META-ANALYSIS

Antidepressant treatment effects and country income: meta-regression analysis of individual participant data from duloxetine trials

Thomas Klein1 | Stefan Weinmann2,3 | Thomas Becker1 | Markus Koesters1

1Department of Psychiatry II, Ulm University, Günzburg, Germany
2Psychiatric Hospital and Rehabilitation Unit, Rudolf-Sophien-Stift, Stuttgart, Germany
3University Psychiatric Hospital, Basel, Switzerland

Correspondence
Thomas Klein, Department of Psychiatry II, Ulm University, Bezirkskrankenhaus Günzburg, Lindenallee 2, D-89312 Günzburg, Germany.
Email: thomas.klein@uni-ulm.de

Funding Information
The study was funded by the Medical Faculty of Ulm University within an independent young researchers programme.

Abstract
Objective: In recent decades, significant numbers of pharmaceutical trials have gradually been relocated to low- and middle-income countries. However, there is little evidence regarding the transferability of trial outcomes across countries. Analysing duloxetine randomised controlled trials (RCTs) conducted in different countries, we investigated whether per capita gross national income (GNI) and healthcare expenditure (HE) are associated with pre-post mean changes of depression severity and differences in duloxetine-placebo effect sizes.

Method: Meta-analyses included RCTs investigating duloxetine efficacy in patients with depression. Individual participant data (IPD) from multi-centre duloxetine trials were provided by the manufacturer. Data extracted from published reports also entered analyses in case of trials conducted in only one country. A meta-regression approach was applied to analyse associations of GNI and HE with standardised pre-post mean change using raw score standardisation (SMCR) and comparative effect size, that is, the mean differences (MD) in pre-post effect size between duloxetine and placebo treatment.

Results: 23 trials with 8417 randomised participants entered analyses. Regression coefficients indicated a negative linear relationship of SMCR with GNI (z-standardised β = −3.61, R² = 14.8%, p < 0.001) and HE (β = −4.72, R² = 24.8%, p < 0.001) for participants treated with duloxetine. Similar associations were found for placebo treatment (GNI: β = −3.52, R² = 23.8%, p < 0.001; β = −3.34, R² = 21.0% p < 0.001). Neither GNI nor HE was associated with the MD between duloxetine and placebo pre-post differences.

Conclusions: Findings challenge the idea of the universal transferability of antidepressant trial outcomes across countries. Understanding the results of antidepressant RCTs demands more sophisticated clarification of context factors involved in determining effectiveness of antidepressant medication and should be discussed with a view to socio-economic context in their countries of origin.

KEYWORDS
duloxetine hydrochloride, global health, major depressive disorder, meta-analysis

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2021 The Authors. Acta Psychiatrica Scandinavica published by John Wiley & Sons Ltd.
1 | INTRODUCTION

While previously pharmacological trials were mainly conducted in North America and Western Europe, a recent trend has been to relocate study sites to and conduct trials in low- and middle-income countries (LAMICs), especially in Eastern Europe, Asia, and Latin America. Conducting trials in LAMICs may be driven by the interest of sponsors to reduce trial costs and the complexity of study management (e.g. participant payments, remunerations for clinical staff, regulatory and ethical consent requirements). Research in LAMICs faces various difficulties, such as fulfilling regulatory standards, lack of financial and human capacity and lack of suitable research infrastructure. Some trials conducted fully or mainly in LAMICs have had deficits with respect to medical ethics and scientific standards.

Ethical considerations aside, only few studies have paid attention to differences in study results between trials performed in LAMICs and those conducted in high-income countries, even though some findings indicate differences in psychiatric treatment outcomes across countries. An examination of 139 meta-analyses showed, on average, more favourable treatment effects of medical interventions in trials on somatic disorders conducted in less developed countries indicated by a summary relative risk of mortality of 1.12 in favour of less developed countries. Although this meta-meta-analysis addressed issues of trial outcome differences across countries, it focused on somatic disease only.

Psychiatric treatment trials may pose particular challenges as research methodology in mental health is particularly prone to bias. This may be enhanced by the influence of regional and cultural factors on assessing psychopathology and other outcomes. In depression treatment, an exploratory analysis of trials submitted to the US Food and Drug Administration (FDA) showed that participants with major depression outside North America showed a better response to both placebo and active antidepressant treatment, whereas relative differences between medication and placebo were similar across countries.

