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# Tolerability of duloxetine in the elderly and in adults: a protocol and preliminary results of a systematic review and meta-analysis of randomised placebo-controlled trials

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**THÈSE D'EXERCICE / UNIVERSITÉ DE RENNES 1**

*sous le sceau de l'Université Bretagne Loire*

Thèse en vue du

**DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE**

présentée par

**Jean-Charles ROY**

Né le 18 octobre 1989 à Saint-Brieuc

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**Évaluation de la  
tolérance à la  
duloxétine entre  
populations adulte et  
âgée : protocole et  
résultats préliminaires  
d'une revue  
systématique de la  
littérature et méta-  
analyse sur données  
individuelles d'essais  
contrôlés randomisés  
contre placebo.**

**Thèse soutenue à Rennes**

**le 11 octobre 2019**

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**Évaluation de la tolérance à la duloxétine entre populations adulte et âgée : protocole et résultats préliminaires d'une revue systématique de la littérature et méta-analyse sur données individuelles d'essais contrôlés randomisés contre placebo.**

**Tolerability of duloxetine in the elderly and in adults: a protocol and preliminary results of a systematic review and meta-analysis of randomised placebo-controlled trials.**

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# **Tolerability of duloxetine in the elderly and in adults: a protocol and preliminary results of a systematic review and meta-analysis of randomised placebo-controlled trials.**

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## RESUME

**Introduction.** La duloxétine est un antidépresseur qui bénéficie d'une approbation de prescription pour de nombreuses pathologies fréquentes chez les personnes âgées. Cependant, contrairement à l'adulte plus jeune, la sécurité d'emploi de la duloxétine chez la personne âgée n'est pas clairement établie. Une comparaison de la tolérance de la duloxétine entre personnes âgées et adultes plus jeunes permettrait de statuer sur cette question.

**Analyse et Méthodes.** Ce protocole présente une revue systématique de la littérature et une méta-analyse sur données individuelles de tous les essais contrôlés randomisés en double-aveugle comparant le nombre d'événements indésirables sévères sous duloxétine comparé au placebo entre des sujets âgés (de 65 ans ou plus) et des adultes plus jeunes (de moins de 65 ans), dans des pathologies où la duloxétine est approuvée par l'Agence Européenne du Médicament (EMA) et la Food and Drug Administration (FDA). Les variables secondaires sont la différence de nombre d'événements indésirables non-sévères sous duloxétine contre placebo entre les sujets âgés et les adultes plus jeunes, ainsi que les effets d'interaction entre l'âge et l'intervention sur les scores cliniques et les scores de qualité de vie. Une revue systématique de la littérature selon les recommandations Cochrane a été effectuée sur des sites d'essais cliniques ClinicalTrials.gov, Clinicaltrialsregister.eu, des plateformes de données (ClinicalStudyDataRequest.com, YODA et Vivli) et à partir des argumentaires officiels de l'EMA et de la FDA. Les promoteurs et auteurs des études éligibles ont été invités à partager leurs données sur les plateformes de partage de données ou directement avec notre équipe de recherche. Une analyse statistique en deux étapes sera effectuée, consistant en une extraction des taux d'incidence des variables principale et secondaires à partir des effets d'interaction entre le traitement alloué et la catégorie d'âge par une régression multiniveaux. Ensuite, une analyse combinée des taux d'incidence issus des études partagées sur des plateformes différentes sera effectuée.

**Résultats qualitatifs à partir des données disponibles :** Sur les 916 études identifiées, 77 ont été retenues comme éligibles soit un total de 25303 sujets. Le partage de données a été approuvé pour 58 études, est en cours de relecture pour 8 études, et a été refusé pour 6 études. 5 sponsors n'ont pas répondu aux invitations de partage soit un total de 5 études. A partir des données disponibles en ligne, 67 essais ont pu être évalués dont 35 jugés à faible risque de biais, 31 à un risque de biais incertain et 1 à haut risque de biais.

**Conclusion.** Cette étude serait la première méta-analyse étudiant directement la sécurité d'emploi de la duloxétine chez les populations âgées dans toutes les pathologies approuvées par les autorités européennes et américaines.

## ABSTRACT

**Introduction.** Duloxetine is an antidepressant which benefits from a wide range of approval in elderly population while its safety of use in elderly population, compared to younger adults, is not clearly assessed. A comparison of tolerability of duloxetine between elderly and younger adults would help to rule on the question.

**Method and design.** This protocol outlines a systematic review and meta-analysis of individual participant data (IPD) of all double-blind randomised controlled trials to compare the number of serious adverse events among individuals taking duloxetine in comparison to placebo between participants at least 65 years and younger adults in conditions approved by the European Medical Agency (EMA) and the Food Drug Administration (FDA). Secondly, will be compared the number of any adverse events, the clinical efficacy on clinical scales and quality of life between elderly individuals and younger adults under duloxetine, in comparison to placebo. Efficacy and tolerability will be compared between young-old (aged between 65 and 75) and old-old participants (aged 75-year-old or more). Relevant studies were selected on ClinicalTrials.gov, Clinicaltrialsregister.eu, data sharing platforms (ClinicalStudyDataRequest.com, YODA and Vivli), FDA drug approval packages and European public assessment report and withdrawn applications from EMA website and from published systematic reviews and meta-analyses of duloxetine on PubMed, following Cochrane's recommendations. Sponsors and authors from eligible studies were invited to share IPD data on data sharing platform or directly with our research team. As data cannot be aggregate into one database, a two step-approach meta-analysis will be undertaken consisting in performing a multilevel regression to extract rate ratios of relevant outcomes from interaction effects between treatment allocation and age, and then pooling extracted rate ratios from each platform.

**Qualitative results from available data.** 77 eligible randomised controlled trials (total of 25303 participants) were identified. 58 studies have been approved for sharing, while our proposal is still under review for 8 trials, no answer has been provided for 5 trials and data sharing has been denied for 6 trials. From online available data, 35 trials were assessed as being at an overall low risk of bias, 31 trials at an unclear risk of bias and 1 at high risk of bias. Evaluation of risk of bias was not feasible for 10 studies.

**Conclusion.** This study would represent the first meta-analysis investigating the safety of duloxetine in elderly population across all conditions approved by European and American regulatory authorities with an overall low risk of bias.

**Registration.** PROSPERO: 2019 CRD42019130488.



## INTRODUCTION

### *Rationale*

Duloxetine is a medication which has been approved for a wide range of pathologies by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), namely major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence. These diseases represent a major public health burden for elderly population<sup>1</sup>. While several guidelines recommend the use of duloxetine as a first-line medication for these diseases in the elderly<sup>2-6</sup>, others formally proscribe it<sup>7</sup>. As a matter of fact, good practice guidelines of duloxetine use are under debate, notably because of mixed evidence for a favorable risk-benefit balance in older populations<sup>5,8</sup>.

For instance, a mixed treatment meta-analysis, mostly based on indirect evidence, suggests that duloxetine had higher response rates than other antidepressants for major depressive disorder in old-age population ( $\geq 65$  years old), in a context of scarce data in this population<sup>9</sup>. In contrast, duloxetine was found to increase the risk of adverse events.<sup>10</sup> In younger adults, several meta-analyses concluded that duloxetine was associated to a disfavoring risk-benefit balance compared to placebo in generalized anxiety disorder and fibromyalgia<sup>11,12</sup>. Meta-regression analyses from Cipriani et al. (2018) found similar results, observing a significant association between mean age of participants and response to duloxetine (OR = 1.86, CI 95% = 1.66-2.08) with an association between age and number of drop-outs under duloxetine (OR = 1.10, CI 95% = 0.97-1.24)<sup>13</sup>, although the latter result did not reach statistical significance.

Concerns about duloxetine use in the elderly have existed since pre-marketing pharmacokinetics studies. Study SAAY brought out a reduced oral clearance of duloxetine of 25% in an elderly class (mean age of 69 years old) compared to a middle-aged class (mean age of 42 years old)<sup>14</sup> of women, under 40mg of duloxetine. Furthermore, AUC measure of exposure was found to be 24% higher in elderly, although not statistically significant in the cohort of 24 participants, but with a half-life elimination reduced by one third in elderly compared to middle-aged individuals. Statistically significant correlation of diminished oral clearance of duloxetine with age was demonstrated, estimated to a reduction of clearance of almost 60% between 23- and 76.8-year-old (Study SAAB)<sup>14</sup>. Skinner et al. (2004) estimated that decrease of oral clearance accelerates at around 52 years of age<sup>15</sup>. Similar results have been reproduced in ulterior pooled analyses of phase III trials<sup>16</sup> with comparable effect sizes (procedure EMEA/H/C/572/II/26 reported a 25 percent-decrease of oral clearance between 29- and 69-year-old individuals). Taken together, these early phase I studies demonstrated an increased systemic exposure to duloxetine in elderly population.

