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Reporting of Adverse Events to Duloxetine in Adults : Systematic Review and Meta-analysis of Randomized Controlled Trials Evaluating Duloxetine vs. Placebo in Adults

Alexis Jutel

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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

Alexis Jutel

Né le 20 août 1991 à Rennes

**Déclaration des
événements
indésirables de la
duloxétine chez
l'adulte : revue de la
littérature et méta-
analyse des essais
contrôlés randomisés
évaluant duloxétine
contre placebo chez
l'adulte.**

**Thèse soutenue à Rennes
le 9 octobre 2020**

devant le jury composé de :

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PU-PH – CHU Pontchaillou / *examineur*

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Déclaration des événements indésirables de la duloxetine chez l'adulte : revue de la littérature et méta-analyse des essais contrôlés randomisés évaluant duloxétine contre placebo chez l'adulte.

Reporting of Adverse Events to Duloxetine in Adults: Systematic Review and Meta-analysis of Randomized Controlled Trials Evaluating Duloxetine vs. Placebo in Adults.

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Reporting of duloxetine adverse events in adults: literature review and meta-analysis of randomized controlled trials evaluating duloxetine versus placebo in adults

RESUME

Introduction: Les méta-analyses représentent le plus haut niveau de preuve en recherche scientifique, guidant les recommandations de bonne pratique clinique médicale. Cependant leur qualité s'avère variable notamment en raison de biais pouvant conduire à surestimer l'efficacité de certains traitements. La sélection exclusive d'études publiées est un biais important pour les méta-analyses pouvant omettre des résultats en défaveur d'un traitement. L'utilisation des données non-publiées apportent alors une informations plus exactes sur les évènements indésirables dans chaque bras d'intervention, pouvant différer des données publiées. Dans le cadre d'une méta-analyse s'intéressant à évaluer les évènements indésirables liées à la duloxétine dans une population adulte, ce travail constitue une analyse préliminaire de l'hétérogénéité et de la transparence des essais ayant étudiés la duloxétine contre placebo chez l'adulte.

Matériel et méthodes : Nous avons réalisé une revue systématique et une méta-analyse sur données agrégées d'essais randomisés contrôlés (RCT) en double aveugle identifiés parmi les essais inclus dans les méta-analyses sur la duloxétine publiées sur PubMed concernant 7 indications autorisées par les autorités sanitaires américaines et européennes. Parmi ces RCT nous avons extrait à chaque fois les informations pour 4 variables : les effets indésirables sévères, le nombre d'effets indésirables, de sortie d'étude et de sortie d'étude pour raison de sécurité. Nous avons alors comparé les données retrouvées sur 4 bases de données différentes : les articles publiés, les registres d'études cliniques (clinicaltrial.gov, clinicaltrialregister.eu, FDA, EMA), les rapports des industriels et les données publiées dans les méta-analyse portant sur la duloxétine. Nous avons ensuite évalué l'hétérogénéité du report de ces différentes variables au sein de chaque base de données et recherché une éventuelle variation de l'effet en fonction de chaque base de données. Une méta-régression a ensuite été réalisée pour rechercher une variation selon la pathologie concernée.

Résultats : Parmi les 405 essais identifiés, 69 ont été retenus dans notre étude. Les SAE étaient rapportés dans 60,5% des articles, 56,8% des rapports d'études industriels, pour 33,3% des études dans les registres et pour 30,4% des études dans les méta-analyses. Aucune variation d'effet n'a été observée entre les différentes bases de données et les différentes valeurs d'intérêt hormis pour les sortie d'étude, les méta-analyses et les registres ne concluant à aucun effet significatif contrairement aux articles publiés et rapports d'étude qui concluent en défaveur de la duloxétine. Nous observons également pour certaines pathologies (CLBP et SUI) une association significative avec la survenue d'effets indésirables et de sortie d'étude en défaveur de la duloxétine, ce qui n'est pas observé pour les autres pathologies.

Conclusion : Notre étude ne met pas en avant de biais dans le report des effets indésirables sévères dans les études portant sur la duloxétine. Il existe toutefois une réserve en raison du manque de certaines données ainsi que de la double extraction qui n'a pas encore été finalisée.

ABSTRACT

Introduction: Meta-analyses represent the highest level of evidence in scientific research, guiding recommendations for good clinical medical practice. However, their quality is variable, in particular due to bias that can lead to overestimating the effectiveness of certain treatments. The exclusive selection of published studies is a significant bias for meta-analyses that may omit results against treatment. The use of unpublished data then provides more accurate information on the adverse events in each intervention arm, which may differ from the published data. As part of a meta-analysis focusing on evaluating adverse events related to duloxetine in an adult population, this work constitutes a preliminary analysis of the heterogeneity and transparency of the trials that studied duloxetine versus placebo in adult.

Method: We performed a systematic review and meta-analysis on aggregated data of double-blind randomized controlled trials (RCTs) identified among the trials included in the meta-analyses on duloxetine published on PubMed for 7 indications authorized by the health authorities. American and European. Among these RCTs, we extracted each time the information for 4 variables: severe adverse events, the number of adverse events, study drop-outs and study drop-outs for safety reasons. We then compared the data found on 4 different databases: published articles, clinical study registers (clinicaltrial.gov, clinicaltrialregister.eu, FDA, EMA), industry reports and data published in the meta-studies. analysis for duloxetine. We then assessed the heterogeneity of the carry over of these different variables within each database and looked for any variation in the effect depending on each database. A meta-regression was then carried out to search for a variation according to the pathology concerned.

Results: Among the 405 trials identified, 69 were retained in our study. SAE was reported in 60.5% of articles, 56.8% of industry study reports, 33.3% of studies in registries, and 30.4% of studies in meta-analyses. No variation in effect was observed between the different databases and the different values of interest except for study withdrawals, meta-analyses and registers not concluding to any significant effect, contrary to the published articles and reports. study which concluded against duloxetine. We also observe for certain pathologies (CLBP and SUI) a significant association with the occurrence of undesirable effects and discontinuation of the study to the detriment of duloxetine, which is not observed for the other pathologies.

Conclusion: Our study does not highlight any bias in the reporting of severe adverse reactions in studies with duloxetine. However, there is a caveat due to the lack of some data as well as the double extraction which has not yet been finalized.

Glossary

-RCT: Randomised controlled trial

-FDA: Food and Drug Administration

-EMA: European Medicines Agency

-SAE: Severe Adverse Event

-AE: Adverse Event

-DO: Drop-Outs

-DOSR: Drop-outs for Safety Reasons

-CLBP: Chronic Low-Back Pain

-SUI: Stress Urinary Incontinence

-OAP: Osteo-Articular Pain

-MDD: Major Depressive Disorder

-GAD: Generalized Anxiety Disorder

-FMG: Fibromyalgia

-DNP: Diabetic Neuropathic Pain

INTRODUCTION

Rationale:

Medical research needs reliable results to guide medical prescription, wherein meta-analysis provides the highest level of evidence by accumulating exhaustive knowledge on a specific practice (1). While more and more meta-analyses are being published, becoming the most cited study design (2, 3), concerns about their quality are raising (3,4,5). Systematic reviews of low methodological quality are estimated to represent half or more of the published meta-analyses (3,4). As a matter of fact, meta-analyses may suffer from several biases depending on the selection of studies, databases or inclusion criteria used (6), which could lead to overestimate the effectiveness of the treatment (7).

In meta-analyses, selected studies are most of the time published studies. However, published studies are known to overestimate the effect of a treatment as the odds for a study to be published are known to depend on its findings (8). This publication bias (9) may affect systematic reviews practice as popular databases, such as MEDLINE or EMBASE (10,11), do not index unpublished studies which can keep them hidden from the reviewers (12). In addition, the quality of the journal where the study is published can have an influence on the visibility of a study and therefore its use in a meta-analysis as it is known that journals of lower quality tend to publish more positive conclusions contrary to journals with high impact factor (13). Hence, studies of discussing quality are likely to bias results from systematic reviews by overestimating the effect of an intervention. While the magnitude and effects of the publication bias are not fully explored (14), less than 10% of meta-analyses explicitly mention assessment for publication bias in their protocol (15).

Industry funding bias could also lead to overestimating benefits from an intervention (16). Indeed, industrial trials could be more subject of conflict of interest by publishing studies more favorable to the treatment tested (17,18). The same phenomenon has been observed in industrial meta-analyses (19), as some reviewers of industrial meta-analyses have advocated a good knowledge of the trials they include while poorly assessing of the risk of bias (20). Industry has a major impact on research as among published studies, analyses of tolerability and efficacy are mostly randomized controlled trials (21) from which more than 80% are sponsored by industrials (22).

Furthermore, systematic reviews can be impaired by heterogenous reports of data across data sources. For instance, information provided by published articles may differ from the one effectively collected, available on study reports or registries (8,23), notably by publishing advantageous data (18,23). This provision bias makes some data difficult to obtain because they are not available in print, might cause heterogeneity between meta-analyses depending on the database from which the studies were selected and might mislead physicians' decisions (23). In order to use every data existing about patients included in the trial and to avoid publication bias, guidelines incite reviewers to include every trial even those which are not published (24). This unpublished literature, called grey literature, is defined as studies or papers which are not controlled by a publisher (25). For instance, clinical trial registries have been considered as an unmissable database for an exhaustive meta-analysis as they provide detailed and comprehensive data rather than pre-analyzed data (26). It has been shown that, while 50% of meta-

analyses use registries for their study searches, only 40% of them find trials to include that were not found on other data sources (26). Demonstration has been made that avoiding grey literature in meta-analysis also leads to over-estimate the effectiveness in interventional group (25,27,28). Nowadays the use of grey literature in systematic reviews is estimated at 77% of systematic reviews (29) versus 33% in 2000 (27), urging for a clear report of the source of data chosen for asserting the effect of an intervention (30,31).

