulant dependence, unspecified
E244z11	Amfetamine or psychostimulant dependence NOS
E246100	Glue sniffing dependence, continuous
E25..00	Nondependent abuse of drugs
E252.00	Nondependent cannabis abuse
E252000	Nondependent cannabis abuse, unspecified
E252100	Nondependent cannabis abuse, continuous
E252200	Nondependent cannabis abuse, episodic
E252z00	Nondependent cannabis abuse NOS
E253.00	Nondependent hallucinogen abuse
E253000	Nondependent hallucinogen abuse, unspecified
E253100	Nondependent hallucinogen abuse, continuous

E253200	Nondependent hallucinogen abuse, episodic
E253z00	Nondependent hallucinogen abuse NOS
E254.00	Nondependent hypnotic or anxiolytic abuse
E254.11	Barbiturate abuse
E254.12	Hypnotic or anxiolytic abuse
E254.13	Sedative abuse
E254.14	Tranquilliser abuse
E254000	Nondependent hypnotic or anxiolytic abuse, unspecified
E254100	Nondependent hypnotic or anxiolytic abuse, continuous
E254200	Nondependent hypnotic or anxiolytic abuse, episodic
E254z00	Nondependent hypnotic or anxiolytic abuse NOS
E255.00	Nondependent opioid abuse
E255000	Nondependent opioid abuse, unspecified
E255100	Nondependent opioid abuse, continuous
E255200	Nondependent opioid abuse, episodic
E255z00	Nondependent opioid abuse NOS
E256.00	Nondependent cocaine abuse
E256000	Nondependent cocaine abuse, unspecified
E256100	Nondependent cocaine abuse, continuous
E256200	Nondependent cocaine abuse, episodic
E256z00	Nondependent cocaine abuse NOS
E257.00	Nondependent amphetamine or other psychostimulant abuse
E257.11	Psychostimulant abuse
E257.12	Stimulant abuse
E257000	Nondependent amphetamine/psychostimulant abuse, unspecified
E257100	Nondependent amphetamine/psychostimulant abuse, continuous
E257200	Nondependent amphetamine or psychostimulant abuse, episodic
E257z00	Nondependent amphetamine or psychostimulant abuse NOS
Eu55.12	[X]Abuse of herbal or folk remedies
Eu55.13	[X]Abuse of steroids or hormones
U609700	[X]Psychostim with abuse potentl caus advers eff therap use
Z416.00	Substance abuse counselling
ZC16.00	Abuse of drugs to lose weight
ZV11400	[V]Personal history of psychoactive substance abuse

8.12. Read or OXMIS Medical Codes and corresponding text for Alcohol Abuse

136W.00	Alcohol misuse
1462	H/O: alcoholism
8CAv.00	Advised to contact primary care alcohol worker

8HkJ.00	Referral to alcohol brief intervention service
9k1A.00	Brief intervention for excessive alcohol consumptn completed
9k1B.00	Extended intervention for excessive alcohol consumptn complt
E01..00	Alcoholic psychoses
E011.00	Alcohol amnestic syndrome
E011000	Korsakov's alcoholic psychosis
E011100	Korsakov's alcoholic psychosis with peripheral neuritis
E012.00	Other alcoholic dementia
E012.11	Alcoholic dementia NOS
E012000	Chronic alcoholic brain syndrome
E015.00	Alcoholic paranoia
E01y.00	Other alcoholic psychosis
E01yz00	Other alcoholic psychosis NOS
E01z.00	Alcoholic psychosis NOS
E23..00	Alcohol dependence syndrome
E23..11	Alcoholism
E230.11	Alcohol dependence with acute alcoholic intoxication
E230000	Acute alcoholic intoxication, unspecified, in alcoholism
E230100	Continuous acute alcoholic intoxication in alcoholism
E230300	Acute alcoholic intoxication in remission, in alcoholism
E230z00	Acute alcoholic intoxication in alcoholism NOS
E231.00	Chronic alcoholism
E231100	Continuous chronic alcoholism
E231300	Chronic alcoholism in remission
E231z00	Chronic alcoholism NOS
E250300	Nondependent alcohol abuse in remission
Eu10011	[X]Acute alcoholic drunkenness
Eu10212	[X]Chronic alcoholism
Eu10511	[X]Alcoholic hallucinosis
Eu10513	[X]Alcoholic paranoia
Eu10514	[X]Alcoholic psychosis NOS
Eu10611	[X]Korsakov's psychosis, alcohol induced
Eu10711	[X]Alcoholic dementia NOS
Eu10712	[X]Chronic alcoholic brain syndrome
F11x000	Cerebral degeneration due to alcoholism
F11x011	Alcoholic encephalopathy
F144000	Cerebellar ataxia due to alcoholism
F25B.00	Alcohol-induced epilepsy
F375.00	Alcoholic polyneuropathy
F394100	Alcoholic myopathy
G555.00	Alcoholic cardiomyopathy
J153.00	Alcoholic gastritis
J611.00	Acute alcoholic hepatitis