However, the clinical interpretation of pharmacokinetics results remains challenging. Many subgroup analyses of pilot trials did not find quantitative differences in tolerability between old and younger adults. One plausible explanation lies in the small sample sizes of elderly participants included in these

studies<sup>16</sup>. As mentioned in the FDA CYMBALTA® Label<sup>17</sup> (revised version of 2017), of the 6781 patients in premarketing clinical studies of duloxetine in all conditions, 15.6% were 65 years of age or over. Although it represents about 1058 subjects, no direct comparison of between-age tolerability across diseases is to be found in the literature. Altogether, it seems that the tolerability of duloxetine in elderly needs clarification.

Therefore, we planned to determine whether use of duloxetine in elderly is associated to a higher risk of serious and non-serious adverse events than in younger adults. Lilly (the sponsor of most duloxetine studies) has a commitment to share their clinical trial data as part of a data sharing policy starting in June 2014. We therefore designed an individual participant meta-analysis of randomised controlled trials of any condition with an FDA or EMA approval of use of duloxetine.

### *Objectives*

Our main objective is to compare the number of serious adverse events (SAE) among individuals taking duloxetine (in comparison to placebo) between participants at least 65 years and younger adults in EMA and FDA approved conditions. Our primary hypothesis is that elderly population is more prone to serious adverse events caused by duloxetine than younger adult population.

Our secondary objectives are to compare the number of any adverse events caused by duloxetine between participants at least 65 years of age and younger adults and to compare both the clinical efficacy of duloxetine on clinical scales and quality of life between elderly individuals and younger adults, separately for each indication. Furthermore, efficacy and tolerability will be compared between young-old (aged between 65 and 75) and old-old participants (aged 75-year-old or more).

## **METHODS AND DESIGN**

This systematic review and meta-analysis of individual patient data will be conducted of interventional, prospective, double-blind, randomised, placebo-controlled trials with an independent duloxetine arm. According to a protocol registered on PROSPERO (systematic review registration—2019 CRD42019130488), we have conducted a systematic literature review of relevant trials underwent on participants with an age  $<$  and  $\geq$  to 65 years old, in population suffering from a condition having an EMA or FDA approval for duloxetine. In this report we describe all eligible studies and present the outcomes that will be extracted for the individual patient data and the methods that will be used for data synthesis.

### *Eligibility criteria*

We used the following eligibility criteria:

- Types of studies: RCTs with both participants  $\geq$  and  $<$  to 65 years of age;

- Types of participants: subjects suffering from a disorder with a known approval for duloxetine by the FDA and the EMA, namely: depression, anxiety, diabetic neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence;
- Types of interventions: duloxetine whatever the dosage, the administration frequency, the route of administration;
- Type of comparator: placebo;
- Types of outcome measures: report of SAE for each participant under duloxetine and placebo arms and/or non-serious adverse events and/or efficacy and or quality of life;

The research was restricted to trials written in English, whatever their publication status (published/unpublished).

### *Information sources*

Searches were conducted in PubMed (to identify individual studies from published systematic reviews and meta-analyses of duloxetine), ClinicalTrials.gov, Clinicaltrialsregister.eu, data sharing platforms (ClinicalStudyDataRequest.com, YODA and Vivli), FDA drug approval packages and on European public assessment report and withdrawn applications from EMA website. The review was performed on studies available on electronic databases from their date of inception to May 31, 2019.

### *Search strategy*

Trials identification was systematic with different search strategies depending on the source. First, we search PubMed for all systematic reviews and meta-analyses involving duloxetine in an approved indication. Then, individual trials were identified from these systematic reviews and meta-analyses. The search terms were as follows: “(Duloxetine AND Meta-Analysis[ptyp])”. In ClinicalTrials.gov, the search was restricted to all interventional studies with adults and older adults, using “duloxetine” as search term. In Clinicaltrialsregister.eu and in data sharing platforms, the search term was “duloxetine” with no filter applied. In FDA website, FDA drug approval packages were downloaded from FDA Approved drug product, entering “duloxetine” as search term. In EMA website, European public assessment reports and withdrawn applications were selected, limited to reports on human with no restriction on the authorization status, using “duloxetine” as search term.

### *Study records*

#### *Data management, selection and collection processes*

Selection and coding of the different study characteristics were performed by two independent reviewers (JCR and AJ) in a blinded manner. A third reviewer (FN) arbitrated in case of disagreement. Studies appearing to duplicate authors, treatment comparisons, sample sizes and outcomes were checked one against another to avoid double-counting and integrating data from several reports on the same study

and in contact with the studies sponsors. A data extraction sheet based on the Cochrane Handbook for Systematic Reviews of Interventions guidelines was developed. In case of missing data, the sponsor of the study and/or corresponding authors were contacted.

### *Collecting IPD*

A data sharing request was sent to all sponsors which trials were spontaneously available on data sharing platforms. For the remaining studies, the request was sent to all correspondent authors and, if possible, a research proposal was addressed to each pharmaceutical sponsor on data sharing platforms (for Eli Lilly, Shionogi, Pfizer and AbbVie trials) or on the sponsor website (for Lundbeck, Takeda and Merck Sharp & Dohme trials). For willing collaborators, the terms of the collaboration will be specified in a data transfer agreement, signed by representatives of the data provider and of the recipients (Clinical Investigation Center, Department of Clinical Pharmacology, Rennes University Hospital, France). Collection of IPD is ongoing.

Participant characteristics requested are baseline age, gender, intervention arm, duloxetine dose, duration of participation in the study, number of serious adverse events from baseline to endpoint, number of non-serious adverse events from baseline to endpoint, study primary outcome and its values at baseline and at endpoint, type of quality of life scale used and its values at baseline and at endpoint. Data will be accepted in any suitable electronic format. Checks on the data will be made to ensure data are correctly coded, that missing data are correctly identified, that extreme values are genuine and to ensure that the data are consistent with published results. Data from all trials will be incorporated into a single database with fields that are consistent across trials.

### *Data items*

For each included study, information was extracted on:

- Characteristics of the study: year, country, number of arms with duloxetine and placebo, funding, disease;
- Characteristic of trial participants: mean age (and its standard deviation), gender, number of patients included in analysis, population of analysis used in the identified report (intention to treat, per protocol, other);
- Type of administration and dose;
- Outcome measures as stated above (including exact definition of outcome/ e.g. MedDRA or other).

### *Outcomes and prioritization*

The main outcome is the number (count) of SAE for each individual patient. In our study, SAE refers exclusively to any undesirable experience associated with the use of a medical product which results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in

persistent or significant disability, or is a congenital anomaly or birth defect. This outcome has the advantages to be simple of interpretation and clinically relevant for safety estimation, containing a severity criterion from its definition.

Additionally, will be assessed as secondary outcomes:

- The number of non-serious adverse events (nsAE). nsAE refers to any untoward medical occurrence in a clinical trial subject administered a medicinal product and which does not have severity criteria for SAE nor necessarily have a causal relationship with this treatment. In a randomised placebo-controlled setting, this outcome provides a global estimate of treatment safety, without the severity feature of SAE.
- The efficacy on clinical scale in each indication (i.e. depression, anxiety, pain, urinary incontinence): different scales in the same indication will be standardized by z-scores. This outcome will evaluate the clinical benefit in patients.
- The quality of life scores in each indication: the different scales will be standardized by z-score. In studies where multiple quality of life scales were used, a hierarchy was established by selecting scales which both resume health data in one unique total score and which were the most used among the duloxetine trials. If the only available instrument in a trial did not permit to resume data into one score (e.g. SF36), its general health subscale was retained as indicator of quality of life (details in table S1). Quality of life scores yield a broad and ecological estimate of the well-being state of the patient.

### *Risk of bias in individual studies*

Two researchers (JCR and AJ) assessed each trial for risk of bias independently, addressing randomisation, allocation concealment, blinding of assessors and of study participants, completeness of outcome assessment, selective reporting and other potential sources of bias according to the Cochrane Collaboration tool for assessing risk of bias in its current version, RoB2<sub>18</sub>, at the study level. Discrepancies were resolved by consensus.

### *Data synthesis*

#### *Main analysis*

As it appeared that all data were not directly downloadable together but rather provided remotely on separate interfaces, we chose a two-step procedure<sup>19</sup> to derive incidence rate ratio (for count of binary outcomes) and mean differences (for quantitative outcomes).

The first step consists in comparing the number (count) of SAE between groups of participants arranged by age using a generalized linear mixed model (with a quasi-Poisson link function) in each individual study. Age (binary variable between “young” participants < 65 years old and “old” participants ≥ 65 years old) and intervention (binary variable between participants under duloxetine to participant under

placebo) will be considered as fixed effects and their interaction will be explored as the main comparison. Incidence rate ratio as well as their variance will be extracted from the interaction between age and intervention.