Taken together, those elements beg the question of data and methodological transparency in clinical trials (32,33) to guarantee better reproducibility in scientific research. This issue is all the more present in psychiatry as antidepressants studies could suffer from publication biases on efficacy (34-36) and safety results (37). Duloxetine is an antidepressant which has been approved by the FDA in United States and the EMA in Europe for a wide range of indications such as depressive disorders, general anxiety disorders, chronic musculo-skeletal pain, diabetic peripheral neuropathic pain, fibromyalgia and stress urinary incontinence. Our team is interested in the evaluation of the safety of use of duloxetine in elderly compared to younger adults, by performing a meta-analysis of randomized controlled trials in this population from published and unpublished data (Registered in PROSPERO CRD42019130488). The systematic review selected 77 studies from 24567 participants across the indication, which may suffer from a putative risk of heterogeneity in the report of safety and efficacy measurements. The present study aims to explore whether the reporting of adverse events is adequate in published research articles in comparison with other sources of information. We compared the reporting of four indicators of treatment safety (adverse events, serious adverse events, drop outs and drop out for safety reasons) in four databases. The result of this study will be an indication of the quality of tolerability reporting for duloxetine.

METHODS AND DESIGN

This systematic review and meta-analysis was conducted on prospective, randomized, double blinded and placebo-controlled trials. A protocol is available at <https://osf.io/5efc9>.

Outcomes

The main outcome is the reporting of serious adverse events (SAE) in published articles for duloxetine. Was defined as 'serious' any adverse event which led to hospitalization (or hospitalization prolongation) or any vital risk including death or suicidal risk (30).

Additionally, secondary outcomes were:

- The reporting of adverse events (AE) and number of subjects who suffer from at least one adverse event during the trial. Adverse events are defined as any untoward medical occurrence in a subject who was administered the treatment which does not necessarily have a causal relationship with the treatment in question. In addition, adverse events do not meet the criteria for severity (30).
- The reporting of Drop Outs (DO) and the number of concerned subjects. Drop outs are defined as the number of subjects who discontinued the trial before its end (30).

- The reporting of Drop Outs for safety reason (DOSR) and the number of concerned subjects. We defined DOSR as the number of patients who discontinued the trial because of the occurrence of an adverse event (30).

Eligibility criteria

We searched for randomized, placebo-controlled trials evaluating duloxetine for any condition with a known approval of use by the Food and Drug Administration (FDA) or by the European Medicines Agency (EMA). Approvals included major depressive disorders, general anxiety disorders, chronic musculo-skeletal pain, diabetic peripheral neuropathic pain, fibromyalgia and stress urinary incontinence. Our study concerns trials with adult participants.

Sources and data collection process

Trials identification was conducted in 2019 from our ongoing meta-analysis registered on PROSPERO (CRD42019130488) and was updated in 2020 to identify all relevant studies concerning duloxetine treatment in adults.

Trials were searched in PubMed from all systematic reviews and meta-analyses involving duloxetine in an FDA or EMA approved indication. The search terms were: "Duloxetine AND Meta-Analysis [ptyp]". The review has been performed on studies available on PubMed, from their date of inception to May 31, 2019. The reference list of selected systematic reviews and meta-analysis is available in appendix. Published articles were found on pubmed using their title as search terms. Pooled studies were found on Pubmed as well, firstly identified with search terms "Duloxetine AND Meta-Analysis [ptyp]", among the pooled studies thus sought, we selected systematic reviews including RCTs studying adult subjects. Those Meta-analyses were used to include trials and then re-used to extract data of interest in text or supplementary materials provided by their authors. As study registries we used ClinicalTrial.gov and Clinicaltrialregistries website using NCT and EudraCT identification number. On FDA website, drug approval packages were downloaded from FDA Approved drug product, search term was "duloxetine". In EMA website, assessment reports and withdrawn applications were selected, selecting human reports only and no restriction on the authorization status, using "duloxetine" as search term. For study reports we searched on industrial websites for clinical study reports synopses selecting duloxetine as product. Missing study reports or published articles were requested by mail from authors or industrials: Lilly and Lundbeck.

Search Strategy and data items

Searches were performed by a single reviewer for this thesis. A second review is expected to be done by an independent reviewer for a double blind research, with arbitration by a third reviewer (JCR or FN) in case of disagreements. A second extraction is currently in progress (KLD) and data will be confronted in double blind manner for publication.

For each trial, we extracted in each intervention group (placebo or duloxetine) severe adverse events, adverse events, drop outs and drop outs for safety reasons. Extraction was performed from published articles using data reported in tables, figures and text. In meta-analyses and systematic reviews we

used published data reported on figures, tables, text and supplementary materials. In clinical trials registries (ClinicalTrial.gov, clinicaltrials.gov) we used raw data reported in tables. For FDA and EMA websites we used data reported in text and tables in each approval packages and European public assessment report. At last we used data reported in text, figures and tables in each clinical studies reports available on industrials websites.

For each included studies from Pubmed we reported: author's name, title of the study, name of the sponsor and sponsor ID, ClinicalTrial.gov Number, year of end of the study, year of publication and study country as well as serious adverse events, adverse events, drop outs and drop outs for safety reason.

Synthesis of results

- **Qualitative analysis**

Consistency in the report of the outcomes across the sources (published articles, pooled studies, study reports and trials registries) was reported for each trial and each outcome. We described the number and percentage of reported, unreported and unpublished data across the sources.

- **Quantitative analysis**

All analyses were performed under R software (version 3.0, R core team, 2017). A significant threshold of two-sided $p < 0.05$ was used for all statistical analyses. To assess the existence of vibration of effects for each outcome, meta-analyses were performed separately by outcome and data source: one for study publications, one for pooled studies, one for study reports and one for information collected on trial registries. The effect of the intervention on the outcome as the 95% confidence interval of the effect was estimated using a random effect model and Peto odds ratio method (Yusuf, 1985).

Within-source heterogeneity in the effect size across studies was assessed by:

- the Q statistics test (Cochran, 1954), indicating whether a common effect size is shared by studies within one source by computing the weighted sum of squared deviations of the mean effect size, across studies, which statistical significance was measured by p-value and
- the I^2 index (Higgins & Thompson, 2002), which describes the proportion of the observed variation in effect size genuinely due to true heterogeneity.

Those meta-analyses were confronted to a comprehensive meta-analysis, which selected for each study the source of information reporting the highest effect in terms of adverse outcomes. This latter meta-analysis was performed under the same random effect model. For each outcome, all meta-analyses were plotted on a graph with effect size as the x axis and p-value on the y axis.

In addition, heterogeneity between the data sources was evaluated by outcome, using the Q statistics and significance test, and the I^2 index.

Finally, meta-regressions on medical conditions were performed from the data of the final meta-analysis by outcome. Statistical analyses and graphs were performed using the {meta} package (Schwarzer et al., 2015), {forestplot} package (Gordon, 2019) and {ggplot2} package (Wickham et al., 2016).

Changes in initial protocol

For each study, consistency between sources were assessed for each outcome (number and percentages).

RESULTS

Literature Searches: Our searches across PubMed database identified 405 randomised controlled trials available in 48 different meta-analysis (corresponding list is available in appendix) including 296 duplicates (Figure 1). Among the 109 original studies, 40 were excluded due to a wrong population or design (open-label, children population).. At last, 69 studies were eligible for qualitative a quantitative synthesis.