J612.00	Alcoholic cirrhosis of liver
J612000	Alcoholic fibrosis and sclerosis of liver
J613000	Alcoholic hepatic failure
J617.00	Alcoholic hepatitis
J617000	Chronic alcoholic hepatitis
J671000	Alcohol-induced chronic pancreatitis
Z191211	Alcohol reduction programme
Z192113	Withdrawal programme
ZV11300	[V]Personal history of alcoholism
136K.00	Alcohol intake above recommended sensible limits
136S.00	Hazardous alcohol use
136T.00	Harmful alcohol use
136W.00	Alcohol misuse
13ZY.00	Disqualified from driving due to excess alcohol
1462	H/O: alcoholism
1B1c.00	Alcohol induced hallucinations
1D19.00	Pain in lymph nodes after alcohol consumption
2577	O/E - breath - alcohol smell
2577.11	O/E - alcoholic breath
63C7.00	Maternal alcohol abuse
66e..00	Alcohol disorder monitoring
66e0.00	Alcohol abuse monitoring
7P22100	Delivery of rehabilitation for alcohol addiction
8BA8.00	Alcohol detoxification
8CAv.00	Advised to contact primary care alcohol worker
8G32.00	Aversion therapy - alcoholism
8H35.00	Admitted to alcohol detoxification centre
8H7p.00	Referral to community alcohol team
8HHe.00	Referral to community drug and alcohol team
8HkG.00	Referral to specialist alcohol treatment service
8HkJ.00	Referral to alcohol brief intervention service
8IAF.00	Brief intervention for excessive alcohol consumptn declined
8IAJ.00	Declined referral to specialist alcohol treatment service
8IAt.00	Extended interven for excessive alcohol consumption declined
8IEA.00	Referral to community alcohol team declined
9k1..00	Alcohol misuse - enhanced services administration
9k12.00	Alcohol misuse - enhanced service completed
9k14.00	Alcohol counselling by other agencies
9k1A.00	Brief intervention for excessive alcohol consumptn completed
9k1B.00	Extended intervention for excessive alcohol consumptn complt
9NN2.00	Under care of community alcohol team
C150500	Alcohol-induced pseudo-Cushing's syndrome
E01..00	Alcoholic psychoses