In the second step, we will pool the extracted incidence rate ratios using a random effect meta-analysis. Similarly, number of non-serious adverse events (count) will be analyzed using a two-step approach based on a generalized linear mixed model (with a quasi-Poisson link function). For both SAE and nsAE, we will use meta-regressions to explore whether these interactions between age and intervention are different across the different conditions (major depressive disorder, generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain and stress urinary incontinence).

Summary measures for the analyses of efficacy and quality of life: in each condition, clinical scales (i.e. depression, pain, chronic anxiety) and quality of life scales will be analyzed separately using a similar two-step approach relying on results of a linear model. As various scales might be used across studies, we will use z-scores to standardize the different scales and populations.

Missing data will be handled by multiple imputation.

### *Sensitivity and subgroup analyses*

A sensitivity analysis will be performed considering the occurrence of SAE in binary (Yes vs No) with the same two step approach relying on a generalized linear mixed model (with a logistic link function) in each individual study.

A subgroup analysis will be performed applying the same methodology as for adverse events, to explore differences between “young-old” participants (between 65 and 75 years old) and “old-old” participants (>75 years old) in terms of adverse events (serious and non-serious) and of efficacy.

### *Meta-biases*

Missing trials will be explicitly reported with their characteristics and results described. Duplicate publications bias will be limited by the selection and precise identification of published and unpublished trials. If one or more trials could not be precisely identified by at least an ID number, these trials will be reported in the study results with explained attempts to obtain identification.

Countries where studies took place will be systematically assessed in the description studies table, to account for possible location bias. In addition, we clearly outline in our methods that our analysis select only studies written in English.

### *Confidence in cumulative evidence*

We will use GRADE to rate the overall certainty (quality) of evidence that includes the evaluation of risk of bias, inconsistency, indirectness, imprecision and publication factors<sup>20</sup>.

## QUALITATIVE RESULTS FROM AVAILABLE DATA

### *Study selection*

Our search identified 448 unique studies that were assessed for eligibility; of these, 77 studies with a total of 25 303 randomised participants fulfilled the eligibility criteria (fig 1). For searches conducted on PubMed, 48 meta-analyses or reviews were selected from 136 results. Lilly has accepted to share IPD data from 58 studies (table 1). Lundbeck, Pfizer and Abbott laboratories are still reviewing the data sharing request for 8 studies. No answer was obtained from the Danish Pain Research Center, the University of Nottingham arthritis research UK, the Northwestern University, the New York State Psychiatric Institute and for one study of Boehringer Ingelheim. Data sharing was denied from 6 trials belonging to Shionogi, Merck Sharp & Dohme and Wake Forest University National Institute of Neurological Disorders and Stroke.

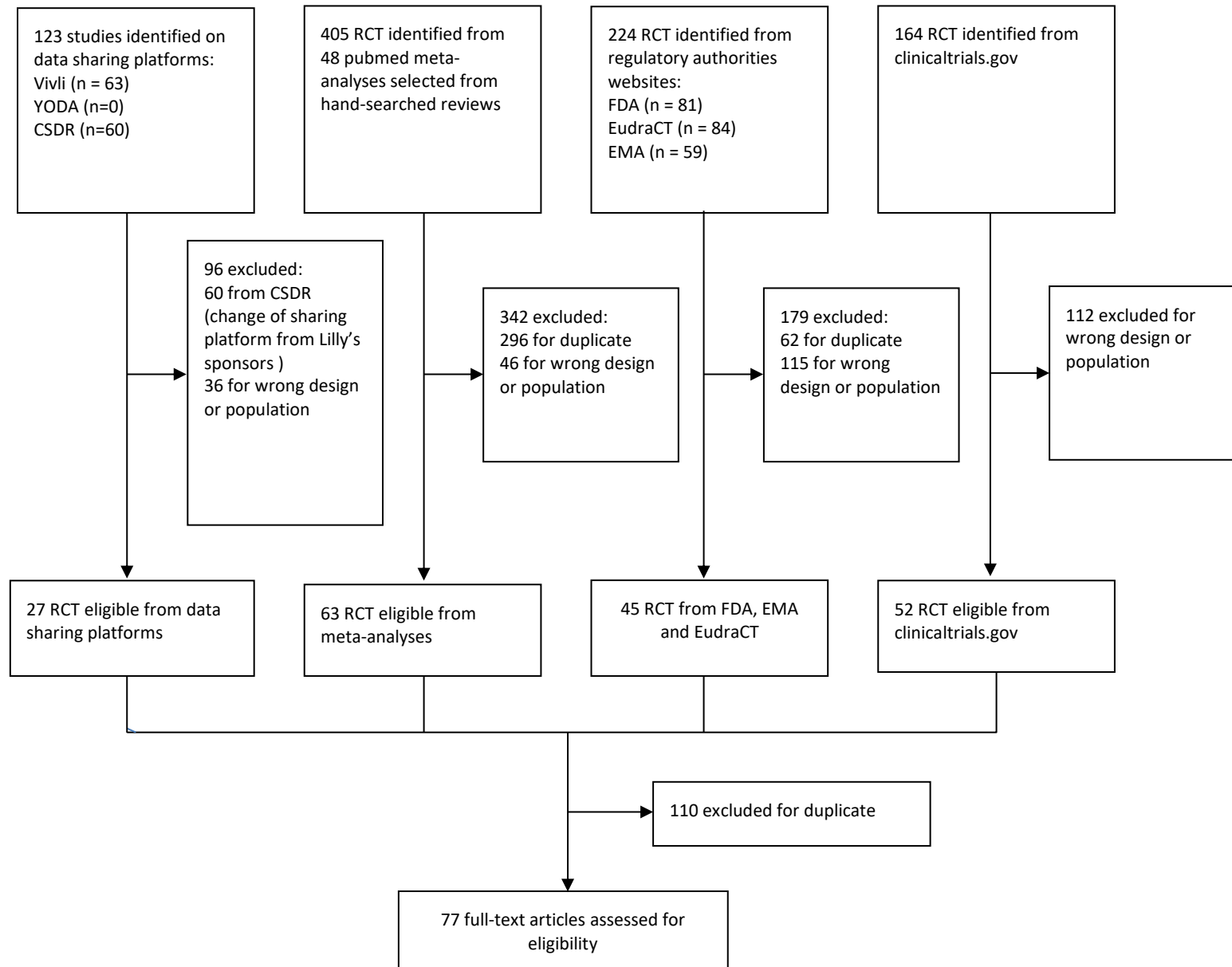
### *Study and participant characteristics*

Table 2 presents the characteristics of eligible studies and their participants. Trials were conducted in 45 countries on five continents (South Africa, Argentina, Brazil, Canada, Mexico, Puerto-Rico, USA, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, The Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain, Sweden, Switzerland, Russia, Spain, Ukraine, China, Hong Kong, India, Israel, Japan, Korea, Malaysia, The Philippines, Taiwan, Turkey and Australia) – even though just one country was represented for Africa (South Africa, with less than <2% of African subjects in those trials). Data on countries were not available online for Detke2004 (HMAW) which took place in 3 countries, FIJ-MC-HMAI which comprised 13 studies, and HMAYa where the number of countries was not reported. Trials enrolled participants of both sexes. Duloxetine dosage was determined in 76/77 trials: dosage ranged from 5 to 120 mg/day. All studies administered oral duloxetine to participants in the intervention arm. Exposition to intervention ranged from 4 to 52 weeks. Twenty-four trials explored duloxetine in major depressive disorder, 18 trials used duloxetine in urinary incontinence, 9 in osteoarthritis pain, 9 in diabetic neuropathic pain, 8 in fibromyalgia, 5 in general anxiety disorder and 4 in chronic low back pain. 71/76 studies were multicenter. All studies were in parallel design. 62/77 studies belong to the same sponsor or associated.

### *Risk of bias within studies*

Graph 1 and 2 provide details of the risk of bias assessment from online available data. 35 trials were assessed as being at an overall low risk of bias. Thirty-one trials were assessed as being at unclear risk of bias and 1 at high risk of bias. In this latter study (Perahia2009, HMDI), participants were randomised to duloxetine or placebo after a 32-week exposition to duloxetine, at risk of selecting subjects with a better tolerability to duloxetine during the double-blind phase.

