Tolerability of duloxetine in the elderly and in adults: a protocol and preliminary results of a systematic review and individual participant data meta-analysis of randomized placebo-controlled trials

Jean-Charles ROY (✉ jean-charles.ROY@chu-rennes.fr)

Université de Rennes 1 Faculté de Médecine <https://orcid.org/0000-0003-0686-4099>

Chloé Rousseau

Université de Rennes 1 Faculté de Médecine

Alexis Jutel

Université de Rennes 1 Faculté de Médecine

Florian Naudet

Université de Rennes 1 Faculté de Médecine

Gabriel Robert

Université de Rennes 1 Faculté de Médecine

Protocol

Keywords: Psychiatry, Geriatric, Meta-analysis, Drug Safety, Duloxetine Hydrochloride

Posted Date: May 22nd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-29775/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background. 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 this issue.

Methods and Design. This protocol outlines a systematic review and meta-analysis of individual participant data (IPD) of all double-blind randomized controlled trials comparing 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, clinical efficacy and quality of life between elderly and younger adults under duloxetine, in comparison to placebo. Relevant studies were selected on ClinicalTrials.gov, Clinicaltrialsregister.eu, data sharing platforms, FDA and EMA websites, and from systematic reviews and meta-analyses of duloxetine on PubMed, following Cochrane's recommendations. Sponsors and authors from eligible studies were invited to share IPD on data sharing platform or directly with our research team. As data cannot be aggregate into a unique database, a two step-approach meta-analysis will be undertaken.

Qualitative results from available data. 77 eligible randomized controlled trials were identified, representing 25303 participants. 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.

Background

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 population¹. While several guidelines recommend the use of duloxetine as a first-line medication for these diseases in the elderly²⁻⁶, others formally proscribe it⁷. 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^{5,8}.

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 (≥ 65 years old), in a context of scarce data in this population⁹. In contrast, duloxetine was found to increase the risk of adverse events.¹⁰ In younger adults, several meta-analyses concluded that duloxetine was associated to a disfavoring risk-benefit balance compared to placebo in osteoarthritis and stress urinary incontinence^{11,12}. 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)¹³, 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)¹⁴ 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)¹⁴. Skinner et al. (2004) estimated that decrease of oral clearance accelerates at around 52 years of age¹⁵. Similar results have been reproduced in ulterior pooled analyses of phase III trials¹⁶ 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 studies¹⁶. As mentioned in the FDA CYMBALTA® Label¹⁷ (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 randomized 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, randomized, 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 following the PRISMA-P recommendations (Additional file 1). The anticipated end date of study is November 2021.

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. The list of included studies, as the list of meta-analyses and of systematic reviews, are reported on additional file 2 and additional file 3, respectively.

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 randomized 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 (detailed in Additional file 4, 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 randomization, 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, RoB2¹⁸, 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 procedure¹⁹ 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 factors²⁰.

Qualitative Results From Online Data

Study selection

Our search identified 448 unique studies that were assessed for eligibility (reported in supplementary file). Of these, 77 studies accounting a total of 25 303 randomized participants fulfilled the eligibility criteria (Figure 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.

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	Approved	
60		M06-850	Abbott Laboratories	Vivli	Approved	
61	Baldwin2012	11984A	Lundbeck	Lundbeck platform	Approved	
62	Boulenger2014	13267A	Lundbeck	Lundbeck platform	Approved	
63	Mahableshwarkar2013	LuAA21004_304	Takeda	Lundbeck platform	Approved	
64	Mahableshwarkar2015a	LuAA21004_315	Takeda	Lundbeck platform	Approved	
65	Mahableshwarkar2015b	Lu_AA21004_202	Takeda	Lundbeck platform	Approved	
66	Sofat2017	11.0126	St George's, University of London, Rosetrees Trus	Pr Harrison Dr Sofat	Approved	
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 :	Denial	Study was never completed

				Pr Eisenach		
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	

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, F1J-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.

