Benefits and harms in clinical trials of duloxetine for treatment of major depressive disorder: comparison of clinical study reports, trial registries, and publications

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Study funding and competing interests
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STUDY QUESTION

Are there inconsistencies between protocols, clinical study reports, and main publicly available sources of trial data (journal articles and trial registries) and within clinical study reports themselves, with respect to benefits and harms of treatments?

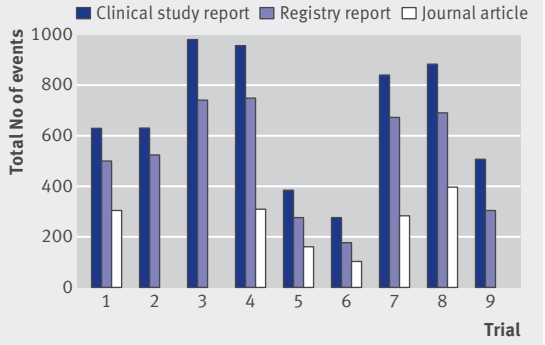
SUMMARY ANSWER

With research on duloxetine for major depressive disorder as an example, there were minor inconsistencies in the population used in the primary efficacy analysis between protocols and clinical study reports and within clinical study reports. There were also inconsistencies between different summaries and tabulations of harms data within clinical study reports.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Meta-analyses of randomised clinical trials based on published data can overestimate the benefits and underestimate the harms of drugs, and a more reliable data source for meta-analyses is clinical study reports. This comparison of data sources showed inconsistencies in reported harms between different summaries and tabulations of data on harms within clinical study reports. Authors of systematic reviews should check clinical study reports for accuracy and consistency whenever possible.

Total number of treatment emergent adverse events (TEAEs) reported in randomised phase in different sources of trial data



Registry reports were from manufacturer's (Eli Lilly) clinical trial registry; journal articles were those describing single trial only. Trials 2 and 3 had no journal article. TEAEs in trial 9 were reported qualitatively in relevant journal article

Participants and setting

We studied a cohort of nine randomised placebo controlled studies of duloxetine (2878 patients) submitted to the European Medicines agency (EMA) for marketing approval for major depressive disorder. We obtained clinical study reports, which included protocols as appendices (total 13 729 pages), from the EMA in 2011. Journal articles, reporting single trials only, were identified through searching relevant literature databases and contacting the manufacturer. Clinicaltrials.gov and the manufacturer's online trial registry were searched for trial results. We focused on duloxetine as it was the only centrally approved product (whereby a single application to the EMA can lead to EU-wide marketing authorisation for a drug).

Design, size, and duration

Our outcomes of interest were the primary efficacy analysis (outcome, measure of precision or variability, time point, analysis, and analysis population), major harms (deaths, serious adverse events, suicides, attempted suicides, and discontinuations because of adverse events), treatment emergent adverse events (adverse events that emerged or worsened after study drug was started), and adverse events that emerged on discontinuation of study drug. For each trial, we compared data for each outcome between the protocol and the clinical study report, within the clinical study report, and between the clinical study report and main publicly available data, for consistency and, when applicable, completeness of reporting.

Main results and the role of chance

Clinical study reports fully described the primary efficacy analysis and major harms. There were, however, minor inconsistencies (for example, the number of patients differed by 0.3% to 3%) in the population included in the primary efficacy analysis between the protocol and clinical study report and within the clinical study report for one trial. Furthermore, we found contradictory information within the reports for seven serious adverse events and eight adverse events that led to discontinuation but with no apparent bias. In contrast with clinical study reports, we found that data on harms were often incompletely reported or absent from publicly available sources. Because of the use of reporting thresholds, data on between a median of 406 (range 177-645) and 166 (100-241) treatment emergent adverse events in the randomised phase per trial were not reported in journal articles and Lilly trial registry reports, respectively. Additionally, we found publication bias in relation to beneficial effects.

Bias, confounding, and other reasons for caution

We used two independent observers for our main data extractions to minimise errors. We were, however, unfamiliar with clinical study reports and dealing with such large quantities of detailed information.

Generalisability to other populations

The generalisability of our findings is unclear given that they are based on nine trials of a single drug from a single company.

Coding of adverse events of suicidality in clinical study reports of duloxetine for the treatment of major depressive disorder: descriptive study

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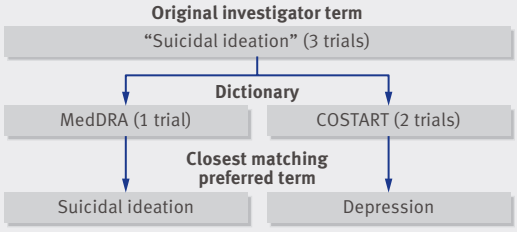
STUDY QUESTION

What are the effects of coding and coding conventions on different summaries and tabulations of adverse events data on suicidality in clinical study reports?

SUMMARY ANSWER

Adverse events data in tables may not accurately represent the underlying individual patient data because of the medical coding dictionaries and coding conventions used. Listings of adverse events for individual patients and narratives of adverse events can provide additional information, including original investigator reported terms, which can enable a more accurate estimate of harms.