**Figure 1. PRISMA flow diagram of included studies**





**Table 1. Status report of requested studies**

N°	Author	Sponsor ID	Sponsor	Contact	Status	Comments
1		F1J-MC-HMAH	Lilly	Vivli	Approved	
2		F1J-MC-HMAI	Lilly	Vivli	Approved	
3	Brannan2005	F1J-US-HMCB	Lilly	Vivli	Approved	
4	Nierenberg2007	F1J-US-HMCR	Lilly	Vivli	Approved	
5	Perahia2009	F1J-MC-HMDI	Lilly	Vivli	Approved	
6		F1J-US-HMFA	Lilly	Vivli	Approved	
7	Gaynor2011a	F1J-US-HMGR	Lilly	Vivli	Approved	
8	Gaynor2011b	F1J-US-HMGU	Lilly	Vivli	Approved	
9	Mundt2007	H8I-MC-HQAC	Lilly	Vivli	Approved	
10	Rynn2008	F1J-MC-HMDT	Lilly	Vivli	Approved	
11	Hartford2007	F1J-MC-HMDU	Lilly	Vivli	Approved	
12	Davidson2008	F1J-MC-HMDV	Lilly	Vivli	Approved	
13	Nicolini2009	F1J-MC-HMDW	Lilly	Vivli	Approved	

14	Koponen2007	F1J-MC-HMBR	Lilly	Vivli	Approved	
15	Arnold2005	F1J-MC-HMCA	Lilly	Vivli	Approved	
16	Arnold2012	F1J-MC-HMGG	Lilly	Vivli	Approved	
17	Arnold2004	F1J-MC-HMBO	Lilly	Vivli	Approved	
18	Wernicke2006	F1J-MC-HMAVa	Lilly	Vivli	Approved	
19	Raskin2005	F1J-MC-HMAVb	Lilly	Vivli	Approved	
20	Goldstein2005	F1J-MC-HMAW	Lilly	Vivli	Approved	
21	Gao2010	F1J-MC-HMEQ	Lilly	Vivli	Approved	
22	Gao2015	F1J-MC-HMGV	Lilly	Vivli	Approved	
23	Skljarevski2010a	F1J-MC-HMEN	Lilly	Vivli	Approved	
24	Skljarevski2009	F1J-MC-HMEO	Lilly	Vivli	Approved	
25	Skljarevski2010b	F1J-MC-HMGC	Lilly	Vivli	Approved	
26	Chappell2009	F1J-MC-HMEP	Lilly	Vivli	Approved	
27	Chappell2011	F1J-MC-HMFG	Lilly	Vivli	Approved	
28		F1J-MC-HMGP	Lilly	Vivli	Approved	

29	Brecht2007	F1J-BI-HMDH	Lilly/Boehringer Ingelheim	Vivli	Approved	
30	Wang2017	F1J-MC-HMGS	Lilly	Vivli	Approved	
31		F1J-MC-HMAG	Lilly	Vivli	Approved	
32	Russell2008	F1J-MC-HMCJ	Lilly	Vivli	Approved	
33	Arnold2010	F1J-US-HMGB	Lilly	Vivli	Approved	
34	Chappell2008	F1J-MC-HMEF	Lilly	Vivli	Approved	
35	Frakes2011	F1J-US-HMGL	Lilly	Vivli	Approved	
36		F1J-MC-SAAL	Lilly	Vivli	Approved	
37	Zinner1998	F1J-MC-SAAB	Lilly	Vivli	Approved	
38		F1J-MC-SAAH	Lilly	Vivli	Approved	
39	Bent2008	F1J-MC-SBBO	Lilly	Vivli	Approved	
40		F1J-MC-SBAB	Lilly	Vivli	Approved	
41	Ghoniem2005	F1J-MC-SBAF	Lilly	Vivli	Approved	
42	Cardozo2004	F1J-MC-SBAM	Lilly	Vivli	Approved	
43	Castro-Diaz2007	F1J-MC-SBBR	Lilly	Vivli	Approved	

44	Cardozo2010	F1J-EW-SBCC	Lilly	Vivli	Approved	
45	Lin2008	F1J-MC-SBBT	Lilly	Vivli	Approved	
46	Mah2006	F1J-MC-SBBU	Lilly	Vivli	Approved	
47	Dmochowski2003	F1J- MC-SBAV	Lilly	Vivli	Approved	
48	Van Kerrebroeck2004	F1J- MC-SBAT	Lilly	Vivli	Approved	
49		F1J-MC-SAAA	Lilly	Vivli	Approved	
50	Millard2004	F1J-MC-SBAX	Lilly	Vivli	Approved	
51		F1J-MC-SBBL	Lilly	Vivli	Approved	
52	Kinchen2005	F1J-MC-SBBA	Lilly	Vivli	Approved	
53		F1J-MC-HMATa	Lilly	Vivli	Approved	
54	Goldstein2004	F1J-MC-HMATb	Lilly	Vivli	Approved	
55	Detke2004	F1J-MC-HMAYa	Lilly	Vivli	Approved	
56	Perahia2006	F1J-MC-HMAYb	Lilly	Vivli	Approved	
57	Detke2002a	F1J-MC-HMBHa	Lilly	Vivli	Approved	
58	Detke2002b	F1J-MC-HMBHb	Lilly	Vivli	Approved	

59	Tourian2009	3151A1-335	Pfizer	Vivli	Under Review	
60		M06-850	Abbott Laboratories	Vivli	Under Review	
61	Baldwin2012	11984A	Lundbeck	Lundbeck platform	Under Review	
62	Boulenger2014	13267A	Lundbeck	Lundbeck platform	Under Review	
63	Mahableshwarkar2013	LuAA21004_304	Takeda	Lundbeck platform	Under Review	
64	Mahableshwarkar2015a	LuAA21004_315	Takeda	Lundbeck platform	Under Review	
65	Mahableshwarkar2015b	Lu_AA21004_202	Takeda	Lundbeck platform	Under Review	
66	Sofat2017	11.0126	St George's, University of London, Rosetrees Trus	Pr Harrison Dr Sofat	Under Review	
67		Dulo2006	Danish Pain Research Center	Danish Pain Research Center	No answer	3 attempts to contact dr Eriksson (two wrong mails) 3 attempts to contact the DPRC 3 attempts to contact the secretary of the DPRC
68	Reckziegel2007	13124	University of Nottingham arthritis research UK	Contact authors : Pr D. Auer Pr Reckziegel	No answer	3 attempts to contact each author by mail
69		1208.10	Boehringer Ingelheim		No answer	
70	Tétrault2016	STU00039556	Lilly/ Northwestern University	Contact author : Pr Apkarian	No answer	

71	Hellerstein2012	# 4967/6363R	Lilly/ New York State Psychiatric Institute	Contact author: Pr D. Hellerstein	No answer	
72		IRB00003943	Wake Forest University National Institute of Neurological Disorders and Stroke (NINDS)	Contact author : Pr Eisenach	Denial	Study was never completed
73		33CL231	Cubist Pharmaceuticals	Merck Sharp & Dohme Platform	Denial	Data not available
74	Yasuda2011	F1J-JE-HMFX	Shionogi	Vivli	Denial	Via Lilly sharing team: Shionogi does not share data of trials which imply medicinal products approved before February 2019
75	Uchio2018	F1J-JE-HMGX	Shionogi	Vivli	Denial	
76	Konno2016	F1J-JE-HMGY	Shionogi	Vivli	Denial	
77	Murakami2015	F1J-JE-HMGZ	Shionogi	Vivli	Denial	

Table 2. Characteristics of eligible studies

Study Name	Sponsor ID	Country	Sponsor	Medical Condition	N° center	ITT or PP	Design	Duration of active treatment (weeks)	Number of arms	Drugs	N° randomised	Mean Age (sd)	% Female	Dose	Primary Outcome	Quality of life score
Skljarevski 2010a	F1J-MC-HMEN	International	Lilly	CLBP	Multi center	ITT	Parallel	13	2	PB	121	51.15 (13.46)	60.3	0-0	BPI	EQ-5D
										DLX	115	51.81 (14.92)	61.7	120		
Skljarevski 2009	F1J-MC-HMEO	Two countries	Lilly	CLBP	Multi center	ITT	Parallel	11	4	PB	177	53.97 (13.52)	54.7	20	BPI	EQ-5D
										DLX	59	52.93 (12.81)	61.0	20		
										DLX	116	53.32 (14.69)	57.8	60		
										DLX	112	54.92 (14.77)	58	120		
Skljarevski 2010b	F1J-MC-HMGC	International	Lilly	CLBP	Multi center	ITT	Parallel	12	2	PB	203	53.43 (14.17)	63.1	0-0	BPI	EQ-5D
										DLX	198	54.87 (13.27)	59.6	60		
Konno 2016	F1J-JE-HMGY	Japan	Shionogi / Lilly	CLBP	Multi center	ITT	Parallel	12	2	PB	226	57.8 (13.7)	54.0	0-0	BPI	EQ-5D
										DLX	232	60.0 (13.2)	50.0	60		
	M06-850	International	Abbott Laboratories	DNP	Multi center	ITT	Parallel	8	2	PB	51			0-0	BPI	EQ-5D
										DLX	57			60		
	33CL231	USA	Merck	DNP	Multi center	ITT	Parallel	4	2	PB	72	56.2 (8.78)	37.5	60	Numeric Pain Rating Scale	
										DLX	77	59.1 (8.71)	50.0	60		
Wernicke 2006	F1J-MC-HMAVa	USA	Lilly	DNP	Multi center	ITT	Parallel	12	3	PB	108	60.81 (10.57)	36.1	0-0	BPI	EQ-5D
										DLX	114	59.71 (11.17)	35.1	60		
										DLX	112	61.46 (9.94)	45.5	120		
Raskin 2005	F1J-MC-HMAVb	USA	Lilly	DNP	Multi center	ITT	Parallel	12	3	PB	116	59.20 (9.84)	54.3	0-0	BPI	EQ-5D