E010.00	Alcohol withdrawal delirium
E011.00	Alcohol amnestic syndrome
E011000	Korsakov's alcoholic psychosis
E011100	Korsakov's alcoholic psychosis with peripheral neuritis
E011z00	Alcohol amnestic syndrome NOS
E012.00	Other alcoholic dementia
E012.11	Alcoholic dementia NOS
E012000	Chronic alcoholic brain syndrome
E013.00	Alcohol withdrawal hallucinosis
E014.00	Pathological alcohol intoxication
E015.00	Alcoholic paranoia
E01y.00	Other alcoholic psychosis
E01y000	Alcohol withdrawal syndrome
E01yz00	Other alcoholic psychosis NOS
E01z.00	Alcoholic psychosis NOS
E23..00	Alcohol dependence syndrome
E23..11	Alcoholism
E23..12	Alcohol problem drinking
E230.00	Acute alcoholic intoxication in alcoholism
E230.11	Alcohol dependence with acute alcoholic intoxication
E230000	Acute alcoholic intoxication, unspecified, in alcoholism
E230100	Continuous acute alcoholic intoxication in alcoholism
E230200	Episodic acute alcoholic intoxication in alcoholism
E230300	Acute alcoholic intoxication in remission, in alcoholism
E230z00	Acute alcoholic intoxication in alcoholism NOS
E231.00	Chronic alcoholism
E231000	Unspecified chronic alcoholism
E231100	Continuous chronic alcoholism
E231200	Episodic chronic alcoholism
E231z00	Chronic alcoholism NOS
E23z.00	Alcohol dependence syndrome NOS
E250.00	Nondependent alcohol abuse
E250.14	Intoxication - alcohol
E250000	Nondependent alcohol abuse, unspecified
E250100	Nondependent alcohol abuse, continuous
E250200	Nondependent alcohol abuse, episodic
E250z00	Nondependent alcohol abuse NOS
Eu10.00	[X]Mental and behavioural disorders due to use of alcohol
Eu10000	[X]Mental & behav dis due to use alcohol: acute intoxication
Eu10011	[X]Acute alcoholic drunkenness
Eu10100	[X]Mental and behav dis due to use of alcohol: harmful use
Eu10200	[X]Mental and behav dis due to use alcohol: dependence syndr
Eu10211	[X]Alcohol addiction

Eu10212	[X]Chronic alcoholism
Eu10300	[X]Mental and behav dis due to use alcohol: withdrawal state
Eu10411	[X]Delirium tremens, alcohol induced
Eu10500	[X]Mental & behav dis due to use alcohol: psychotic disorder
Eu10511	[X]Alcoholic hallucinosis
Eu10512	[X]Alcoholic jealousy
Eu10513	[X]Alcoholic paranoia
Eu10514	[X]Alcoholic psychosis NOS
Eu10600	[X]Mental and behav dis due to use alcohol: amnesic syndrome
Eu10611	[X]Korsakov's psychosis, alcohol induced
Eu10711	[X]Alcoholic dementia NOS
Eu10712	[X]Chronic alcoholic brain syndrome
Eu10800	[X]Alcohol withdrawal-induced seizure
Eu10y00	[X]Men & behav dis due to use alcohol: oth men & behav dis
Eu10z00	[X]Ment & behav dis due use alcohol: unsp ment & behav dis
F11x000	Cerebral degeneration due to alcoholism
F11x011	Alcoholic encephalopathy
F144000	Cerebellar ataxia due to alcoholism
F25B.00	Alcohol-induced epilepsy
F375.00	Alcoholic polyneuropathy
F394100	Alcoholic myopathy
G555.00	Alcoholic cardiomyopathy
G852300	Oesophageal varices in alcoholic cirrhosis of the liver
J153.00	Alcoholic gastritis
J610.00	Alcoholic fatty liver
J611.00	Acute alcoholic hepatitis
J612.00	Alcoholic cirrhosis of liver
J612000	Alcoholic fibrosis and sclerosis of liver
J613.00	Alcoholic liver damage unspecified
J613000	Alcoholic hepatic failure
J617.00	Alcoholic hepatitis
J617000	Chronic alcoholic hepatitis
J670800	Alcohol-induced acute pancreatitis
J671000	Alcohol-induced chronic pancreatitis
R103.00	[D]Alcohol blood level excessive
SM0..00	Alcohol causing toxic effect
SM00.00	Ethyl alcohol causing toxic effect
SM00z00	Ethyl alcohol causing toxic effect NOS
SM0z.00	Alcohol causing toxic effect NOS
U209.00	[X]Intent self poison/exposure to alcohol
U209000	[X]Int self poison/exposure to alcohol at home
U209y00	[X]Int self poison alcohol other spec place
U209z00	[X]Intent self poison alcohol unspecif place