These findings question the assumption of universal clinical applicability of trial results across countries. Differences in psychotropic drug treatment outcomes across countries as seen in geographical differences in response rates have been explained by differences in genetic or biological predisposition across populations. Some researchers have suggested methods to account for these factors by applying intelligent study designs and using defined dosing algorithms to assure comparable dosages between different patient groups. However, most studies examining ethnic differences in antidepressant response have not found differences of clinical relevance. Genetic or ethnic differences may interact with environmental and cultural (behavioural) determinants. Pharmacokinetic differences in clomipramine metabolism between Asian and British Caucasian patients were found but not confirmed in Asian subjects who had moved to the UK and changed dietary habits. The role of intrapsychic and (socio-)contextual factors for depression treatment outcome has been emphasised, for example patient and professional concepts of mental illness, somatisation proneness, patient and staff expectations of treatment, and other facilitating or inhibiting contextual factors such as level of healthcare infrastructure.

Some studies suggest a link between a region’s wealth and the prevalence of mental disorders. Differences in mental health treatment outcomes could also be related to levels of economic development, mental healthcare infrastructure and individual-level deprivation. An intervention addressing physician knowledge and management of depression in primary care in the USA showed that people suffering individual financial strains at baseline benefitted more from a depression than people not facing monetary strains. National economic status can be considered a major determinant and indicator of mental healthcare expenditure and infrastructure, for example of accessibility and quality of psychiatric services.

Summation

- Findings suggest that the higher economic wealth and healthcare infrastructure in the country an antidepressant trial was conducted, the weaker is the standardised mean change in depressive symptoms (GNI: \( r = -0.38 \), HE: \( r = -0.50 \)), while the mean difference between duloxetine and placebo was stable across countries.
- This finding implies that effectiveness of duloxetine varies across countries, which, in light of the globalisation of clinical trials, is of relevance when comparing these trials.

Limitations

- Because of the availability of the data, our analyses focused on individual participant data from duloxetine trials. The data were distributed unevenly across countries where trials had been conducted, with most data for the USA and only few data for African, Asian and South-American countries. Per capita income and health expenditure are rather generic indicators of wealth that might not adequately reflect individuals’ situations within countries.
1.1 | Aims of the study

This study investigates differences in treatment outcome between patient populations that were recruited in countries with different levels of economic wealth and health care expenditure and received identical antidepressant medication or placebo in RCT settings. We assumed that antidepressant treatment outcome was associated with a country’s economic strength and the level of healthcare expenditure. We chose duloxetine, a selective serotonin-noradrenaline reuptake inhibitor, to test this assumption. For duloxetine, individual participant data (IPD) were available which allowed a detailed analysis of factors potentially affecting treatment effect sizes.

2 | METHOD

This study used meta-analytical methodology. Since the results of multi-national trials are not reported per country, it was necessary to use individual participant data (IPD) which allowed the calculation of country-level data. Anonymised IPD for duloxetine were requested through ‘http://www.clinicalstudydatarequest.com’, a consortium of clinical study data providers. At the time of the start of our project (end of 2015), duloxetine was the antidepressant with the most comprehensive data set available. In preparation of the request, we conducted a systematic review of randomised controlled duloxetine trials for the treatment of depression in major electronic databases (eg Medline, Embase and PsycInfo), public clinical trial registers (eg www.clinicaltrials.gov, www.clinicaltrialsregister.eu) and the manufacturer database (www.lillytrials.com) to identify all published and unpublished trials. Search for and selection of studies followed the same approach that has been described in more detail elsewhere.25

We submitted the research protocol together with a list of requested trial data.26 The protocol (see Document S1) was reviewed by an Independent Review Panel at ‘http://www.clinicalstudydatarequest.com’ before the data-sharing agreement was signed. With one exception (study origin unclear), IPD were requested for multinational trials only. The research protocol was developed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for IPD meta-analyses.27

2.1 | Study selection

Only randomised controlled clinical trials (RCTs) examining the effects of duloxetine monotherapy in the acute treatment phase on depressive symptom severity with one or more comparative treatment arms were included in the meta-analysis. Trial samples from any study time were included if they comprised participants with a major depressive disorder. Based on the initial systematic search of randomised controlled trials, we also included single-country studies. The focus of the analysis was on exploring country-specific effects rather than efficacy, and we restricted the data analysis to trials conducted by the duloxetine manufacturer in order to avoid other sources of variance.

2.2 | Data extraction

The requested IPD were available as full raw data sets including the original study reports and information on data nomenclature. Further data extraction from multi-national studies was unnecessary as the IPD permitted direct calculation from the raw data of primary studies. These data were accessible online via the clinical trial data transparency (CTDT) portal by SAS (Statistical Analysis Systems). IPD were checked in terms of completeness and plausibility by randomly examining subsets of each included trial data set. Data for both the duloxetine and placebo condition were aggregated at country level within each trial for which country-level means and standard deviations (SDs) were computed. These country-level data were then nested within each trial separately. No IPD were requested for studies conducted in only one country. Two researchers extracted data that were subsequently checked by a third.