Coding of suicidal ideation using different medical coding dictionaries



Narratives were the only data format to provide both verbatim and preferred terms, and therefore to allow definitive reconciliation of events between different summaries and tabulations of harms data. Narratives with data on adverse events relating to suicidal ideation were only available for three of the nine trials

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

For statisticians to analyse adverse events recorded in a clinical trial, it is necessary that events described by the original investigators are coded to terms in a specialised medical coding dictionary. Miscoding of harms can prevent an accurate risk assessment of harms. The use of coding dictionaries and coding conventions used may inadvertently obscure events that are important in summary tables.

Participants and setting

We used clinical study reports (total 13 729 pages) of nine randomised placebo controlled trials of duloxetine submitted to the European Medicines Agency for marketing approval for major depressive disorder.

Design, size, and duration

We performed systematic electronic searches for adverse events of suicidality in tables, narratives, and listings of adverse events for individual patients in the clinical study reports. For each event, where possible, we extracted the original investigator reported term, medical coding dictionary coded term, and medical coding dictionary used. We attempted to reconcile data on the same event between the different summaries and tabulations of adverse events data within the clinical study report using the patient's trial identification number.

Main results and the role of chance

Six trials (1586 patients) used the medical coding dictionary COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) and three (1292 patients) used MedDRA (Medical Dictionary for Regulatory Activities). Suicides were clearly identifiable in all formats of adverse event data in clinical study reports. Suicide attempts presented in tables included both definitive and provisional diagnoses. Suicidal ideation and preparatory behaviour were obscured in some tables owing to the lack of specificity of the medical coding dictionary, especially in trials using COSTART where the closest matching term available was depression. Furthermore, we found one event of suicidal ideation described in narrative text that was absent from table and individual patient adverse event listings. The reason for this is unclear, but may result from the common coding convention that if symptoms and a definitive diagnosis are both provided, only the diagnosis is coded.

Bias, confounding, and other reasons for caution

Our analysis of discrepancies in adverse events data was limited to comparing data already coded in tables to those of narratives, which included verbatim and coded terms, of patients who had adverse events that were serious, led to discontinuation of the study drug, or were non-serious but clinically important, and to individual patient listings with verbatim terms only.

Generalisability to other populations

Our study is based on a small number of trials for a single drug manufactured by a single company.

Study funding/potential competing interests

This study is part of a PhD (EM) funded by Rigshospitalet's Research Council. The funding source had no role in the design and conduct of the study; data collection, management, analysis, and interpretation; preparation, review, and approval of the manuscript; or the decision to submit the paper for publication.

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Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study

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STUDY QUESTION

How do dietary protein sources in early adulthood affect the risk of breast cancer in premenopausal and postmenopausal women?

SUMMARY ANSWER

This analysis supports an association between higher consumption of total red meat during early adulthood and an increased risk of breast cancer that was not clearly restricted to cancers in premenopausal women and tumor status. Moreover, higher consumption of poultry was related to a lower incidence of breast cancer in postmenopausal women.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Substituting a combination of poultry, fish, legumes, and nuts as protein sources for red meat during early life seems to be beneficial for the prevention of breast cancer.

Participants and setting

88 803 premenopausal women from the Nurses' Health Study II cohort who were 26 to 45 years of age and had completed a questionnaire on diet in 1991.

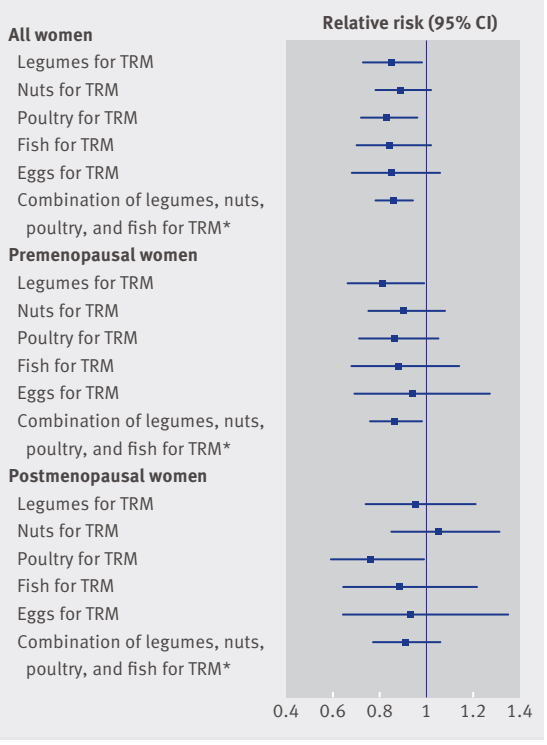
Design, size, and duration

We documented 2830 cases of breast cancer during 20 years of follow-up.