U409.00	[X]Poisoning/exposure, ? intent, to alcohol
U409000	[X]Poison/exposure ?intent, to alcohol at home
U409200	[X]Pois/exp ?intent alcohol school/pub admin area
U409400	[X]Pois/expos ?intent alcohol in street/highway
U409z00	[X]Pois/expos ?intent to alcohol unspecif place
U81..00	[X]Evid of alcohol involv determind by level of intoxication
Z191.00	Alcohol detoxification
Z191100	Alcohol withdrawal regime
Z191200	Planned reduction of alcohol consumption
Z191211	Alcohol reduction programme
Z192113	Withdrawal programme
Z4B1.00	Alcoholism counselling
ZC22200	Advice to change alcoholic drink intake
ZC2H.00	Advice to change alcohol intake
ZV11300	[V]Personal history of alcoholism
ZV11311	[V]Problems related to lifestyle alcohol use
ZV57A00	[V]Alcohol rehabilitation
ZV6D600	[V]Alcohol abuse counselling and surveillance

8.13. Read or OXMIS Medical Codes and corresponding text for Charlson Comorbidity Index

Refer to: N Khan, R Perera et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. BMC Family Practice 2010, 11:1

8.14. Read or OXMIS Medical Codes and corresponding text for family history of suicidality

1289	FH: Suicide
13MB.00	Suicide of close relative

8.15. Antidepressant Drugs (other than SNI/SSRI class)

83	Amitriptyline 10mg tablets	Amitriptyline hydrochloride
49	Amitriptyline 25mg tablets	Amitriptyline hydrochloride
74	Dosulepin 75mg tablets	Dosulepin hydrochloride
1888	Amitriptyline 50mg tablets	Amitriptyline hydrochloride
84	Dosulepin 25mg capsules	Dosulepin hydrochloride
742	Mirtazapine 30mg tablets	Mirtazapine
114	Lofepramine 70mg tablets	Lofepramine hydrochloride
6795	Mirtazapine 15mg tablets	Mirtazapine

6854	Mirtazapine 45mg tablets	Mirtazapine
3355	Trazodone 50mg capsules	Trazodone hydrochloride
2320	Prothiaden 75mg tablets (Teofarma)	Dosulepin hydrochloride
1809	Imipramine 25mg tablets	Imipramine hydrochloride
1169	Prothiaden 25mg capsules (Teofarma)	Dosulepin hydrochloride
1730	Trazodone 100mg capsules	Trazodone hydrochloride
4020	Trazodone 150mg tablets	Trazodone hydrochloride
3670	Clomipramine 25mg capsules	Clomipramine hydrochloride
3925	Clomipramine 50mg capsules	Clomipramine hydrochloride
6421	Mirtazapine 15mg orodispersible tablets	Mirtazapine
3183	Nortriptyline 10mg tablets	Nortriptyline hydrochloride
6481	Mirtazapine 45mg orodispersible tablets	Mirtazapine
3194	Clomipramine 10mg capsules	Clomipramine hydrochloride
6488	Mirtazapine 30mg orodispersible tablets	Mirtazapine
3196	Trimipramine 50mg capsules	Trimipramine maleate
2093	Gamanil 70mg tablets (Merck Serono Ltd)	Lofepramine hydrochloride
3903	Nortriptyline 25mg tablets	Nortriptyline hydrochloride
2039	Trimipramine 25mg tablets	Trimipramine maleate
1310	Imipramine 10mg tablets	Imipramine hydrochloride
3554	Doxepin 25mg capsules	Doxepin hydrochloride
2356	Reboxetine 4mg tablets	Reboxetine mesilate
3657	Anafranil 25mg capsules (Novartis Pharmaceuticals UK Ltd)	Clomipramine hydrochloride
7751	Tryptizol 25mg Tablet (Merck Sharp & Dohme Ltd)	Amitriptyline hydrochloride
7515	Anafranil 10mg capsules (Novartis Pharmaceuticals UK Ltd)	Clomipramine hydrochloride
2531	Surmontil 50mg capsules (Sanofi)	Trimipramine maleate
2532	Surmontil 25mg tablets (Sanofi)	Trimipramine maleate
6442	Trazodone 50mg/5ml oral solution sugar free	Trazodone hydrochloride
4321	Phenelzine 15mg tablets	Phenelzine sulfate
6255	Mianserin 30mg tablets	Mianserin hydrochloride
8661	Clomipramine 75mg modified-release tablets	Clomipramine hydrochloride
5073	Doxepin 50mg capsules	Doxepin hydrochloride
3083	Mianserin 10mg tablets	Mianserin hydrochloride
2883	Moclobemide 150mg tablets	Moclobemide
4310	Trimipramine 10mg tablets	Trimipramine maleate
3842	Doxepin 10mg capsules	Doxepin hydrochloride
4726	Zispin 30mg tablets (Organon Laboratories Ltd)	Mirtazapine
4874	Molipaxin 50mg capsules (Zentiva)	Trazodone hydrochloride
6312	Amitriptyline 25mg/5ml oral solution sugar free	Amitriptyline hydrochloride
7910	Tofranil 25mg tablets (Novartis Pharmaceuticals UK Ltd)	Imipramine hydrochloride
7693	Anafranil 50mg capsules (Novartis Pharmaceuticals UK Ltd)	Clomipramine hydrochloride
2525	Amitriptyline 75mg modified-release capsules	Amitriptyline Hydrochloride