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° random
Skljarevski 2010a	F1J-MC-HMEN	International	Lilly	CLBP	Multi center	ITT	Parallel	13	2	PB	121
										DLX	115
Skljarevski 2009	F1J-MC-HMEO	Two countries	Lilly	CLBP	Multi center	ITT	Parallel	11	4	PB	177
										DLX	59
										DLX	116
										DLX	112
Skljarevski 2010b	F1J-MC-HMGC	International	Lilly	CLBP	Multi center	ITT	Parallel	12	2	PB	203
										DLX	198
Konno 2016	F1J-JE-HMGY	Japan	Shionogi / Lilly	CLBP	Multi center	ITT	Parallel	12	2	PB	226
										DLX	232
	M06-850	International	Abbott Laboratories	DNP	Multi center	ITT	Parallel	8	2	PB	51
										DLX	57
	33CL231	USA	Merck	DNP	Multi center	ITT	Parallel	4	2	PB	72
										DLX	77
Wernicke 2006	F1J-MC-HMAVa	USA	Lilly	DNP	Multi center	ITT	Parallel	12	3	PB	108
										DLX	114
										DLX	112
Raskin 2005	F1J-MC-HMAVb	USA	Lilly	DNP	Multi center	ITT	Parallel	12	3	PB	116
										DLX	101
										DLX	116
Goldstein 2005	F1J-MC-HMAW	International	Lilly	DNP	Multi center	ITT	Parallel	12	4	PB	115
										DLX	115
										DLX	114
										DLX	113
Gao 2010	F1J-MC-HMEQ	China	Lilly	DNP	Multi center	ITT	Parallel	12	2	PB	109
										DLX	106
Gao 2015	F1J-MC-HMGV	China	Lilly	DNP	Multi center	ITT	Parallel	11	2	PB	202

										DLX	201
Yasuda 2011	F1J-JE-HMFX	Japan	Shionogi / Lilly	DNP	Multi center	ITT	Parallel	12	2	PB	167
										DLX	171
	IRB00003943	USA	Wake Forest University	DNP	Multi center	ITT	Parallel	6	2	PB	6
										DLX	5
Arnold 2005	F1J-MC-HMCA	USA	Lilly	FMG	Multi center	ITT	Parallel	12	3	PB	120
										DLX	118
										DLX	116
Arnold 2012	F1J-MC-HMGG	International	Lilly	FMG	Multi center	ITT	Parallel	12	2	PB	153
										DLX	155
Russel 2008	F1J-MC-HMCJ	USA and Puerto-Rico	Lilly	FMG	Multi center	ITT	Parallel	14-13	4	PB	144
										DLX	79
										DLX	150
										DLX	147
Arnold 2010	F1J-US-HMGB	USA	Lilly	FMG	Multi center	ITT	Parallel	12	2	PB	267
										DLX	263
Murakami 2015	F1J-JE-HMGZ	Japan	Shionogi / Lilly	FMG	Multi center	ITT	Parallel	9	2	PB	191
										DLX	195
Arnold 2004	F1J-MC-HMBO	USA	Lilly	FMG/ MDD	Multi center	ITT	Parallel	10	2	PB	103
										DLX	103
Chappell 2008	F1J-MC-HMEF	International	Lilly	FMG/ MDD	Multi center	ITT	Parallel	27	2	PB	168
										DLX	162
	Dulo2006	Denmark	Danish Pain Research Center	FMG/ DNP	Single center						
Rynn 2008	F1J-MC-HMDT	USA	Lilly	GAD	Multi Center Multi	ITT	Parallel	6	2	PB	159
										DLX	168
Hartford 2007	F1J-MC-HMDU	USA	Lilly	GAD	center	ITT	Parallel	6	2	PB	162
										DLX	162
Davidson 2008	F1J-MC-HMDV	International	Lilly	GAD	Multi center	ITT	Parallel	7	2	PB	213
										DLX	213
Nicolini et al 2009	F1J-MC-HMDW	International	Lilly	GAD	Multi center	ITT	Parallel	6	3	PB	170
										DLX	84