											DLX	101	58.29 (10.88)	58.6	60		
											DLX	116	58.98 (9.58)	47.4	120		
Goldstein 2005	F1J-MC- HMAW	International	Lilly	DNP	Multi center	ITT	Paral lel	12	4		PB	115	60.42 (10.50)	48.7	0-0	BPI	EQ-5D
											DLX	115	60.31 (10.86)	34.8	20		
											DLX	114	59.21 (11.61)	30.7	60		
											DLX	113	60.50 (10.84)	39.8	120		
											PB	109	59.90 (9.52)	54.1	60-120		
Gao 2010	F1J-MC- HMEQ	China	Lilly	DNP	Multi center	ITT	Paral lel	12	2		DLX	106	58.59 (10.37)	51.9	60-120	BPI	EQ-5D
											PB	202	61.17 (9.42)	55	0-0		
Gao 2015	F1J-MC- HMGV	China	Lilly	DNP	Multi center	ITT	Paral lel	11	2		DLX	201	61.56 (9.65)	55.2	60	BPI	SDS
											PB	167			0-0		
Yasuda 2011	F1J-JE- HMFY	Japan	Shionogi / Lilly	DNP	Multi center	ITT	Paral lel	12	2		DLX	171		40-60	Average pain item of the BPI		
											PB	6	60	36.4	0-0	Visual Analogic Scale for Pain	
Arnold 2005	F1J-MC- HMCA	USA	Lilly	FMG	Multi center	ITT	Paral lel	12	3		PB	120	49.19 (11.83)	100	0-0	Average pain item of the BPI	QLDS
											DLX	118	48.33 (10.54)	100	60		
											DLX	116	51.28 (23.31)	100	120		
Arnold 2012	F1J-MC- HMGG	International	Lilly	FMG	Multi center	ITT	Paral lel	12	2		PB	153	50.72 (12.45)	96.1	0-0	Average pain item of the BPI	FIQ
											DLX	155	50.89 (11.90)	94.2	30-60		
Russel 2008	F1J-MC- HMCJ	USA and Puerto-Rico	Lilly	FMG	Multi center	ITT	Paral lel	14-13	4		PB	144	50.28 (10.92)	95.14	0-0	Average pain item of the BPI PGI-I	SDS
											DLX	79	51.75 (10.63)	90.67	20		
											DLX	150	51.04 (10.85)	97.28	60		
											DLX	147	50.93 (11.37)	96.20	120		
Arnold 2010	F1J-US- HMGB	USA	Lilly	FMG	Multi center	ITT	Paral lel	12	2		PB	267	49.62 (10.84)	93.6	0-0	PGI-I	SF-36



											DLX	263	50.74 (11.26)	92.8	60-120		
Murakami 2015	FIJ-JE- HMGZ	Japan	Shionogi / Lilly	FMG	Multi center	ITT	Paral lel	9	2	PB	191	49.5 (11.7)	84.1	0-0	BPI	FIQ	
										DLX	195	47.8 (12.0)	82.2	60			
Arnold 2004	FIJ-MC- HMBO	USA	Lilly	FMG/ MDD	Multi center	ITT	Paral lel	10	2	PB	103			0-0	FIS total Score and FIS pain item	SDS	
										DLX	103			120			
Chappell 2008	FIJ-MC- HMEF	International	Lilly	FMG/ MDD	Multi center	ITT	Paral lel	27	2	PB	168	50.17 (11.36)	95.24	0-0	Average pain item of the BPI	SDS	
										DLX	162	50.69 (10.05)	91.36	60-120			
	Dulo2006	Denmark	Danish Pain Research Center	FMG/ DNP	Single center												
Rynn 2008	FIJ-MC- HMDT	USA	Lilly	GAD	Multi Center Multi center	ITT	Paral lel	6	2	PB	159	40.98 (14.19)	62.26	0-0	HAMA	SDS	
										DLX	168	42.22 (13.93)	61.31	120			
Hartford 2007	FIJ-MC- HMDU	USA	Lilly	GAD	Multi Center Multi center	ITT	Paral lel	6	2	PB	162	41.85 (14.23)	61.49	0-0	HAMA	SDS	
										DLX	162	40.35 (13.58)	64.20	60-120			
Davidson 2008	FIJ-MC- HMDV	International	Lilly	GAD	Multi center	ITT	Paral lel	7	2	PB	213	45.68 (14.05)	58.69	0-0	MINI Clinical Global Improvement scale	SDS	
										DLX	213	44.98 (13.62)	61.11	60-120			
Nicolini et al 2009	FIJ-MC- HMDW	International	Lilly	GAD	Multi center	ITT	Paral lel	6	3	PB	170	42.57 (12.11)	63.53	20	HAMA	SDS	
										DLX	84	44.75 (13.45)	48.81	20			
										DLX	158	42.58 (12.58)	56.96	60-120			
Koponen 2007	FIJ-MC- HMBR	International	Lilly	GAD	Multi center	ITT	Paral lel	6	3	PB	175	44.12 (13.42)	66.86	0-0	HAMA	SDS	
										DLX	168	43.11 (12.92)	64.29	60			
										DLX	170	44.10 (43.87)	72.35	120			
	1208.10	Europe	BI	MDD	Multi center	ITT	Paral lel	7	2	PB	165			0-0	Average pain item of the BPI		
										DLX	162			60			
	FIJ-MC- HMAH	One country	Lilly	MDD	Multi center	ITT	Paral lel	10	2	PB	88	37.51 (10.28)	55.7	0-0	HAMD17		

										DLX	89		59.6	20-30		
										PB	126	41.35 (12.36)	66.7	0-0		
	F1J-MC-HMAI	International	Lilly	MDD	Multi center	ITT	Parallel	8	4	DLX	130	43.14 (12.16)	66.9	5	HAMD17	
										DLX	129	42.45 (10.10)	64.3	10		
										DLX	131	41.53 (11.45)	64.1	20		
										PB	90	42.21 (14.49)	65.6	0-0		
	F1J-MC-HMATa	USA	Lilly	MDD	Multi center	ITT	Parallel	8	3	DLX	91	43.36 (15.25)	68.1	40	HAMD17	QLDS
										DLX	84	43.68 (14.65)	60.7	80		
Goldstein2004	F1J-MC-HMATb	USA	Lilly	MDD	Multi center	ITT	Parallel	8	3	PB	89	40.14 (12.94)	64.0	0-0		
										DLX	86	40.69 (10.04)	55.8	40	HAMD17	QLDS
										DLX	91	40.89 (11.90)	61.5	80		
Detke 2004	F1J-MC-HMAYa		Lilly	MDD	Multi center	ITT	Parallel	8	3	PB	93	43.67 (12.16)	74.2	0-0		
										DLX	95	43.09 (11.14)	73.7	80	HAMD17	SDS
										DLX	93	44.72 (10.71)	75.3	120		
Perahia 2006	F1J-MC-HMAYb	International	Lilly	MDD	Multi center	ITT	Parallel	7	3	PB	99	44.67 (10.05)	65.7	0-0		
										DLX	93	46.47 (12.70)	66.7	80	HAMD17	SDS
										DLX	103	45.37 (10.75)	74.8	120		
Detke 2002a	F1J-MC-HMBHa	USA	Lilly	MDD	Multi center	ITT	Parallel	11	2	PB	122	42.34 (12.58)	68.0	0-0		
										DLX	123	42.44 (13.74)	65.0	60	HAMD17	QLDS
Detke 2002b	F1J-MC-HMBHb	USA	Lilly	MDD	Multi center	ITT	Parallel	11	2	PB	139	41.04 (14.66)	71.2	0-0		
										DLX	128	40.83 (12.56)	66.4	60	HAMD17	QLDS
Brannan 2005	F1J-US-HMCB	USA	Lilly	MDD	Multi center	ITT	Parallel	9 to 5	2	PB	141	40.3 (13.5)	62.4	0-0	Average pain item on BPI	
										DLX	141	40.8 (13.5)	68.1	60		
Nierenberg 2007	F1J-US-HMCR	USA	Lilly	MDD	Multi center	ITT	Parallel	8	2	PB	137	42.5 (12.3)	67.9	0-0		SDS