Figure 1. PRISMA flow Diagram of included studies

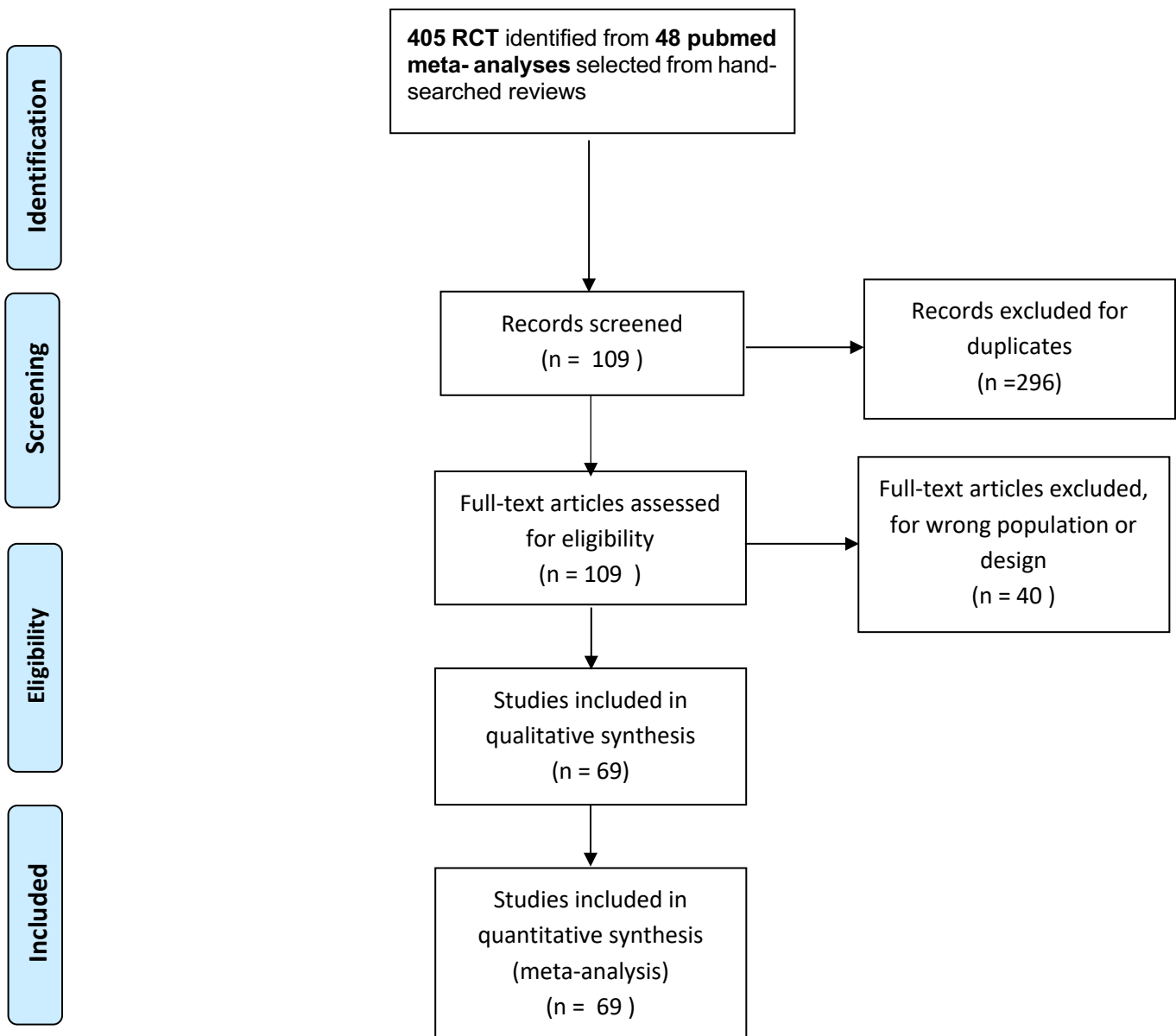


Table 1: Characteristics of included studies

Author	Sponsor ID	Title	Medical Condition	Year of publication	End of the study	Published	Sponsor Name	Country	NCT
Skjarevski et al.	F1J-MC-HMEN	Efficacy and safety of duloxetine in patients with chronic low back pain.	CLBP	2010	2008	Yes	Lilly	International	NCT00424593
Skjarevski et al.	F1J-MC-HMEO	A double-blind, randomized trial of duloxetine versus placebo in the management of chronic low back pain.	CLBP	2009	2007	Yes	Lilly	International	NCT00408876
Skjarevski et al.	F1J-MC-HMGC	Duloxetine versus placebo in patients with chronic low back pain: a 12-week, fixed-dose, randomized, double-blind trial.	CLBP	2010	2009	Yes	Lilly	International	NCT00767806
Gao et al.	F1J-MC-HMEQ	Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China.	DNP	2010	2008	Yes	Lilly	China	NCT00408993
Gao et al.	F1J-MC-HMGV	Treatment of patients with diabetic peripheral neuropathic pain in China: a double-blind randomised trial of duloxetine vs. placebo.	DNP	2015	2013	Yes	Lilly	China	NCT01179672
Goldstein et al.	F1J-MC-HMAW	Duloxetine vs. placebo in patients with painful diabetic neuropathy.	DNP	2005	2002	Yes	Lilly	International	
Raskin et al.	F1J-MC-HMAVb	A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain.	DNP	2005	2004	Yes	Lilly	USA	NCT00058968
Wernicke et al.	F1J-MC-HMAVa	A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain.	DNP	2006	2003	Yes	Lilly	USA	NCT00058968
Yasuda et al.	F1J-JE-HMFX	Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan.	DNP	2011	2009	Yes	Lilly	Jpan	NCT00552175
Rowbotham	M06-850		DNP	2012	2008	0	Abbott	International	NCT00507936
Arnold et al.	F1J-MC-HMCA	A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder.	FMG	2005	2003	Yes	Lilly	USA	NCT00489073
Arnold et al.	F1J-MC-HMGG	Efficacy and safety of duloxetine 30 mg/d in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study.	FMG	2012	2010	Yes	Lilly	International	NCT00965081
Arnold et al.	F1J-US-HMGB	Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial.	FMG	2010	2009	Yes	Lilly	USA+Puerto Rico	NCT00673452
Murakami et al.	F1J-JE-HMGZ	A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese fibromyalgia patients.	FMG	2015	2013	Yes	Lilly	Japon	NCT01552057
Russel et al.	F1J-MC-HMCJ	Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial.	FMG	2008	2007	Yes	Lilly	USA+Puerto Rico	NCT00190866
Arnold et al.	F1J-MC-HMBO	A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheum 50: 2974-2984.	FMG	2004	2002	Yes	Lilly	USA	
Chappell et al.	F1J-MC-HMEF	A six-month double-blind, placebo-controlled, randomized clinical trial of duloxetine for the treatment of fibromyalgia	FMG	2008	2007	Yes	Lilly	USA+Canada	NCT00233025

Alaka et al.	F1J-MC-HMGF	Efficacy and safety of duloxetine in the treatment of older adult patients with generalized anxiety disorder: a randomized, double-blind, placebo-controlled trial.	GAD	2014	2012	Yes	Lilly	International	NCT01118780
Davidson et al.	F1J-MC-HMDV	Duloxetine treatment for relapse prevention in adults with generalized anxiety disorder: A double-blind placebo-controlled trial	GAD	2008	2007	Yes	Lilly	International	NCT00122863
Hartford et al.	F1J-MC-HMDU	Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial.	GAD	2008	2006	Yes	Lilly	USA	NCT00122850
Koponen et al.	F1J-MC-HMBR	Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians.	GAD	2007	2005	Yes	Lilly	International	NCT00122824
Nicolini	F1J-MC-HMDW	Improvement of psychic and somatic symptoms in adult patients with generalized anxiety disorder: examination from a duloxetine, venlafaxine extended-release and placebo-controlled trial.	GAD	2009	2007	Yes	Lilly	International	NCT00122837
Rynn et al.	F1J-MC-HMDT	Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial.	GAD	2008	2005	Yes	Lilly	USA	NCT00475969
Baldwin et al.	11984A	A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD).	MDD	2012	2009	Yes	Lundbeck	International	NCT00635219
Boulenger et al.	13267A	Efficacy and safety of vortioxetine (Lu AA21004), 15 and 30 mg/day: a randomized, double-blind, placebo-controlled, duloxetine-referenced study in the acute treatment of adult patients with major depressive disorder.	MDD	2014	2011	Yes	Lundbeck	International	NCT01140906
Brannan et al.	F1J-US-HMCB	Duloxetine 60 mg once-daily in the treatment of painful physical symptoms in patients with major depressive disorder.	MDD	2005	2002	Yes	Lilly	USA	NCT00036335
Brecht et al.	F1J-BI-HMDH	Efficacy and safety of duloxetine 60 mg once daily in the treatment of pain in patients with major depressive disorder and at least moderate pain of unknown etiology: a randomized controlled trial.	MDD	2007	2006	Yes	Lilly	International	NCT00191919
Detke	F1J-MC-HMAYa	Duloxetine in the acute and long-term treatment of major depressive disorder: a placebo- and paroxetine-controlled trial.	MDD	2004	2002	Yes	Lilly	USA	
Detke	F1J-MC-HMBHa	Duloxetine, 60 mg once daily, for major depressive disorder: a randomized double-blind placebo-controlled trial.	MDD	2002a	2001	Yes	Lilly	USA	
Detke	F1J-MC-HMBHb	Duloxetine 60 mg once daily dosing versus placebo in the acute treatment of major depression.	MDD	2002b	2001	Yes	Lilly	USA	
Gaynor et al.	F1J-MC-HMGU	Duloxetine versus placebo in the treatment of major depressive disorder and associated painful physical symptoms: a replication study.	MDD	2011b	2011	Yes	Lilly	International	NCT01070329
Gaynor et al.	F1J-MC-HMGR	A randomized placebo-controlled trial of duloxetine in patients with major depressive disorder and associated painful physical symptoms.	MDD	2011a	2010	Yes	Lilly	International	NCT01000805
Katona et al.	12541A	A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder.	MDD	2012	2010	Yes	Lundbeck	International	NCT00811252
Mahableshwarkar et al.	LuAA21004_304	A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder.	MDD	2013	2008	Yes	Lundbeck	USA	NCT00672620
Mahableshwarkar et al.	LuAA21004_315	A randomized, double-blind, duloxetine-referenced study comparing efficacy and tolerability of 2 fixed doses of vortioxetine in the acute treatment of adults with MDD.	MDD	2015a	2012	Yes	Lundbeck	USA	NCT01153009
Mundt et al.	H8I-MC-HQAC	Anchoring Perceptions of Clinical Change on Accurate Recollection of the Past: Memory Enhanced Retrospective Evaluation of Treatment	MDD	2007	2003	Yes	Lilly	USA	
Nierenberg et al.	F1J-US-HMCR	Duloxetine versus escitalopram and placebo in the treatment of patients with major depressive disorder: onset of antidepressant action, a non-inferiority study.	MDD	2007	2005	Yes	Lilly	USA	NCT00073411

Perahia	F1J-MC-HMAYb	Duloxetine in the treatment of major depressive disorder: a placebo- and paroxetine-controlled trial.	MDD	2006	2002	Yes	Lilly	International	
Raskin et al.	F1J-MC-HMBV	Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial.	MDD	2007	2004	Yes	Lilly	USA	NCT00062673
Robinson et al.	F1J-US-HMFA	Acute and long-term treatment of late-life major depressive disorder: duloxetine versus placebo.	MDD	2014	2009	Yes	Lilly	International	NCT00406848
Tourian et al.	3151A1-335	Desvenlafaxine 50 and 100 mg/d in the treatment of major depressive disorder: an 8-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial and a post hoc pooled analysis of three studies.	MDD	2009	2007	Yes	Pfizer	USA	NCT00384033
	F1J-MC-HMAH		MDD		1995	No	Lilly	One Country	
	F1J-MC-HMAI		MDD		1996	No	Lilly	International	
	F1J-MC-HMATa		MDD		2001	No	Lilly	USA	
Goldstein	F1J-MC-HMATb	Duloxetine in the Treatment of Depression: A Double-Blind Placebo-Controlled Comparison With Paroxetine	MDD	2004	2001	Yes	Lilly	International	
	F1J-MC-HMAG		MDD		1994	No	Lilly		
Perahia et al.	F1J-MC-HMDI	Duloxetine in the prevention of depressive recurrences: a randomized, double-blind, placebo-controlled trial.	MDD	2009	2008	Yes	Lilly	International	NCT00105989
Abou-rya	alexmed116619163	Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial.	OAP	2012	2011	Yes	University of Alexandria	Egypt	NCT01425827
Chappell et al.	F1J-MC-HMEP	Duloxetine, a centrally acting analgesic, in the treatment of patients with osteoarthritis knee pain: a 13-week, randomized, placebo-controlled trial	OAP	2009	2007	Yes	Lilly	International	NCT00408421
Chappell et al.	F1J-MC-HMFG	A double-blind, randomized, placebo-controlled study of the efficacy and safety of duloxetine for the treatment of chronic pain due to osteoarthritis of the knee.	OAP	2011	2008	Yes	Lilly	International	NCT00433290
Frakes et al.	F1J-US-HMGL	Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial.	OAP	2011	2011	Yes	Lilly	USA	NCT01018680
Bent et al.	F1J-MC-SBBO	Duloxetine compared with placebo for the treatment of women with mixed urinary incontinence.	SUI	2008	2006	Yes	Lilly	International	NCT00190814
Cardozo et al.	F1J-MC-SBAM	Pharmacological treatment of women awaiting surgery for stress urinary incontinence.	SUI	2004	2006	Yes	Lilly	International	NCT00190619
Cardozo et al.	F1J-EW-SBCC	Short- and long-term efficacy and safety of duloxetine in women with predominant stress urinary incontinence	SUI	2010	2006	Yes	Lilly	International	NCT00190996
Castro-Diaz et al.	F1J-MC-SBBR	Effect of dose escalation on the tolerability and efficacy of duloxetine in the treatment of women with stress urinary incontinence.	SUI	2007	2006	Yes	Lilly	International	NCT00190827
Dmochowski et al.	F1J- MC-SBAV	Duloxetine vs placebo in the treatment of north american women with stress urinary incontinence	SUI	2003	2001	Yes	Lilly	USA	
Ghoniem et al.	F1J-MC-SBAF	A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence	SUI	2005	2006	Yes	Lilly	International	NCT00190606