4011	Nefazodone 200mg tablets	Nefazodone hydrochloride
4554	Nefazodone 100mg tablets	Nefazodone hydrochloride
3783	Tranylcypromine 10mg tablets	Tranylcypromine sulfate
3349	Nardil 15mg tablets (Archimedes Pharma UK Ltd)	Phenelzine sulfate
12129	Sinequan 25mg capsules (Pfizer Ltd)	Doxepin hydrochloride
3777	Amitriptyline 10mg/5ml sugar free oral solution	Amitriptyline Hydrochloride
8726	Tryptizol 10mg Tablet (Merck Sharp & Dohme Ltd)	Amitriptyline hydrochloride
7059	Doxepin 75mg capsules	Doxepin hydrochloride
4003	Molipaxin 150mg tablets (Zentiva)	Trazodone hydrochloride
7894	Anafranil SR 75mg tablets (Novartis Pharmaceuticals UK Ltd)	Clomipramine hydrochloride
5187	Moclobemide 300mg tablets	Moclobemide
10083	Zispin SolTab 30mg orodispersible tablets (Merck Sharp & Dohme Ltd)	Mirtazapine
8332	Tryptizol 50mg Tablet (Merck Sharp & Dohme Ltd)	Amitriptyline hydrochloride
24152	Amitriptyline 10mg tablets (Teva UK Ltd)	Amitriptyline hydrochloride
4194	Molipaxin 100mg capsules (Zentiva)	Trazodone hydrochloride
6846	Zispin SolTab 15mg orodispersible tablets (Merck Sharp & Dohme Ltd)	Mirtazapine
10413	Sinequan 10mg capsules (Pfizer Ltd)	Doxepin hydrochloride
24147	Amitriptyline 25mg tablets (Teva UK Ltd)	Amitriptyline hydrochloride
4690	Amitriptyline 50mg/5ml oral solution sugar free	Amitriptyline hydrochloride
15632	Dothapax 75 tablets (Ashbourne Pharmaceuticals Ltd)	Dosulepin hydrochloride
8928	Surmontil 10mg tablets (Sanofi)	Trimipramine maleate
3391	Dutonin 100mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Nefazodone hydrochloride
4297	Dutonin 200mg tablets (Bristol-Myers Squibb Pharmaceuticals Ltd)	Nefazodone hydrochloride
595	Amitriptyline 25mg / Perphenazine 2mg tablets	Amitriptyline hydrochloride/Perphenazine
10787	Parnate 10mg Tablet (Goldshield Pharmaceuticals Ltd)	Tranylcypromine sulfate
15268	Zispin SolTab 45mg orodispersible tablets (Merck Sharp & Dohme Ltd)	Mirtazapine
4218	Lofepramine 70mg/5ml oral suspension sugar free	Lofepramine hydrochloride
40494	Agomelatine 25mg tablets	Agomelatine
12207	Isocarboxazid 10mg tablets	Isocarboxazid
8831	Tryptizol mr 75mg Modified-release capsule (Merck Sharp & Dohme Ltd)	Amitriptyline Hydrochloride
12125	Sinequan 50mg capsules (Pfizer Ltd)	Doxepin hydrochloride
1940	Dothapax 25 capsules (Ashbourne Pharmaceuticals Ltd)	Dosulepin hydrochloride
9206	Manerix 150mg tablets (Meda Pharmaceuticals Ltd)	Moclobemide
21819	Prepadine 75mg tablets (Teva UK Ltd)	Dosulepin hydrochloride
15163	Edronax 4mg tablets (Pfizer Ltd)	Reboxetine mesilate
8585	Bolvidon 30mg Tablet (Organon Laboratories Ltd)	Mianserin hydrochloride
7468	Bolvidon 10mg Tablet (Organon Laboratories Ltd)	Mianserin hydrochloride