											DLX	273	41.1 (11.6)	63.5	60	Maier subscale of the HAMD17	
Perahia 2009	F1J-MC- HMDI	International	Lilly	MDD	Multi center	ITT	Paral lel	52	2	PB	142	48.01 (12.29)	74.6	0-0	time to recurrence	SDS	
										DLX	146	47.07 (12.84)	68.5	60-120			
Gaynor 2011a	F1J-US-- HMGR	International	Lilly	MDD	Multi center	ITT	Paral lel	7	2	PB	266	45.73 (12.85)	69.2	0-0	MADRS Average pain item on BPI	SDS	
										DLX	262	46.15 (13.27)	68.7	60			
Gaynor 2011b	F1J-US- HMGR	International	Lilly	MDD	Multi center	ITT	Paral lel	7	2	PB	266	44.21 (12.38)	66.9	0-0	MADRS Average pain item on BPI	SDS	
										DLX	261	45.15 (12.47)	70.1	60			
Mundt 2007	H8I-MC- HQAC	USA	Lilly	MDD	Multi center	ITT	Paral lel	4	2	PB	35			0-0	Daily Telephone Assessment		
										DLX	17			60			
Brecht 2007	F1J-BI- HMDH	International	Lilly / BI	MDD	Multi center	ITT	Paral lel	7	2	PB	165	52.3 (12.1)	71.5	0-0	Average pain item on BPI		
										DLX	162	48.1 (13.5)	75.9	60			
Hellerstein 2012	# 4967 / 6363R	USA	New York State Psychiatric Institute	MDD	Single center	ITT	Paral lel	10	2	PB	33	42.1 (11.4)	31.3	0-0	MADRS	SAS	
										DLX	32	41 (11.7)	54.5	30-120			
Baldwin 2012	11984A	International	Lundbeck	MDD	Multi center	ITT	Paral lel	8	2	PB	148	43.4 (12.5)	69.6	0	MADRS	SDS	
										DLX	155	45.3 (12.0)	67.7	60			
Boulenger 2014	13267A	International	Lundbeck	MDD	Multi center	ITT	Paral lel	8	2	PB	158	45.6 (13.6)	69.6	0-0	MADRS	SDS	
										DLX	147	48.1 (13.1)	69.4	60			
Tourian 2009	3151A1-335	USA	Pfizer	MDD	Multi center	ITT	Paral lel	8	2	PB	161	39.24 (12.74)	58.4	0-0	HAMD17		
										DLX	157	38.94 (12.01)	66.2	60			
Mahableshwarkar 2015a	LuAA21004 _202	International	Takeda	MDD	Multi center	ITT	Paral lel	8	2	PB	194	45.0 (12.07)	61.3	0-0	Digit symbol substitution test	SDS	
										DLX	210	45.7 (11.46)	65.7	30-60			
Mahableshwarkar 2013	LuAA21004 _304	USA	Takeda	MDD	Multi center	ITT	Paral lel	7	2	PB	151	42.6 (13.76)	60.8	0-0	HAMD24	SDS	
										DLX	150	42.7 (14.38)	59.9	60			

Mahableshwarkar 2015a	LuAA21004 _315	USA	Takeda	MDD	Multi center	ITT	Paral lel	7	2	PB	161	42.4 (12.55)	72.0	0-0	MADRS	SDS
										DLX	152	43.4 (12.24)	73.8	60		
	F1J-MC- HMAG		Lilly	MDD	Single center		Paral lel	10	2	PB	52	40.28 (10.00)	55.8	0-0	HMAD17 MADRS	
										DLX	53	40.58 (10.46)	54.7	20		
Frakes 2011	F1J-US- HMGL	USA	Lilly	OAP	Multi center	ITT	Paral lel	8	2	PB	260	60.32 (9.17)	56.5	0-0	Average pain item of the BPI	
										DLX	264	61.63 (9.24)	57.6	60-120		
Chappell 2009	F1J-MC- HMEP	International	Lilly	OAP	Multi center	ITT	Paral lel	13	2	PB	120	62.48 (9.30)	67.50	0-0	Average pain item of the BPI	EQ-5D
										DLX	111	62.07 (9.63)	63.06	60-120		
Chappell 2011	F1J-MC- HMFG	International	Lilly	OAP	Multi center	ITT	Paral lel	12	2	PB	128	61.90 (9.20)	83.6	0-0	Average pain item of the BPI	EQ-5D
										DLX	128	63.16 (8.75)	69.5	60-120		
	F1J-MC- HMGP	International	Lilly	OAP	Multi center	ITT	Paral lel	12	2	PB	207	63.40 (9.90)	71.0	0-0	Average pain item of the BPI	EQ-5D
										DLX	217	64.18 (10.06)	65.0	60		
Wang 2017	F1J-MC- HMGS	China	Lilly	OAP	Multi center	ITT	Paral lel	12	2	PB	177	59.83 (8.40)	74.8	0-0	Average pain item of the BPI	
										DLX	172	61.17 (8.19)	78.0	60		
Tétreault 2016	STU000395 56	USA	Northwestern University	OAP	Multi center	ITT	Paral lel	15	2	PB	19	58.9 (8.6)	47.6	0-0	Brain Gray Matter Volume	
										DLX	21	58.6 (4.2)	52.6	60		
Sofat 2017	11.0126	UK	St George's, University of London	OAP	Single center	ITT	Paral lel	9	2	PB	21			0-0	Australian/Can adian Hand Osteoarthritis Index score	
										DLX	22			60-30		
Reckziegel 2017	13124	UK	University of Nottingham	OAP	Single center	ITT	Paral lel	4	2	PB	27			0-0	Brain functional connectivity	
										DLX	54			60		
Uchio 2018	F1J-JE- HMGX	Japan	Shionogi / Lilly	OAP	Multi center	ITT	Paral lel	12	2	PB	176	66.4 (8.4)	75.0	0-0	Average pain item of the BPI	EQ-5D
										DLX	178	65.5 (8.0)	80.2	60		
			Lilly	UI-M	Multi	NA		8	2	PB	16			0-0		

	FIJ-MC-SAAL				center		Cross-over			DLX	34		30-40			
Zinner 1998	FIJ-MC-SAAB	Lilly	UI-M	Multi center	Parallel	6	4	PB	67		100	0-0	One-hour Stress Pad Test weight	I-QOL		
								DLX	75		100	20				
								DLX	69		100	30				
								DLX	77		100	30-40				
F1J-MC-SAAH	Lilly	UI-M	Single center	Parallel	3	PB			84.4	0-0	Detrusor Activity Index					
						DLX			84.4	30						
						DLX			84.4	40						
Bent 2008	FIJ-MC-SBBO	International	Lilly	UI-M	Multi center	ITT	Parallel	8	2	PB	288	54.2 (11.6)	100	0-0	IEF	I-QOL
										DLX	300	53.2 (12.5)	100	80		
Ghoniem 2005	FIJ-MC-SBAF	International	Lilly	UI-S	Multi center	ITT	Parallel	12	2	PB	47	51	100	0-0	IEF	EQ-5D
										DLX	52	53	100	60		
Cardozo 2004	FIJ-MC-SBAM	International	Lilly	UI-S	Multi center	ITT	Parallel	8	2	PB	54	52.4 (10.4)	100	0-0	IEF	I-QOL
										DLX	55	54.5 (9.7)	100	80-120		
Castro-Diaz 2007	FIJ-MC-SBBR	International	Lilly	UI-S	Multi center	ITT	Parallel	8	4	PB	120	52.7 (9.2)	100	0-0	IEF	I-QOL
										DLX	133	53.5 (10.6)	100	20		
										DLX	127	52.3 (10.4)	100	40-80		
										DLX	133	53.3 (11.8)	100	40-80		
Cardozo 2010	FIJ-EW-SBCC	International	Lilly	UI-S	Multi center	ITT	Parallel	6	2	PB	1380	55.47 (11.62)	100	0-0	IEF	KHQ
										DLX	1378	55.51 (11.77)	100	80		
Lin 2008	FIJ-MC-SBBT	Taiwan	Lilly	UI-S	Multi center	ITT	Parallel	8	2	PB	61	56.31 (10.25)	100	0-0	IEF	I-QOL
										DLX	60	56.31 (11)	100	80		
Mah 2006	FIJ-MC-SBBU	Korea	Lilly	UI-S	Multi center	ITT	Parallel	8	2	PB	60	48.52 (8.05)	100	0-0	IEF	I-QOL
										DLX	61	50.67 (9.01)	100	80		