										DLX	158
Koponen 2007	F1J-MC-HMBR	International	Lilly	GAD	Multi center	ITT	Parallel	6	3	PB	175
										DLX	168
										DLX	170
	1208.10	Europe	BI	MDD	Multi center	ITT	Parallel	7	2	PB	165
										DLX	162
	F1J-MC-HMAH	One country	Lilly	MDD	Multi center	ITT	Parallel	10	2	PB	88
										DLX	89
	F1J-MC-HMAI	International	Lilly	MDD	Multi center	ITT	Parallel	8	4	PB	126
										DLX	130
										DLX	129
										DLX	131
	F1J-MC-HMATa	USA	Lilly	MDD	Multi center	ITT	Parallel	8	3	PB	90
										DLX	91
										DLX	84
Goldstein2004	F1J-MC-HMATb	USA	Lilly	MDD	Multi center	ITT	Parallel	8	3	PB	89
										DLX	86
										DLX	91
Detke 2004	F1J-MC-HMAYa		Lilly	MDD	Multi center	ITT	Parallel	8	3	PB	93
										DLX	95
										DLX	93
Perahia 2006	F1J-MC-HMAYb	International	Lilly	MDD	Multi center	ITT	Parallel	7	3	PB	99
										DLX	93
										DLX	103
Detke 2002a	F1J-MC-HMBHa	USA	Lilly	MDD	Multi center	ITT	Parallel	11	2	PB	122
										DLX	123
Detke 2002b	F1J-MC-HMBHb	USA	Lilly	MDD	Multi center	ITT	Parallel	11	2	PB	139
										DLX	128
Brannan 2005	F1J-US-HMCB	USA	Lilly	MDD	Multi center	ITT	Parallel	9 to 5	2	PB	141
										DLX	141

Nierenberg 2007	F1J-US-HMCR	USA	Lilly	MDD	Multi center	ITT	Parallel	8	2	PB	137
										DLX	273
Perahia 2009	F1J-MC-HMDI	International	Lilly	MDD	Multi center	ITT	Parallel	52	2	PB	142
										DLX	146
Gaynor 2011a	F1J-US-HMGR	International	Lilly	MDD	Multi center	ITT	Parallel	7	2	PB	266
										DLX	262
Gaynor 2011b	F1J-US-HMGU	International	Lilly	MDD	Multi center	ITT	Parallel	7	2	PB	266
										DLX	261
Mundt 2007	H8I-MC-HQAC	USA	Lilly	MDD	Multi center	ITT	Parallel	4	2	PB	35
										DLX	17
Brecht 2007	F1J-BI-HMDH	International	Lilly / BI	MDD	Multi center	ITT	Parallel	7	2	PB	165
										DLX	162
Hellerstein 2012	# 4967 / 6363R	USA	New York State Psychiatric Institute	MDD	Single center	ITT	Parallel	10	2	PB	33
										DLX	32
Baldwin 2012	11984A	International	Lundbeck	MDD	Multi center	ITT	Parallel	8	2	PB	148
										DLX	155
Boulenger 2014	13267A	International	Lundbeck	MDD	Multi center	ITT	Parallel	8	2	PB	158
										DLX	147
Tourian 2009	3151A1-335	USA	Pfizer	MDD	Multi center	ITT	Parallel	8	2	PB	161
										DLX	157
Mahableshwarkar 2015a	LuAA21004_202	International	Takeda	MDD	Multi center	ITT	Parallel	8	2	PB	194
										DLX	210
Mahableshwarkar 2013	LuAA21004_304	USA	Takeda	MDD	Multi center	ITT	Parallel	7	2	PB	151
										DLX	150
Mahableshwarkar 2015a	LuAA21004_315	USA	Takeda	MDD	Multi center	ITT	Parallel	7	2	PB	161
										DLX	152
	F1J-MC-HMAG		Lilly	MDD	Single center		Parallel	10	2	PB	52
										DLX	53
Frakes 2011	F1J-US-HMGL	USA	Lilly	OAP	Multi center	ITT	Parallel	8	2	PB	260
										DLX	264