33090	Amitriptyline 10mg tablets (A A H Pharmaceuticals Ltd)	Amitriptyline hydrochloride
20026	Domical 25mg Tablet (Berk Pharmaceuticals Ltd)	Amitriptyline hydrochloride
16154	Mirtazapine 15mg/ml oral solution sugar free	Mirtazapine
12192	Norval 30mg Tablet (Bencard)	Mianserin hydrochloride
21820	Prepadine 25mg capsules (Teva UK Ltd)	Dosulepin hydrochloride
12503	Marplan 10mg Tablet (Cambridge Laboratories Ltd)	Isocarboxazid
8878	Tryptizol 10mg/5ml sugar free Oral solution (Merck Sharp and Dohme Ltd)	Amitriptyline Hydrochloride
12368	Norval 10mg Tablet (Bencard)	Mianserin hydrochloride
7756	Protriptyline 5mg tablet	Protriptyline Hydrochloride
2579	Tofranil 10mg Tablet (Novartis Pharmaceuticals UK Ltd)	Imipramine hydrochloride
8640	Allegron 25mg tablets (King Pharmaceuticals Ltd)	Nortriptyline hydrochloride
33624	Amitriptyline 50mg tablets (Teva UK Ltd)	Amitriptyline hydrochloride
7678	Nortriptyline 25mg Capsule	Nortriptyline Hydrochloride
34782	Amitriptyline 25mg tablets (A A H Pharmaceuticals Ltd)	Amitriptyline hydrochloride
6054	Dosulepin 25mg/5ml oral solution sugar free	Dosulepin Hydrochloride
14519	Sinequan 75mg capsules (Pfizer Ltd)	Doxepin hydrochloride
26213	Domical 10mg Tablet (Berk Pharmaceuticals Ltd)	Amitriptyline hydrochloride
8720	Clomipramine 25mg/5ml oral solution	Clomipramine hydrochloride
4118	Nortriptyline 10mg Capsule	Nortriptyline Hydrochloride
7981	Desipramine 25mg tablets	Desipramine
8144	Bolvidon 20mg Tablet (Organon Laboratories Ltd)	Mianserin hydrochloride
24145	Amitriptyline 25mg tablets (Actavis UK Ltd)	Amitriptyline hydrochloride
8174	Molipaxin 50mg/5ml oral liquid (Sanofi)	Trazodone hydrochloride
34274	Amitriptyline 50mg tablets (A A H Pharmaceuticals Ltd)	Amitriptyline hydrochloride
48698	Mirtazapine 15mg orodispersible tablets sugar free	
10948	Dosulepin 75mg/5ml oral solution sugar free	Dosulepin Hydrochloride
8719	Anafranil 25mg/5ml syrup (Novartis Pharmaceuticals UK Ltd)	Clomipramine hydrochloride
12353	Aventyl 25mg Capsule (Eli Lilly and Company Ltd)	Nortriptyline Hydrochloride
7755	Concordin 10 Tablet (Merck Sharp & Dohme Ltd)	Protriptyline Hydrochloride
7677	Allegron 10mg tablets (King Pharmaceuticals Ltd)	Nortriptyline hydrochloride
9534	Nefazodone Starter pack	Nefazodone Hydrochloride
49820	Mirtazapine 45mg orodispersible tablets sugar free	
34046	Lofepramine 70mg tablets (A A H Pharmaceuticals Ltd)	Lofepramine hydrochloride
34058	Dosulepin 75mg tablets (Teva UK Ltd)	Dosulepin hydrochloride
27008	Domical 50mg Tablet (Berk Pharmaceuticals Ltd)	Amitriptyline hydrochloride
31824	Dosulepin 25mg capsules (IVAX Pharmaceuticals UK Ltd)	Dosulepin hydrochloride
11956	Norval 20mg Tablet (Bencard)	Mianserin hydrochloride
23426	Dosulepin 25mg capsules (A A H Pharmaceuticals Ltd)	Dosulepin hydrochloride
3652	Amoxapine 100mg tablets	Amoxapine
7816	Concordin 5 Tablet (Merck Sharp & Dohme Ltd)	Protriptyline Hydrochloride
34223	Dosulepin 25mg capsules (Teva UK Ltd)	Dosulepin hydrochloride