Kinchen et al.	F1J-MC-SBBA	Impact of duloxetine on quality of life for women with symptoms of urinary incontinence	SUI	2005	2003	Yes	Lilly	USA	
Lin et al.	F1J-MC-SBBT	Duloxetine versus placebo for the treatment of women with stress predominant urinary incontinence in Taiwan: a double-blind, randomized, placebo-controlled trial	SUI	2008	2005	Yes	Lilly	Taiwan	NCT00475358
Mah et al.	F1J-MC-SBBU	Duloxetine versus Placebo for the Treatment of Korean Women with Stress Predominant Urinary Incontinence	SUI	2006	2004	Yes	Lilly	Korea	NCT00475397
Millard et al.	F1J-MC-SBAX	Duloxetine vs placebo in the treatment of stress urinary incontinence: a four-continent randomized clinical trial	SUI	2004	2002	Yes	Lilly	International	
Schagen van Leeuwen	1208.22 / F1J-BI-SBCM	Efficacy and safety of duloxetine in elderly women with stress urinary incontinence or stress-predominant mixed urinary incontinence.	SUI	2008	2007	Yes	Lilly	International	NCT00244296
Van Kerrebroeck et al.	F1J- MC-SBAT	Duloxetine versus placebo in the treatment of European and Canadian women with stress urinary incontinence	SUI	2004	2002	Yes	Lilly	International	
Zinner	F1J-MC-SAAB		SUI	1998	1996	Yes	Lilly		
	F1J-MC-SAAL		SUI		1996	No	Lilly		
	F1J-MC-SAAH		SUI		1997	No	Lilly		
	F1J-MC-SBAB		SUI		2006	No	Lilly		NCT00190567
	F1J-MC-SAAA		SUI		1995	No	Lilly		
	F1J-MC-SBBL		SUI		2001	No	Lilly		

Qualitative analysis

Results of the qualitative analysis are summarized in figure 2. Among the 69 studies 10 were not published (14,45%).

Serious Adverse Events were reported in 42 (60,8%) published articles, 21 (30,4%) pooled studies, 39 (56,5%) study reports and for 23 trials (33,3%) data were available in study registries. Information were consistent between the sources for 27 (39,13%) studies, inconsistent for 11 (15,9%) and 31 were missing or isolated (44,9%).

Adverse Events were reported in 40 (57,97%) published articles, 30 (43,4%) pooled studies, 39 (56,5%) study reports and for 26 trials (37,7%) data were available in study registries. Information were consistent between the sources for 21 (30,4%) studies, inconsistent for 17 (24,6%) and 31 were missing or isolated (44,9%).

Drop Outs were reported in 52 (76,36%) published articles, 17 (24,6%) pooled studies, 45 (65,2%) study reports and for 35 trials (50,7%) data were available in study registries. Information were consistent between the sources for 35 (50,7%) studies and inconsistent for 15 (21,7%) and 19 were missing or isolated (27,5%).

Drop Outs for Safety Reasons were reported in 54 (78,2%) published articles, 34 (49,3%) pooled studies, 42 (60,9%) study reports and for 35 trials (50,7%) data were available in study registries. Information were consistent between the sources for 39 (56,5%) studies and inconsistent for 13 (18,8%) while 17 were missing or isolated (24,6%).

Analyses of heterogeneity of effect

Variation in effect size across the sources are represented in figure 3 and 4. The results of the comprehensive meta-analysis selecting, the highest value of adverse events across all sources for each trial and each outcome are presented in figure S1, in appendix.

Within-source heterogeneity

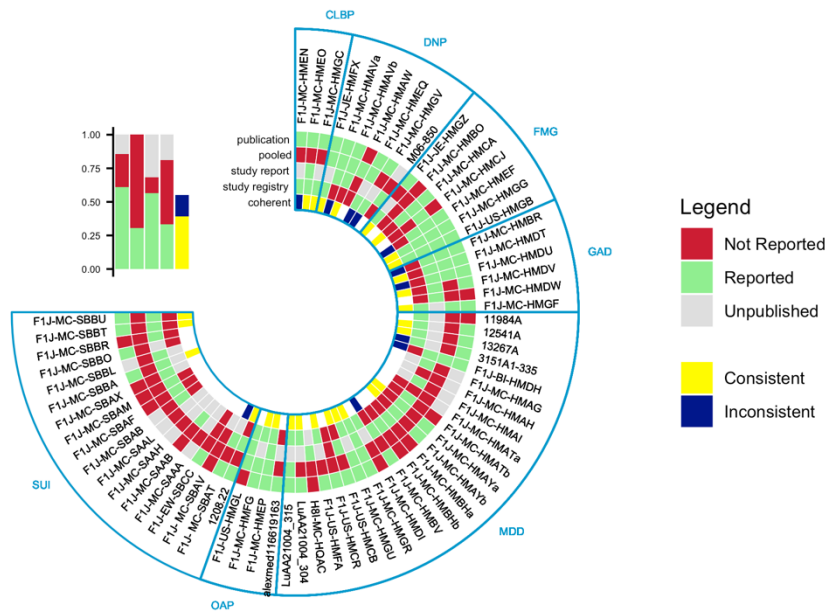
For serious adverse events, between-trial effect sizes significantly varied for study reports ($Q-p=0,04$; $I^2=76,45\%$) and all sources ($Q-p<0,01$; $I^2=33,7\%$), suggesting that variation in effect size could not account for the excess of dispersion when sources are combined. On the other hand, effect sizes did not significantly varied for publications ($Q-p= 0,05$; $I^2= 28,14\%$), pooled studies ($Q-p=0,11$; $I^2=29,87\%$) and study registries ($Q-p=0,15$; $I^2=23,66\%$).

For adverse events, effect sizes significantly varied in study reports ($Q-p=0,04$; $I^2=82,71\%$) and in all sources combined ($Q-p<0,001$; $I^2=45,88\%$), while seemingly homogeneous for published articles ($Q-p=0,05$; $I^2=35,35\%$), pooled studies ($Q-p=0,11$; $I^2=40,61\%$) and study registries ($Q-p=0,15$; $I^2=17,31\%$).

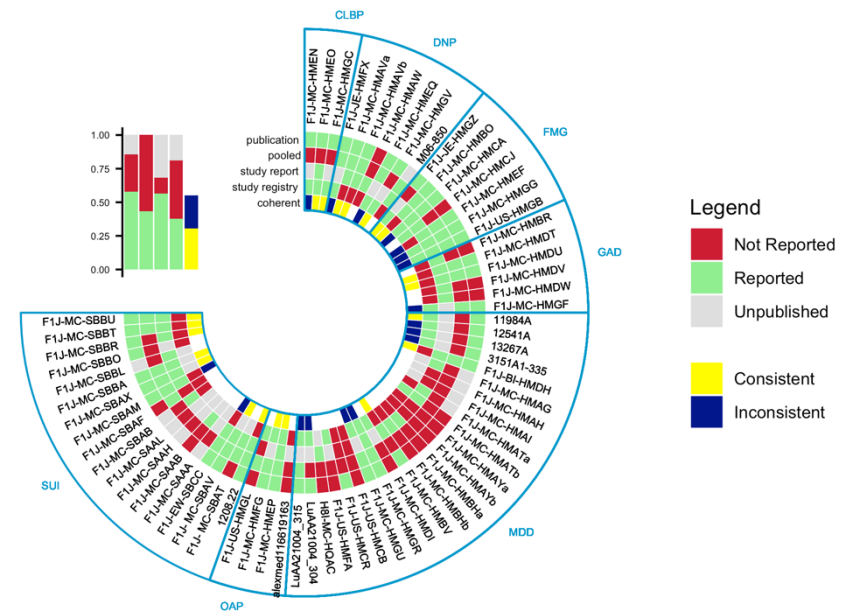
Concerning drop outs for safety reasons, effect sizes differed within each type of source be it publications (Q-p<0,001 ; I2=71,87%), pooled studies (Q-p<0,001 ; I2=62,08%), study reports (Q-p<0,001 ; I2=60,7%), study registries (Q-p<0,001 ; I2=55,81%) or all sources (Q-p<0,001 ; I2=69,17%). Finally, drop-outs varied for each data source (Publications: Q-p<0,001 ; I2=81,81%, pooled studies: Q-p<0,001 ; I2=69,23%, study reports: Q-p<0,001 ; I2=83,05%, all sources: Q-p<0,001; I2=80,83%), while not being clearly due to genuine vibration of effect for study registries (Q-p=0,001 ; I2=37,82%).

Figure 2. Polar plot: outcomes reporting and consistency between sources.