Chappell 2009	F1J-MC-HMEP	International	Lilly	OAP	Multi center	ITT	Parallel	13	2	PB	120
										DLX	111
Chappell 2011	F1J-MC-HMFG	International	Lilly	OAP	Multi center	ITT	Parallel	12	2	PB	128
										DLX	128
	F1J-MC-HMGP	International	Lilly	OAP	Multi center	ITT	Parallel	12	2	PB	207
										DLX	217
Wang 2017	F1J-MC-HMGS	China	Lilly	OAP	Multi center	ITT	Parallel	12	2	PB	177
										DLX	172
Tétreault 2016	STU00039556	USA	Northwestern University	OAP	Multi center	ITT	Parallel	15	2	PB	19
										DLX	21
Sofat 2017	11.0126	UK	St George's, University of London	OAP	Single center	ITT	Parallel	9	2	PB	21
										DLX	22
Reckziegel 2017	13124	UK	University of Nottingham	OAP	Single center	ITT	Parallel	4	2	PB	27
										DLX	54
Uchio 2018	F1J-JE-HMGX	Japan	Shionogi / Lilly	OAP	Multi center	ITT	Parallel	12	2	PB	176
										DLX	178
	F1J-MC-SAAL		Lilly	UI-M	Multi center	NA	Cross- over	8	2	PB	16
										DLX	34
Zinner 1998	F1J-MC-SAAB		Lilly	UI-M	Multi center		Parallel	6	4	PB	67
										DLX	75
										DLX	69
										DLX	77
	F1J-MC-SAAH		Lilly	UI-M	Single center		Parallel		3	PB	
										DLX	
										DLX	
Bent 2008	F1J-MC-SBBO	International	Lilly	UI-M	Multi center	ITT	Parallel	8	2	PB	288
										DLX	300
Ghoniem 2005	F1J-MC-SBAF	International	Lilly	UI-S	Multi center	ITT	Parallel	12	2	PB	47
										DLX	52
Cardozo 2004	F1J-MC-SBAM	International	Lilly	UI-S	Multi center	ITT	Parallel	8	2	PB	54
										DLX	55
Castro-Diaz	F1J-MC-SBBR	International	Lilly	UI-S	Multi	ITT	Parallel	8	4	PB	120

2007											DLX	133
											DLX	127
											DLX	133
Cardozo 2010	F1J-EW-SBCC	International	Lilly	UI-S	Multi center	ITT	Parallel	6	2	PB	1380	
										DLX	1378	
Lin 2008	F1J-MC-SBBT	Taiwan	Lilly	UI-S	Multi center	ITT	Parallel	8	2	PB	61	
										DLX	60	
Mah 2006	F1J-MC-SBBU	Korea	Lilly	UI-S	Multi center	ITT	Parallel	8	2	PB	60	
										DLX	61	
Dmochowski 2003	F1J- MC-SBAV	USA	Lilly	UI-S	Multi center	ITT	Parallel	12	2	PB	339	
										DLX	344	
Van Kerrebroeck 2004	F1J- MC-SBAT	International	Lilly	UI-S	Multi center	ITT	Parallel	12	2	PB	247	
										DLX	247	
Millard 2004	F1J-MC-SBAX	International	Lilly	UI-S	Multi center	ITT	Parallel	12	2	PB	231	
										DLX	227	
Kinchen 2005	F1J-MC-SBBA	USA	Lilly	UI-S	Multi center	ITT	Parallel	36	2	PB	227	
										DLX	224	
	F1J-MC-SBAB		Lilly	UI-S	Multi center		Parallel	4		PB		
										DLX		
	F1J-MC-SAAA		Lilly	UI-S	Multi center		Parallel	3	2	PB	37	
										DLX	55	
	F1J-MC-SBBL		Lilly	UI-S	Multi center		Parallel	12	2	PB		
										DLX		
	F1J-JE-323G	Japan	Shionogi / Lilly	UI-S	Multi center		Parallel	4		PB		
										DLX		

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: Urinary Incontinence

DLX: Duloxetine, PB: Placebo

BPI: Brief Pain Inventory, HAMD: Hamilton Depression Rating Scale, FIS: Fibromyalgia Intensity Score, IEF: Incontinence Episode Frequency, MADRS: Montgon 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 Disability Scale, SF-36: 36-Item Short Form Survey, UPSA: University of California, San Diego, Performance-Based Skills Assessment.

Risk of bias within studies

Figure 2 provides details of the risk of bias assessment from data available online. 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 randomized to duloxetine or placebo after a 32-week exposition to duloxetine, at risk of selecting subjects with a better tolerability to duloxetine.

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.

Abbreviations

CI: Confidence Interval

EMA: European Medical Agency

FDA: Food Drug Administration

IPD: Individual participant data

nsAE: Non-serious adverse event

OR: Odds-Ratio

RCT: Randomized controlled trial

SAE: Serious adverse event

SF36: 36-Item Short Form Survey

Declarations

Patient's and Public Involvement

Patients were not involved in the development of the research question and study design.

Availability of data and materials

The dataset analyzed during the current study is not publicly available due to the terms of the data sharing agreements signed with Vivli but are available from the Vivli data sharing platform on reasonable request. For one study, the data are available from the corresponding author on reasonable request.

Competing interests

All authors have no conflict of interests to declare.

Author's 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.

All authors read and approved the final manuscript.