Dmochowski 2003	F1J- MC- SBAV	USA	Lilly	UI-S	Multi center	ITT	Paral lel	12	2	PB	339	53.3 (11.5)	100	0-0	IEF I-QOL	I-QOL
										DLX	344	52.3 (10.4)	100	80		
Van Kerrebroeck 2004	F1J- MC- SBAT	International	Lilly	UI-S	Multi center	ITT	Paral lel	12	2	PB	247	54 (10)	100	0-0	IEF I-QOL	I-QOL
										DLX	247	52 (11)	100	80		
Millard 2004	F1J-MC- SBAX	International	Lilly	UI-S	Multi center	ITT	Paral lel	12	2	PB	231	52.6	100	0-0	IEF I-QOL	I-QOL
										DLX	227	53.7	100	80		
Kinchen 2005	F1J-MC- SBBA	USA	Lilly	UI-S	Multi center	ITT	Paral lel	36	2	PB	227	53.3 (13)	100	0-0	I-QOL	I-QOL
										DLX	224	52.7 (13)	100	80		
	F1J-MC- SBAB		Lilly	UI-S	Multi center		Paral lel	4		PB			100	0-0	IEF	
										DLX			100	20-40		
	F1J-MC- SAAA		Lilly	UI-S	Multi center		Paral lel	3	2	PB	37	37	98.9	0-0		
										DLX	55	55	98.9	20		
	F1J-MC- SBBL		Lilly	UI-S	Multi center		Paral lel	12	2	PB			100	0-0	24-hour diary	
										DLX			100	40-60		
	F1J-JE- 323G	Japan	Shionogi / Lilly	UI-S	Multi center		Paral lel	4		PB				0-0	HAMD MADRS	
										DLX				5-20		

**Legend :**

ITT: Intention to treat, PP: Per-Protocol,

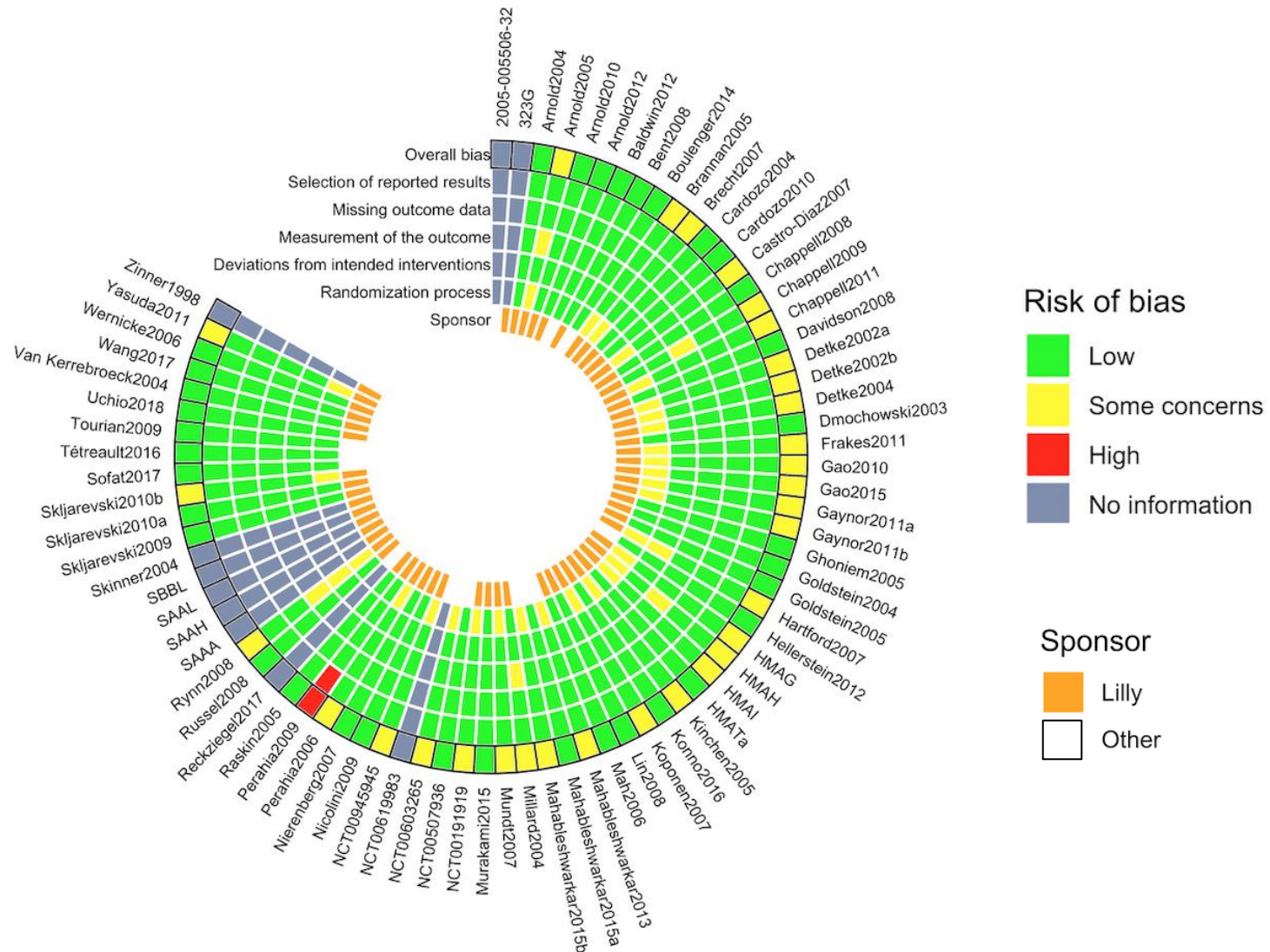
CLBP: Chronic Low Back Pain, DNP: Diabetic Neuropathic Pain, FMG: Fibromyalgia, GAD: Generalized Anxiety Disorder, MDD: Major Depressive Disorder, OAP: Osteoarthritis Pain, UI-M: Mixed Urinary Incontinence, UI-S: Stress Urinary Incontinence

DLX: Duloxetine, PB: Placebo

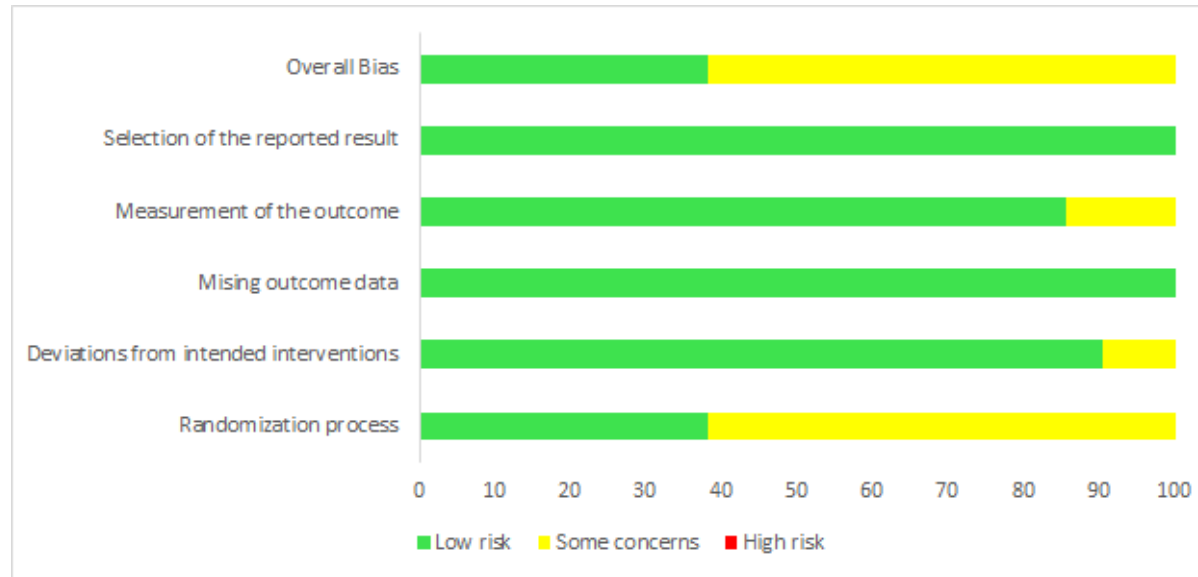
BPI: Brief Pain Inventory, HAMD: Hamilton Depression Rating Scale, FIS: Fibromyalgia Intensity Score, IEF: Incontinence Episode Frequency, MADRS: Montgomery Asberg Depression Rating Scale, MIN: Mini International Psychiatric Interview, PGI-I: Patient Global Impression of Improvement,

EQ-5D: EuroQol 5 Dimensions, FIQ: Fibromyalgia Impact Questionnaire, KHQ: King Health Questionnaire, I-QOL: Incontinence Quality of Life, QLDS: Quality of Life in Depression Scale, SAS: Social Adjustment Scale, SDS: Sheehan Disability Scale, SF-36: 36-Item Short Form Survey, UPSA: University of California, San Diego, Performance-Based Skills Assessment.