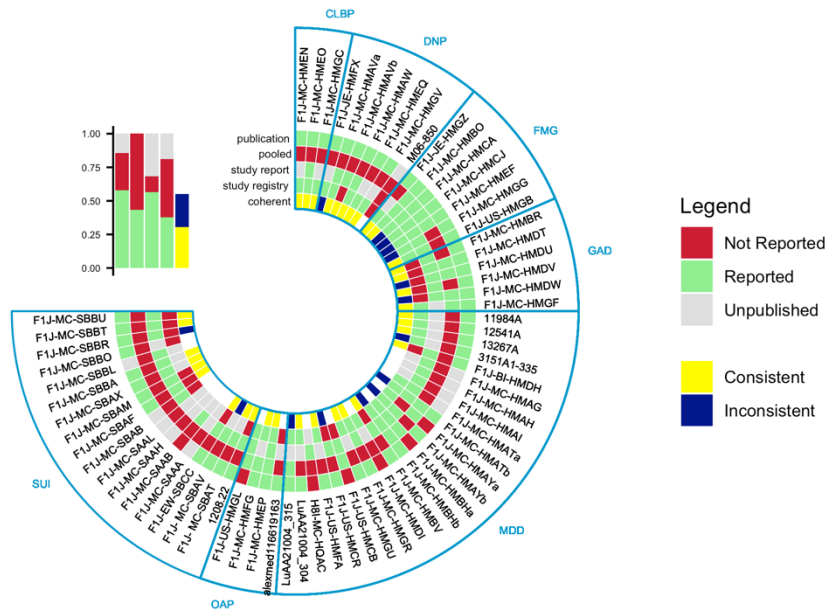
Legend: *In red*= data not reported. *In green*= data reported. *In grey*= study not available in data source, *in yellow*= consistent between sources data report, *in blue*= inconsistent between sources data report. *Published*= an article has been published for the concerned trial. *Publication*= data reported in published article. *Pooled analysis* = data reported in pooled analysis including study in question. *Study report* = data reported in industrial clinical study report. *Study registries*= data reported in clinical study registries (higher value reported between FDA, EMA, clinicaltrial.gov and clinicaltrialregistries.eu). *Coherence*= the data reported in each source are identical. *MDD*= Major Depressive Disorder. *GAD*= General Anxiety Disorder. *OAP*= osteoarthritis pain. *FMG*= Fibromyalgia. *CLBP*= Chronic Low Back Pain. *SIU*= Stress urinary incontinence . *DNP*= Diabetic Neuropathic Pain