Acknowledgments

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

References

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2017.
2. MacQueen GM, Frey BN, Ismail Z, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 6. Special Populations: Youth, Women, and the Elderly [published correction appears in Can J Psychiatry. 2017 May; 62(5):356]. Can J Psychiatry. 2016;61(9):588–603.
3. Aharony L, De Cock J, Nuotio MS, Pedone C, Rifel J, Vande Walle N, Velghe A, Vella A, Verdejo-Bravo C. Consensus document on the management of urinary incontinence in older people. Eur Geriatr Med. 2017 ; 8:202–209.
4. Katzman MA, Bleau P, Blier P, et al. Canadian clinical practice guidelines for the management of anxiety, posttraumatic stress and obsessive-compulsive disorders. BMC Psychiatry. 2014;14 Suppl 1(Suppl 1):S1.
5. American Diabetes Association (2018). 10. Microvascular complications and foot care: standards of medical care in diabetes—2018. Diabetes Care, 41(Supplement 1), S105-S118.
6. Macfarlane GJ, Kronisch C, Dean LE, Atzeni F, Häuser W, Fluß E, Choy E, Kosek E, Amris K, Branco J, Dincer F, Leino-Arjas P, Longley K, McCarthy GM, Makri S, Perrot S, Sarzi-Puttini P, Taylor A, Jones GT. EULAR revised recommendations for the management of fibromyalgia. Annals of the rheumatic diseases 2017;76(2):318-28.
7. Towards better patient care: drugs to avoid in 2016. Prescrire International 2016;25: 105–11.
8. M.G. Lucas (Chair), D. Bedretdinova (Guidelines Associate), L.C. Berghmans, J.L.H.R. Bosch, F.C. Burkhard, F. Cruz, A.K. Nambiar, C.G. Nilsson, A. Tubaro, R.S. Pickard; European Association of Urology. EAU guidelines on surgical treatment of urinary incontinence. 2015.
9. Krause M, Gutmiedl K, Bighelli I, Schneider-Thoma J, Chaimani A, Leucht S. Efficacy and tolerability of pharmacological and non-pharmacological interventions in older patients with major depressive disorder: A systematic review, pairwise and network meta-analysis. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology 2019;29(9):1003-22.
10. Anne Tham, Ulf Jonsson, Gerhard Andersson, Anne Söderlund, Per Allard, Göran Bertilsson. Efficacy and tolerability of antidepressants in people aged 65 years or older with major depressive disorder - A systematic review and a meta-analysis. J Affect Disord. 2016 Nov 15; 205: 1–12.
11. Osani MC, Bannuru RR. Efficacy and safety of duloxetine in osteoarthritis: a systematic review and meta-analysis. The Korean journal of internal medicine 2019;34(5):966-73.
12. Maund E, Guski LS, Göttsche PC. Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports. CMAJ. 2017;189(5):E194–E203.
13. Cipriani A, Furukawa TA, Salanti G, et al. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet. 2018;391(10128):1357–1366. Suppl 1.
14. FDA, 2001. Food and Drug Administration. New-Drug Application NDA 21-427 Duloxetine Hydrochloride: Clinical Pharmacology and Biopharmaceutics. 2004. Available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021427_s000_Cymbalta_BioPharmr_P2.pdf.
15. Skinner MH, Kuan HY, Skerjanec A, Seger ME, Heathman M, O'Brien L, Reddy S, Knadler MP. Effect of age on the pharmacokinetics of duloxetine in women. British journal of clinical pharmacology 2004;57(1):54-61.
16. EMA, 2008. European Medicines Agency. Refusal assessment report for Cymbalta. International non-proprietary name/common name: (duloxetine hydrochloride) Procedure No. EMEA/H/C/572/II/26. Available at www.ema.europa.eu/docs/en_GB/document_library/EPAR-AssessmentReport-

17. FDA, 2017. FDA labeling (Duloxetine Delayed-Release Capsules) for Oral Use
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021427s049lbl.pdf. Access 1 February 2017
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomized trials. *BMJ (Clinical research ed.)* 2019;366:l4898.
19. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Statistics in medicine*, 2017;36(5):855-75.
20. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*, 2011;64:383–94.

Figures

Figure 1. PRISMA flow diagram of included studies

Figure 1

PRISMA flow diagram of included studies

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study

Figure 2

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

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1.docx](#)
- [Additionalfile2.docx](#)
- [Additionalfile4.docx](#)
- [Additionalfile3.docx](#)