17183	Aventyl 10mg Capsule (Eli Lilly and Company Ltd)	Nortriptyline Hydrochloride
14398	Asendis 50mg Tablet (Wyeth Pharmaceuticals)	Amoxapine
5832	Manerix 300mg tablets (Meda Pharmaceuticals Ltd)	Moclobemide
15380	Asendis 25mg Tablet (Wyeth Pharmaceuticals)	Amoxapine
12309	Viloxazine hcl 50mg tablets	Viloxazine Hydrochloride
42078	Amitriptyline 25mg tablets (Almus Pharmaceuticals Ltd)	Amitriptyline hydrochloride
31826	Dosulepin 75mg tablets (IVAX Pharmaceuticals UK Ltd)	Dosulepin hydrochloride
4411	Amoxapine 150mg tablets	Amoxapine
11187	Protriptyline 10mg tablet	Protriptyline Hydrochloride
12111	Vivalan 50mg Tablet (AstraZeneca UK Ltd)	Viloxazine Hydrochloride
38274	Clomipramine 50mg/5ml oral suspension	Clomipramine hydrochloride
34745	Dosulepin 25mg capsules (Actavis UK Ltd)	Dosulepin hydrochloride
32121	Dosulepin 75mg tablets (A A H Pharmaceuticals Ltd)	Dosulepin hydrochloride
22070	Amitriptyline 10mg/5ml Oral solution (Rosemont Pharmaceuticals Ltd)	Amitriptyline Hydrochloride
34580	Trazodone 100mg capsules (A A H Pharmaceuticals Ltd)	Trazodone hydrochloride
39145	Nortriptyline 10mg/5ml Liquid	Nortriptyline Hydrochloride
46801	Amitriptyline 10mg/5ml oral solution	Amitriptyline hydrochloride
19186	Dosulepin 75mg tablets (Actavis UK Ltd)	Dosulepin hydrochloride
44853	Dosulepin 25mg capsules (Kent Pharmaceuticals Ltd)	Dosulepin hydrochloride
30983	Trazodone 150mg tablets (Generics (UK) Ltd)	Trazodone hydrochloride
34470	Trazodone 150mg tablets (Zentiva)	Trazodone hydrochloride
19779	Amitriptyline 10mg/ml injection	Amitriptyline Hydrochloride
60591	Lofepramine 70mg tablets (Teva UK Ltd)	Lofepramine hydrochloride
46668	Mirtazapine 15mg tablets (Arrow Generics Ltd)	Mirtazapine
41627	Lofepramine 70mg Tablet (Teva UK Ltd)	Lofepramine hydrochloride
43242	Mirtazapine 15mg tablets (Genus Pharmaceuticals Ltd)	Mirtazapine
34916	Amitriptyline 10mg Tablet (Berk Pharmaceuticals Ltd)	Amitriptyline hydrochloride
24134	Amitriptyline 25mg tablets (Kent Pharmaceuticals Ltd)	Amitriptyline hydrochloride

8.16. Mock statistical table of cox regression analysis:

	Model 1		Model 2		Model 3	
Variable	HR	95% CI	HR	95% CI	HR	95% CI
Duloxetine Status	x.xx	x.xx – x.xx	x.xx	x.xx – x.xx	x.xx	x.xx – x.xx
Comorbid Depression			x.xx	x.xx – x.xx	x.xx	x.xx – x.xx
History of Depression			x.xx	x.xx – x.xx	x.xx	x.xx – x.xx
Comorbid Psych Condition					x.xx	x.xx – x.xx
History of Psych Hospitalization					x.xx	x.xx – x.xx

History of Suicide Attempt			x.xx	x.xx – x.xx

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