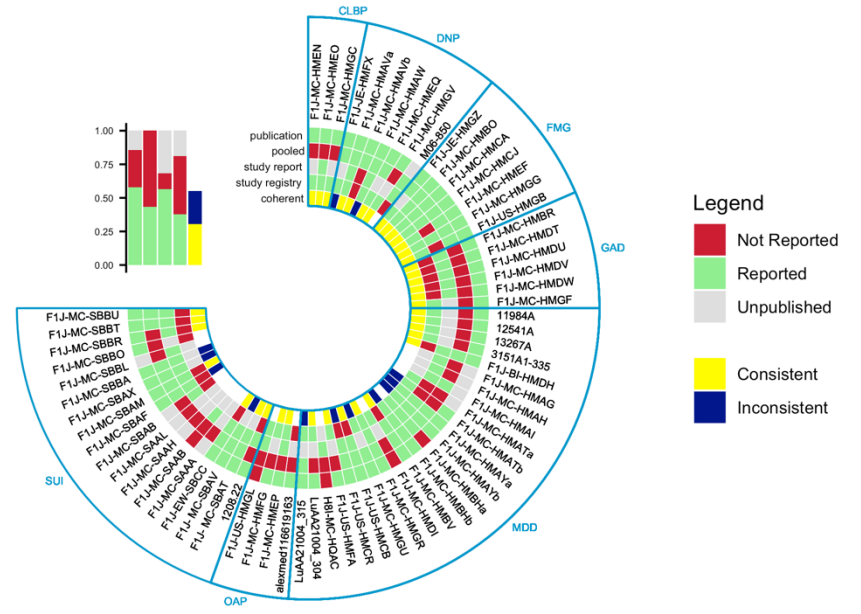
A. Serious Adverse Events



B. Adverse Events

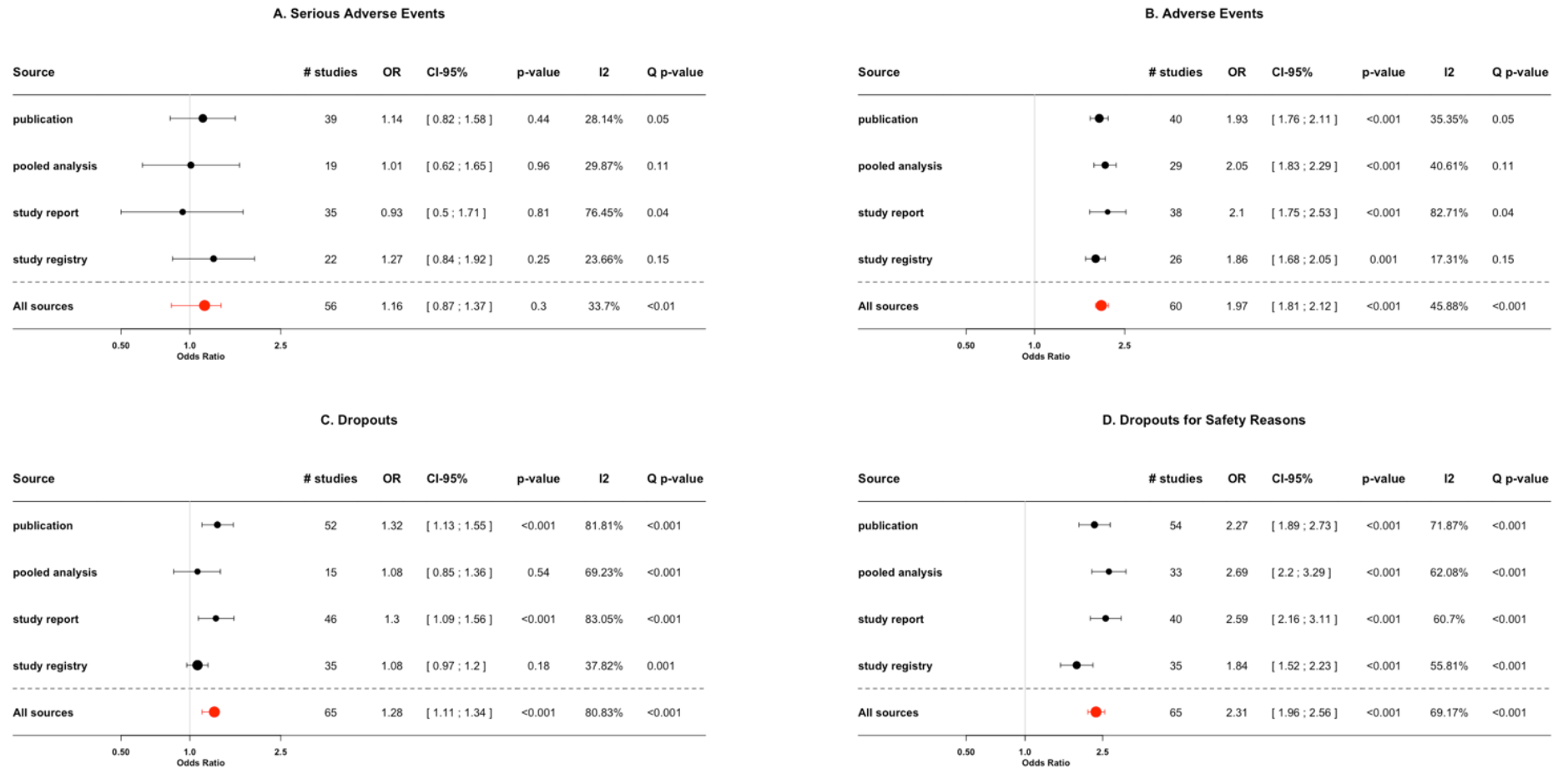


C. Drop outs



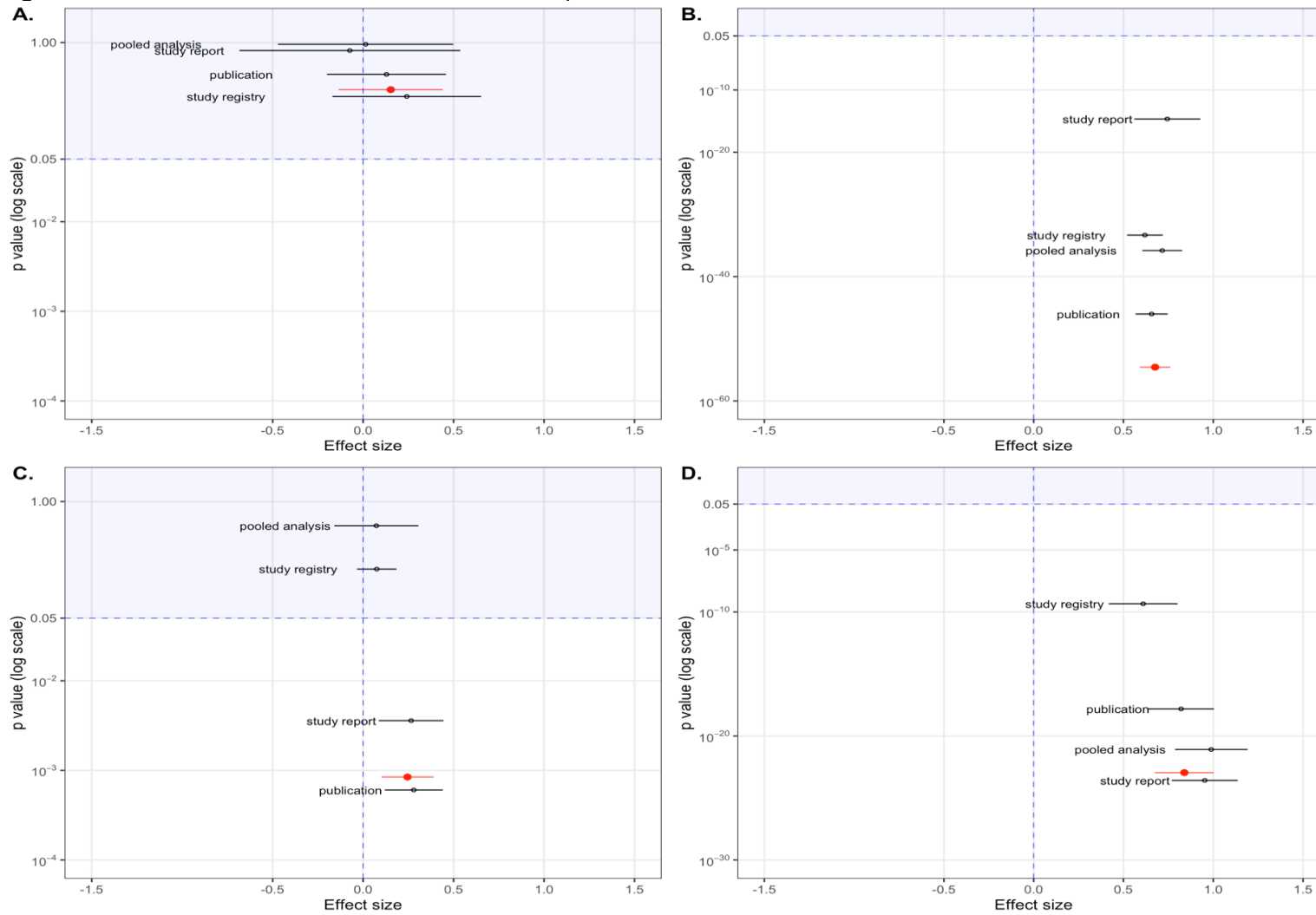
D. Drop out for safety reason

Figure 3: Heterogeneity between sources for each outcome



Legend: Publication= data reported in published article. Pooled analysis = data reported in pooled analysis including study in question. Study report = data reported in industrial clinical study report. Study registries= data reported in clinical study registries (higher value reported between FDA, EMA, clinicaltrial.gov and clinicaltrialregistries.eu). All sources= meta-analysis of maximal effects across all sources. # studies= number of studies present in concerned source. OR= odd ratio obtained on data reported in the concerned source. CI-95%= confidence interval

Figure 4 : Vibration of effect of adverse events with respect to data source



Legend: X-axis= p-value (logarithmic scale). Y-axis= effect size A= Severe Adverse Events B= Adverse Events C= Drop-Outs D= Drop-Outs for Safety Reason

Between-sources heterogeneity

For each outcome, we assessed the vibration of effect between each source.

While each source of SAE conjointly reported non-significant effect of duloxetine on SAE ($Q = 0.61$, $Q\text{-}df < 0$, $p\text{-value} = 0.894$), a significant effect of duloxetine on adverse events and drop-outs for safety reasons was reported homogenously across the sources (respectively, $Q = 2.83$, $Q\text{-}df < 0$, $p\text{-value} = 0.418$; $Q = 6.32$, $Q\text{-}df = 3.32$, $p\text{-value} = 0.097$).

Drop-outs showed various results depending on the source ($Q = 9.12$, $Q\text{-}df = 6.12$, $p\text{-value} = 0.027$), publications, study reports and combined sources finding significative results (all $p < 0.001$) not reached for pooled analyses ($p = 0.54$) and study registries ($p = 0.18$).

Meta-Regression on medical conditions

We performed a meta-regression (Figure 5) to assess the putative effect of medical condition on the occurrence of adverse events.

No significative result can be retained concerning SAE: SUI (OR = 0,46; CI 95% = [0,12; 1,76]), CLBP (OR = 2,57; CI 95% = [0,78; 8,45]), DNP (OR = 0,33; CI 95% = [0,08; 1,36]), FMG (OR = 0,23; CI 95% = [0,05; 1,09]), GAD (OR = 0,52; CI 95% = [0,10; 2,57]), MDD (OR = 0,49; CI 95% = [0,14; 1,80]), OAP (OR = 0,48; CI 95% = [0,08; 2,68]).

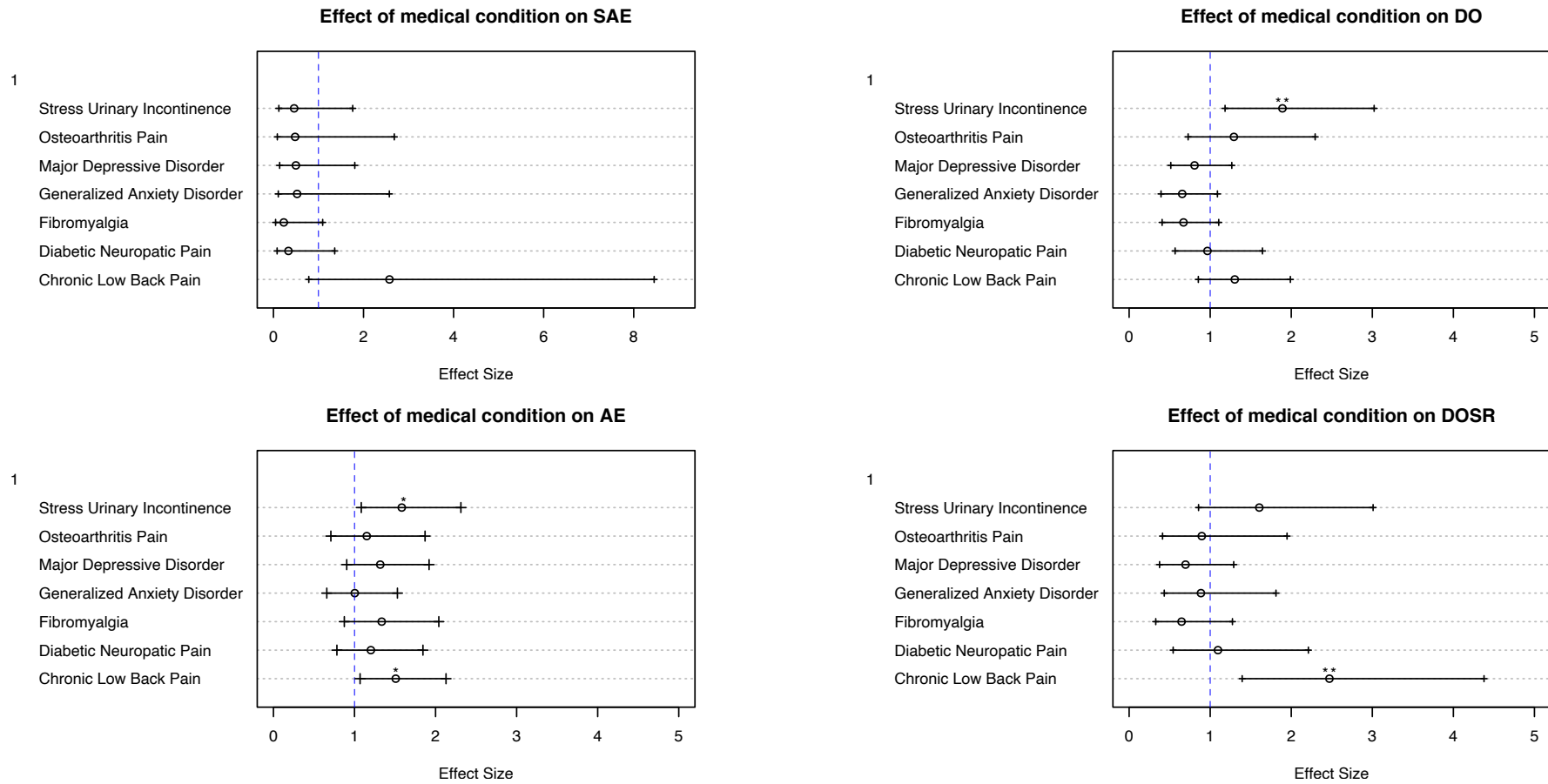
For AE we found significant results for: SUI (OR = 1,58; CI 95% = [1,08; 2,31]) and CLBP (OR = 1,50; CI 95% = [1,06; 2,12]). The results are not significant in the other indications: DNP (OR = 1,20; CI 95% = [0,78; 1,84]), FMG (OR = 1,33; CI 95% = [0,87; 2,04]), GAD (OR = 1,00; CI 95% = [0,65; 1,52]), MDD (OR = 1,31; CI 95% = [0,90; 1,92]), OAP (OR = 1,15; CI 95% = [0,70; 1,87]).

For DO we found significant results for: SUI (OR = 1,89; CI 95% = [1,18; 3,02]). The results are not significant in the other indications: CLBP (OR = 1,30; CI 95% = [0,85; 1,98]), DNP (OR = 0,96; CI 95% = [0,56; 1,64]), FMG (OR = 0,67; CI 95% = [0,40; 1,10]), GAD (OR = 0,65; CI 95% = [0,39; 1,08]), MDD (OR = 0,80; CI 95% = [0,51; 1,26]), OAP (OR = 1,29; CI 95% = [0,72; 2,29]).

For DOSR we found significant results for: CLBP (OR = 2,47; CI 95% = [1,39; 4,37]). The results are not significant in the other indications: SUI (OR = 1,60; CI 95% = [0,85; 3,01]), DNP (OR = 1,09; CI 95% = [0,54; 2,21]), FMG (OR = 0,64; CI 95% = [0,32; 1,27]), GAD (OR = 0,88; CI 95% = [0,43; 1,81]), MDD (OR = 0,69; CI 95% = [0,37; 1,29]), OAP (OR = 0,89; CI 95% = [0,41; 1,94]).

Figure 5: Meta-regression on medical condition

Legend: Dots represent the effect sizes of condition on each outcome with their respective 95% confidence interval. *SAE*= serious adverse event *DO*= drop-outs *AE*= adverse events *DOSR*= drop-outs for safety reason



legend

* = p<0.05 ** = p<0.01 *** = p<0.001

DISCUSSION

We found homogenous results across data sources in the number of SAE, AE and DOSR, while the effect of duloxetine on the number of DO could vary as a function of the source. Meta-regression on medical condition shows that the AE and DO were significantly higher in SUI condition, while AE and DOSR were higher in CLBP patients. We observed that a large proportion of trials data was missing or present in a single data source (not making it possible to assess inter-source consistency) preventing an evaluation of consistency. When the evaluation was feasible, data were most often consistent from one source to another.