**Graph1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study**



**Graph 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**





## CONCLUSION

To our knowledge, this study would represent the first meta-analysis investigating the safety and utility of duloxetine in elderly population across all conditions approved by European and American regulatory authorities.

Reported results are solely based on online available data. While these suggest an overall low risk of bias across eligible studies, sponsors are yet to be contacted to fully describe characteristic of patients and studies, as to appraise the effective risk of bias of each study. Afterward, a comparison between our current results and results obtained after personal communication with the sponsor can provide an interesting indicator of sponsors' transparency on trials with duloxetine.

While 58 studies have been approved for sharing data, these studies all belong to the same sponsor, owner of the duloxetine. The other sponsors are still evaluating our proposal, have not answered to our proposal or have denied to share their data. In addition, IPD data can only be processed in independent platforms forbidding the direct aggregation of data from other data sharing platforms. These hurdles highlight current issues in realizing one-step IPD meta-analysis when multiple sources are concerned, for both industrial and academic sponsors.

The scope of our meta-analysis is intended to benefit to a wide range of medical specialties as an help for the prescribers and as a better care for elderly population. Furthermore, our study exemplifies current possibilities and limits of sharing of individual data in meta-research.

## Authors' contributions

JCR participated in the development of the study protocol and writing of the manuscript and is responsible for data extraction and eligibility review. CR participated in the study protocol analysis plan and will be responsible for final analyses. AJ is responsible for data and eligibility review. FN developed the study design and protocol analysis plan and supervises the realization of the study. GR participated in the development of the study protocol and supervises the realization of the study.

We are thankful to Charles Khouri for sharing his plotting code.

## SUPPLEMENTS

*Appendix 1. Reference list of included studies*

*Appendix 2. Reference list of selected meta-analyses and systematic reviews*

*Supplementary Table S2. Table of quality of life scales selected per study*

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## Appendix 1. Reference list of eligible studies

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## Appendix 2. Reference list of selected meta-analyses and systematic reviews

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### Supplementary Table S2. Quality of life scales selected per eligible study

Reported quality of life scales are summarized in table S2 (legend at the end of the table).

Quality of life scales were selected hierarchically by first privileging scales which are valid for summarizing health in one total score. Then, the most frequent scales across duloxetine trials were selected. If the only available instrument in a trial did not permit to resume data into one score, a chosen general health subscale was used as indicator of quality of life.

Quality of life scales are ordered by type (one total score versus sub-scores) and by prevalence. Scales in grey-blue and blue-azur cells refer to one-scored instruments, blue-azur scales referring to instruments used in just one trial. Yellow scales refer to multidimensional scores, thus implying the selection of an item representing general health. The only irreducible scale encountered was the 36-Item Short Form Survey (SF-36), for which the sub-score “General Health Perception” was kept. Studies with reported quality of life scales are colored in green while studies without reported quality of life scale are colored in blue. Studies without online information enabling to conclude to the presence or absence of quality of life scales are uncolored.

Author	Sponsor ID	Medical Condition	QALY	Number of QALY	Quality of Life Scales												
					SDS	EQ-5D	I-QOL	QLDS	FIQ	ICIQ-SF	Q-LES-Q-SF	SAS	EWPS	UPSA	KHQ	SF-36	Undefined
<b>Total sum of Quality of life scales</b>					<b>18</b>	<b>16</b>	<b>11</b>	<b>7</b>	<b>6</b>	<b>2</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>21</b>	<b>1</b>
Arnold 2005	F1J-MC-HMCA	FMG	1	3				1	1							1	
Arnold2012	F1J-MC-HMGG	FMG	1	2					1							1	
Arnold2010	F1J-US-HMGB	FMG	1	1												1	
Arnold2004	F1J-MC-HMBO	FMG/MDD	1	4	1			1	1							1	
Baldwin2012	11984A	MDD	1	1	1												
Bent2008	F1J-MC-SBBO	UI-M	1	2			1			1							









	F1J-MC-HMAG	MDD	Unknown																			
	F1J-MC-SAAL	UI+	Unknown																			
	F1J-MC-SAAH	UI+	Unknown																			
	F1J-MC-SBAB	UI-S	Unknown																			
	F1J-MC-SBBL	UI-S	Unknown																			
	F1J-JE-323G	MDD	Unknown																			

**Legend :**  
*QALY : Quality of Life Scale, EQ-5D: EuroQol 5 Dimensions, EWPS: Endicott Work Productivity Scale, FIQ: Fibromyalgia Impact Questionnaire, KHQ: King Health Questionnaire, ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form , I-QOL: Incontinence Quality of Life , QLDS: Quality of Life in Depression Scale, Q-LES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire, SAS: Social Adjustment Scale, SDS : Sheehan Disability Scale, SF-36: 36-Item Short Form Survey, UPSA: University of California, San Diego, Performance-Based Skills Assessment.*

**ROY Jean-Charles****Évaluation de la tolérance à la duloxétine entre populations adulte et âgée : protocole et résultats préliminaires d'une revue systématique de la littérature et méta-analyse sur données individuelles d'essais contrôlés randomisés contre placebo.**

[60 feuilles., 4 illustrations., 2 graphiques., 3 tableaux], 30 cm. –

Thèse : (Médecine) ; Rennes 1; 2011 ; N° .

**Résumé**

**Introduction.** La duloxétine est un antidépresseur qui bénéficie d'une approbation de prescription pour de nombreuses pathologies fréquentes chez les personnes âgées. Cependant, contrairement à l'adulte plus jeune, la sécurité d'emploi de la duloxétine chez la personne âgée n'est pas clairement établie. Une comparaison de la tolérance de la duloxétine entre personnes âgées et adultes plus jeunes permettrait de statuer sur cette question. **Analyse et Méthodes.** Ce protocole présente une revue systématique de la littérature et une méta-analyse sur données individuelles de tous les essais contrôlés randomisés en double-aveugle comparant le nombre d'événements indésirables sévères sous duloxétine comparé au placebo entre des sujets âgés (de 65 ans ou plus) et des adultes plus jeunes (de moins de 65 ans), dans des pathologies où la duloxétine est approuvée par l'Agence Européenne du Médicament (EMA) et la Food and Drug Administration (FDA). Les variables secondaires sont la différence de nombre d'évènements indésirables non-sévères sous duloxétine contre placebo entre les sujets âgés et les adultes plus jeunes, ainsi que les effets d'interaction entre l'âge et l'intervention sur les scores cliniques et les scores de qualité de vie. Une revue systématique de la littérature selon les recommandations Cochrane a été effectuée sur des sites d'essais cliniques ClinicalTrials.gov, Clinicaltrialsregister.eu, des plateformes de données (ClinicalStudyDataRequest.com, YODA et Vivli) et à partir des argumentaires officiels de l'EMA et de la FDA. Les promoteurs et auteurs des études éligibles ont été invités à partager leurs données sur les plateformes de partage de données ou directement avec notre équipe de recherche. Une analyse statistique en deux étapes sera effectuée, consistant en une extraction des taux d'incidence des variables principale et secondaires à partir des effets d'interaction entre le traitement alloué et la catégorie d'âge par une régression multiniveaux. Ensuite, une analyse combinée des taux d'incidence issus des études partagées sur des plateformes différentes sera effectuée. **Résultats qualitatifs à partir des données disponibles :** Sur les 916 études identifiées, 77 ont été retenues comme éligibles soit un total de 25303 sujets. Le partage de données a été approuvé pour 58 études, est en cours de relecture pour 8 études, et a été refusé pour 6 études. 5 sponsors n'ont pas répondu aux invitations de partage soit un total de 5 études. A partir des données disponibles en ligne, 67 essais ont pu être évalués dont 35 jugés à faible risque de biais, 31 à un risque de biais incertain et 1 à haut risque de biais. **Conclusion.** Cette étude serait la première méta-analyse étudiant directement la sécurité d'emploi de la duloxétine chez les populations âgées dans toutes les pathologies approuvées par les autorités européennes et américaines.

Rubrique de classement : Psychiatrie

Mots-clés : Psychiatrie de la personne âgée, méta-analyse, tolérance médicamenteuse, Duloxetine

Mots-clés anglais MeSH: Psychiatry, Geriatric; Meta-analysis; Drug Safety; Duloxetine Hydrochloride.

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