Main results and the role of chance

Higher intake of total red meat was associated with an increased risk of breast cancer overall (relative risk 1.22, 95% confidence interval 1.06 to 1.40; P_{trend}=0.01, for highest fifth *v* lowest fifth of intake). However, higher intakes of poultry, fish, eggs, legumes, and nuts were not related to breast cancer overall. When the association was evaluated by menopausal status, higher intake of poultry was associated with a lower risk of breast cancer in postmenopausal women (0.73, 0.58 to 0.91; P_{trend}=0.02, for highest fifth *v* lowest fifth of intake) but not in premenopausal women (0.93, 0.78 to 1.11; P_{trend}=0.60, for highest fifth *v* lowest fifth of intake). In estimating the effects of exchanging different protein sources, substituting one serving/day of legumes for one serving/day of red meat was associated with a 15% lower risk of breast cancer among all women (0.85, 0.73 to 0.98) and a 19% lower risk among premenopausal women (0.81, 0.66 to 0.99). Also, substituting one serving/day of poultry for one serving/day of red meat was associated with a 17% lower risk of breast cancer overall (0.83, 0.72 to 0.96) and a 24% lower risk of postmenopausal breast cancer (0.76, 0.59 to 0.99). Furthermore, substituting one serving/day of combined legumes, nuts, poultry, and fish for one serving/day of red meat was associated with a 14% lower risk of breast cancer overall (0.86, 0.78 to 0.94) and premenopausal breast cancer (0.86, 0.76 to 0.98).

Multivariable relative risk and 95% confidence intervals for breast cancer associated with substitution of dietary sources of protein for total red meat (TRM) among women in the Nurses' Health Study II



Bias, confounding, and other reasons for caution

Residual confounders are a concern in observational studies. Because dietary intake was assessed by food frequency questionnaires, some degree of measurement error is inevitably present. We indirectly estimated the effects of substitution of legumes, poultry, and other protein sources for red meat on risk of breast cancer. We made multiple comparisons in this analysis, therefore we cannot exclude the possibility of type I errors. However, the central finding of an association with red meat was a prior hypothesis.

Generalizability to other populations

The participants were predominantly white, educated US adults. Generalizability to other race or ethnic groups is likely as race/ethnic specific risk factors for breast cancer have not been documented.

Study funding/potential competing interests

This study was supported by the National Institutes of Health grant (R01CA050385). We have no potential competing interests.

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Impact of community based, specialist palliative care teams on hospitalisations and emergency department visits late in life and hospital deaths: a pooled analysis

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STUDY QUESTION

Do specialist palliative care teams providing services in patients' homes change the risk of hospitalisation in the last two weeks of life when compared with usual community based palliative care?

SUMMARY ANSWER

A pooled study of 11 community based specialist palliative care teams showed significant reduction in the risk of being in hospital at the end of life, despite variation in team composition and geography served.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous trials have examined a single community based palliative care intervention using different team compositions, outcomes, and health financing systems, making it difficult to compare and generalise. This pooled analysis compared 11 teams in the same healthcare system, allowing investigation whether the core elements of the specialist teams would be effective at reducing acute care use.

Selection criteria for studies

Through linked administrative databases, this study conducted a pooled analysis using a retrospective cohort study in Ontario, Canada, where 3109 decedents treated by one of 11 specialist palliative care teams in 2009-11 (exposed) were matched by propensity score to 3109 similar decedents who received usual community based palliative care (unexposed). A specialist team was defined as including at least a core group of palliative care physicians, nurses, and family physicians who provide integrated palliative care to patients in their homes. The teams' role was to manage symptoms, provide education and care, coordinate services, and be available without interruption regardless of time or day. Additional inclusion criteria were the teams had to be the only such team in their respective regions and have little or no change in staffing between 2009 until 2012. However, team size, team members, geography, and referral capacity could vary. Across the province, 11 teams met these criteria, and their patients served were eligible for inclusion. Patients were excluded if they were alive after fiscal year 2011, were <18 years old, or had an invalid or missing provincial health insurance number.

Primary outcome

The main outcome was being in hospital (that is, occupying an inpatient bed) in the last two weeks of life.

Main results and role of chance

Our pooled results show that 970 (31.2%) of the exposed group was in hospital in the last two weeks of life compared with 1219 (39.3%) of the unexposed group (P<0.001). The pooled relative risk of being in hospital in the last two weeks of life for exposed versus unexposed patients was 0.68 (95% confidence interval 0.61 to 0.76), and six of the 11 teams had significantly lower relative risk (figure).

Bias, confounding, and other reasons for caution

While our study uniquely used propensity score matching in our observational data to reduce selection bias in the control group, propensity scores cannot adjust for unmeasured covariates, such as patient preferences for hospital care and availability of existing caregiver support. This study's teams served cancer patients primarily, which limits the generalisability of the results to teams primarily serving another disease group.

Study funding/potential competing interests

This study was funded by the Canadian Institutes of Health Research and used databases maintained by the Institute for Clinical Evaluative Sciences, which receives funding from the Ontario Ministry of Health and Long-Term Care.

Relative risk of being in hospital in the last two weeks of life