A large proportion of data could not be found or were present in a single data source (not making it possible to assess inter-source consistency). This is particularly the case for AE and SAE, where 45% of the data are absent or isolated. When the evaluation was feasible, it was observed that the data were most often consistent from one source to another. Data reporting is less exhaustive in pooled analyses or in registries, unlike publications or study reports where the data reporting is the most complete. A previous study showed that the clinical study reports reported fairly complete results (40), these results tend to be confirmed by our study which compares different data sources between them. Indeed, it has to be noted that the SAE are reported in only 60% of publications and study reports and can be found in only a third of the study registries and meta-analyses. Although tedious, a fairly complete data collection (91.3% for SAE) may be realizable, but efforts still need to be made to make it faster, easier and more transparent. Progress has been made with the commissioning of data sharing platforms such as Vivli.

Our assessment of the vibration of effect shows that all sources conjointly conclude that duloxetine is significantly associated with increased AE and DOSR while not being associated to an increased risk of SAE. On the other hand, a significant vibration of effect was found for drop-outs with publications and study reports concluding to a significant increased risk of DO under duloxetine, not found in pooled studies and registries. Interestingly, effect sizes of DO were significantly heterogeneous within each data source, except for study registries, with less than one third of true variance across the studies. For pooled studies, their low number whose reported DO could have lowered the power of our pooled analysis. Hence, while combined sources suggest an increased risk of DO under duloxetine, it is unclear whether this risk is true due to heterogeneity within and between data sources.

Meta-regression found heterogeneity of effect between medical conditions, with increased AE and DOSR under duloxetine in CLBP, and higher AE and DOSR in SUI condition. Regarding SUI, our result suggests that the benefit-risk balance is more unfavorable in this indication as it was shown in precedent studies (38). On the other hand, as only three trials reported data for CLBP, the higher risk found for CLPB suffers from robustness.

The significance of these results may need to be moderate as there is still a lack of data. On the one hand, there is a selective publication with 14.5% of unpublished studies and therefore as many results not available for the study. On the other hand, we regret that many study reports are still missing, 18 (26% of studies) are currently requested from industrial Lilly and Lundbeck and will be available for the final study. No significant heterogeneity is observed regarding the data sought and, by crossing the sources, it is possible to find 91.3% of the data for the SAE and 86.9% for the AE. However, it is not

possible to exclude that studies not specifying their data for these outcomes are associated with unfavorable results for the treatment, as previously reported (39). Hence, it is likely that the missing data, even few in number, could have a significant impact on the conclusion of a meta-analysis. These results can be further refined with the contribution of the missing study reports and therefore need to be qualified, but we can still note that some data are difficult to obtain. Indeed these results are for the moment those of a thesis work, a double extraction will be carried out with the help of a second reviewer (KLD).

CONCLUSION

Our study aimed to find the existence of reporting bias regarding the adverse effects of Duloxetine. During our research, we were unable to demonstrate the existence of such biases, which is rather reassuring. However, we still lack the data to make a fully reliable statement and we expect to strengthen the completeness of this data in the coming weeks. In fact, data concerning Duloxetine are difficult to obtain, which has raised the question of transparency in research and the importance of the exchange of scientific data which is still insufficient. In addition, we were able to observe that the report of severe adverse events remained insufficient for such an important data.

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APPENDIX

Appendix 1: List of eligible studies

1. Abou-Raya2012 (alexmed116619163, NCT01425827): Abou-Raya, S., Abou-Raya, A., & Helmii, M. (2012). Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age and ageing*, 41(5), 646-652.
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in patients with major depressive disorder. *Journal of psychiatric research* 2005;39(1):43-53.
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58. Study F1J-MC-HMAT – Group A
59. Study F1J-MC-SAAA
60. Study F1J-MC-SAAL
61. Study F1J-MC-SAAH
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Appendix 2: List of included Meta-analyses

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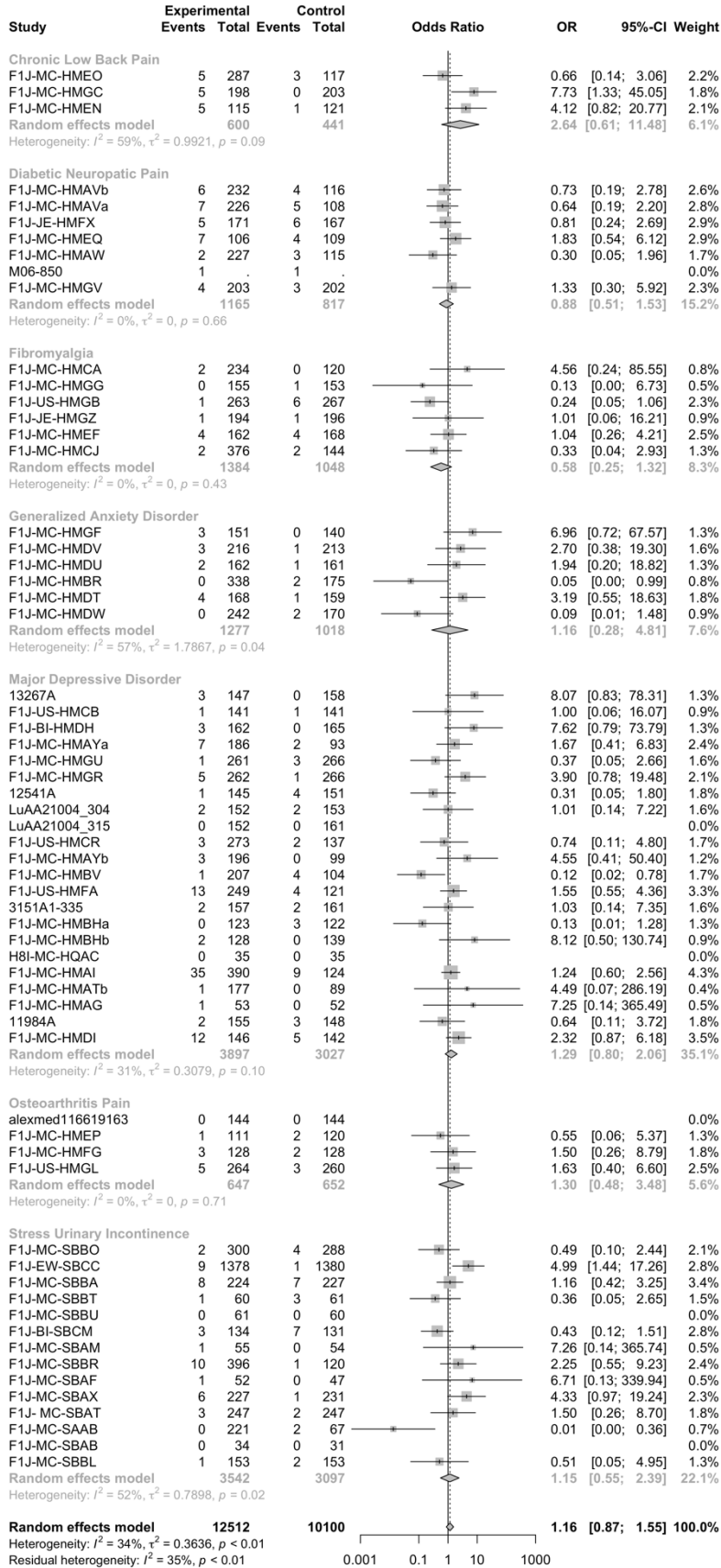
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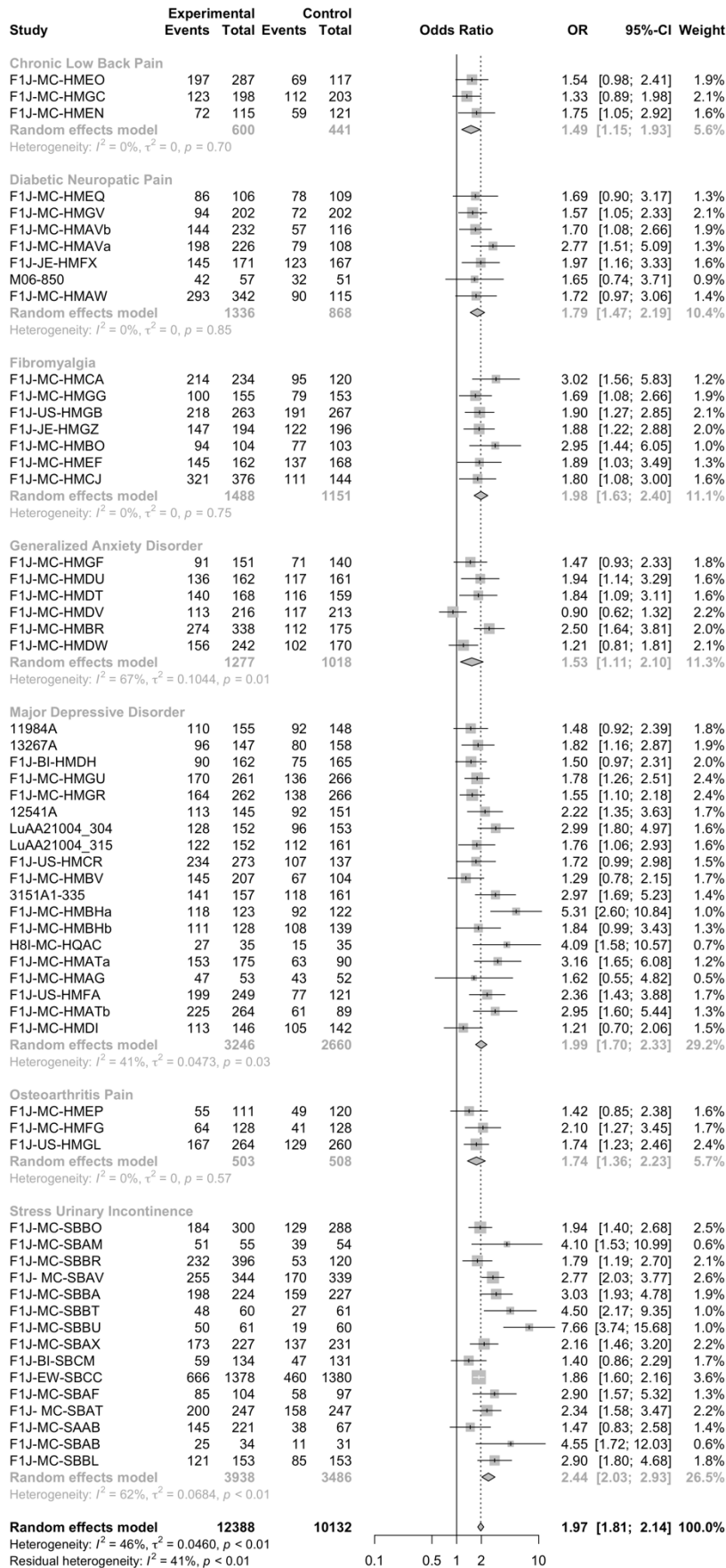
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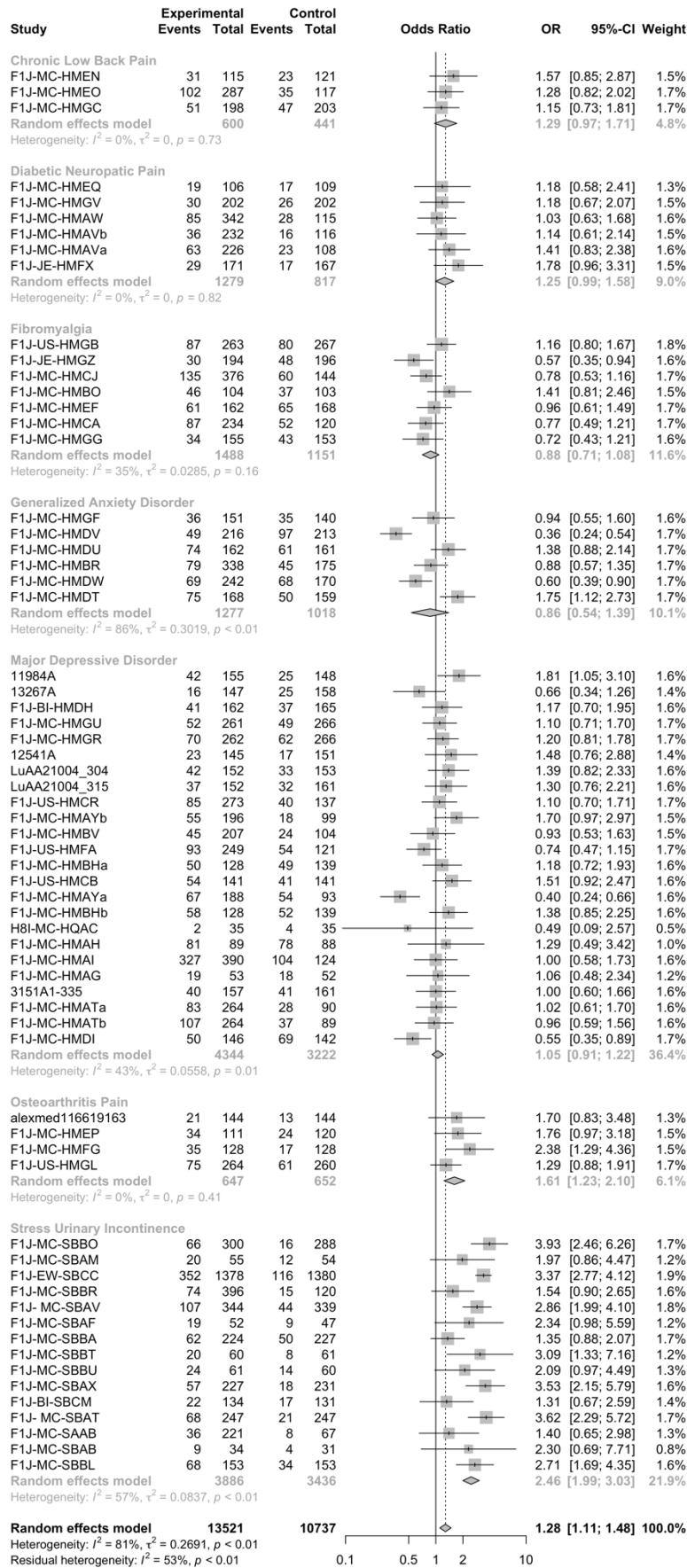
Figure S1: Meta-Analysis on higher values for each source

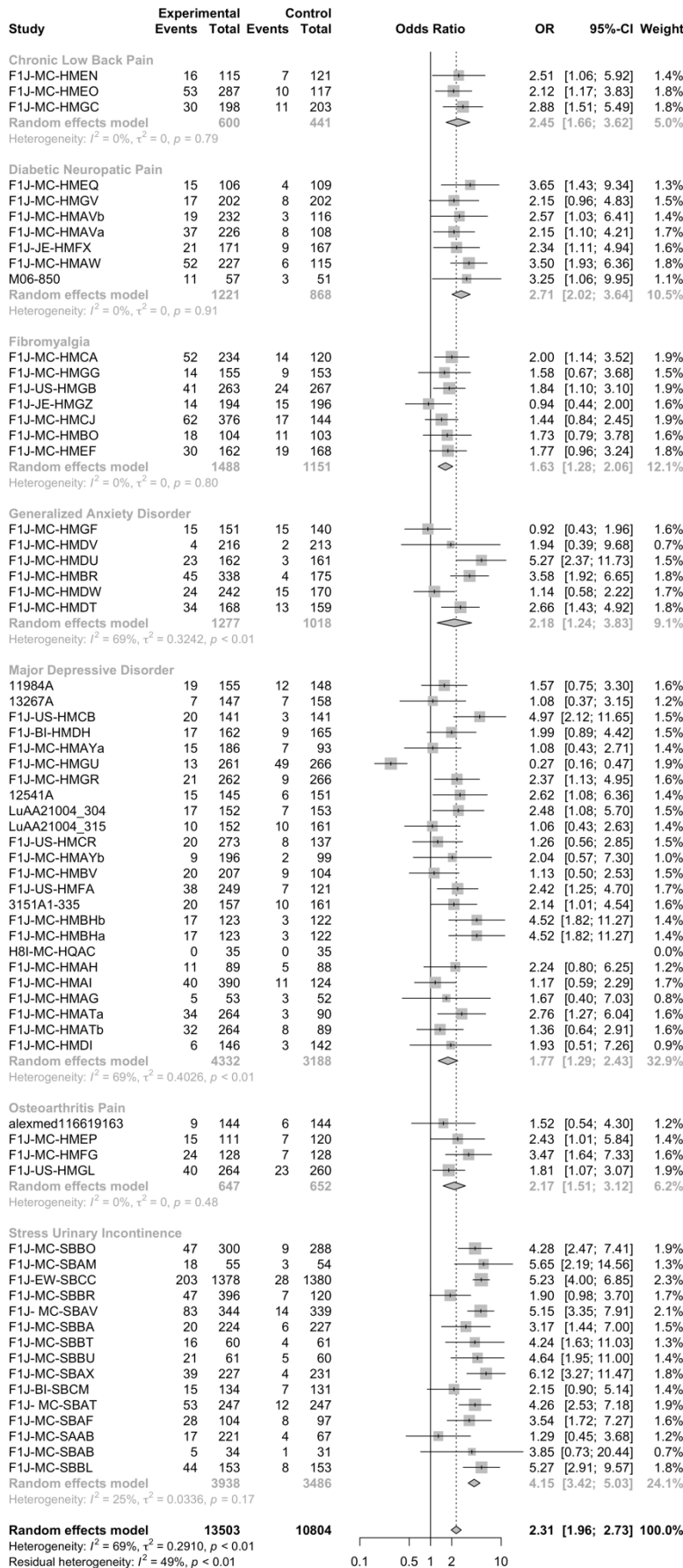
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JUTEL, Alexis : Déclaration des événements indésirables de la duloxetine chez l'adulte : revue de la littérature et méta-analyse des essais contrôlés randomisés évaluant duloxétine contre placebo chez l'adulte.**Résumé français :**

Les méta-analyses constituent le type d'étude assurant le plus haut niveau de preuve scientifique. Leur réalisation nécessite cependant de la rigueur et un accès exhaustif et transparent aux données des essais cliniques ce qui n'est pas toujours le cas. A l'instar d'autres traitements, la sécurité d'emploi de la duloxetine, un anti-dépresseur inhibiteur non sélectif de la recapture de la sérotonine, doit être étudiée avec attention notamment concernant son usage chez la personne âgée. Cette évaluation peut être réalisée grâce à une méta-analyse mais pour cela il faut s'assurer de la fiabilité des données reportées à propos des effets indésirables de ce médicament, c'est l'objet de notre étude qui compare le rapport des effets indésirables dans plusieurs bases de données.

Nous avons réalisé une revue systématique et une méta-analyse sur données agrégées d'essais randomisés contrôlés en double aveugle identifiés parmi les essais inclus dans les méta-analyses sur la duloxetine publiées sur PubMed concernant 7 indications autorisées par les autorités sanitaires américaines et européennes. Parmi ces RCT nous avons extrait à chaque fois les informations pour 4 variables : les effets indésirables sévères, qui constitue le critère de jugement principal ainsi que le nombre d'effets indésirables, de drop-outs et drop-outs pour raison de sécurité. Nous avons alors comparé les données retrouvées sur 4 bases de données différentes : les articles publiés, les registres d'études cliniques (clinicaltrial.gov, clinicaltrialregister.eu, FDA, EMA), les rapports des industriels et les données publiées dans les méta-analyse portant sur la duloxetine. Nous avons ensuite évalué l'hétérogénéité du report de ces différentes variables au sein de chaque base de données et recherché une éventuelle variation de l'effet en fonction de chaque base de données. Une meta-regression a ensuite été réalisée pour rechercher une variation selon la pathologie concernée.

Rubrique de classement : PSYCHIATRIE

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