The following study characteristics were extracted or calculated from primary data: study title, whether the study data were IPD, study start year, the mean dose of duloxetine and the type of depression rating scale used in the study. When more than one depression rating scale was used in a study, we extracted data from one scale per trial, with preference given to the Hamilton Depression Rating Scale (HAMD)28 over the Montgomery-Åsberg Depression Rating Scale (MADRS)29 and the Beck Depression Inventory (BDI)30 or other depression rating scales.

For all studies included, the following data were extracted or calculated: number of randomised participants, mean age, mean severity of depressive symptoms at baseline and endpoint assessment with the corresponding SDs, type of depression rating scale, scale maximum score, pre-post correlations and the number of participants who showed a response to and/or remission after treatment, as defined in the study.

Data for gross national income (GNI) per capita of countries included in the study were extracted from the World Bank website.31 GNI was measured in constant international dollars of the year 2011 adjusted for purchasing power parity (https://data.worldbank.org/indicator/NY.GNP.MKTP.PP.KD). Data for health expenditure (HE) per capita were extracted using the same data source. Both indicators were extracted per country of trial location and for the respective year of study baseline (first patient in) to ensure a uniform
procedure. If scores were not available from the World Bank website, we used the record for health expenditure closest in time that we could identify.

Per capita income has drastically increased throughout the world over the last 50 years (https://data.worldbank.org/indicator/NY.GNP.MKTP.PP.KD) and we calculated the quotient of GNI per capita of country X in year Y divided by the world mean GNI per capita in year Y in order to standardize GNI per capita and to increase comparability across years. The same procedure was used to calculate a standardised HE index. Table S1 illustrates per capita GNI and HE of the included trial countries using World Bank data of year 2000.

Two independent raters assessed study quality using the Cochrane risk of bias tool32 on the basis of reports, study protocols and publications for both single-country studies and IPD studies. Possible sources of bias were judged to be ‘high’, ‘low’ or ‘unclear’. The risk of bias judgements was summarised across studies. Disagreements between the two raters were discussed until consensus was reached.

2.3 | Statistical analysis

Data structure in the present meta-analysis differs from other meta-analytical approaches because, in contrast to the conventional concept of meta-analysis, the subjects of analysis were not data at study level but on a country level. Data were structured along each country within each study, thus considering the between-study heterogeneity and avoiding ecological bias.33 All analyses were conducted separately for duloxetine and placebo treatment.

Data analysis included the acute treatment phase from baseline to endpoint assessment (preferably 8 to 12 weeks) only. Two primary outcomes were defined a priori: First, the pre-post effect size between baseline and endpoint assessment of depressive symptom severity was calculated as the standardised mean change using raw score standardisation (SMCR).34,35 Standardised values were calculated in order to ensure comparability of effect sizes across studies, for example when their assessment incorporated different depression scales. To calculate the variance of the pre-post effect size, the pre-post correlation was taken into account and calculated from IPD. Second, comparative effect sizes were calculated as the mean difference (MD) between the pre-post effect sizes of the duloxetine- and the placebo group.36 Comparisons were made between the treatment groups within country and study when both treatment groups were existent.

The last observation carried forward (LOCF) approach was applied to endpoint data for participants in the IPD studies assessed at least once post-baseline. Missing SDs of baseline or endpoint depression severity or pre-post correlations in non-IPD studies were imputed from IPD data based on the pooled means from IPD data sets of participants from identical treatment, rating scale and country groups where possible.

Other secondary outcome variables were response and remission rate. Response was defined as endpoint score ≤50% baseline score of depression severity for all studies. Remission was defined as a depression severity endpoint score of ≤7 on HAMD-17 or ≤10 on MADRS and BDI irrespective of baseline score. For publication-based data, remission rates were extracted as defined in the respective study. Analyses of dropout rates and dropout rates related to adverse events were used as measures of acceptability.

Meta-analyses used a random effects model with the restricted maximum-likelihood method (REML) following a two-stage approach. At stage 1, the effect size was estimated within each data point. These effect size estimates were weighted by the variance inverse and aggregated (stage 2). The amount of between-study heterogeneity was examined by $\hat{\tau}^2$.

Meta-regression techniques for mixed-effects models were applied to analyse the impact of the year-standardised index of GNI per capita, or respectively HE per capita, as moderators of symptom change after treatment, as well as comparative effects between duloxetine vs placebo treatment. The relationships of outcome variables with these standardised World Bank indices were tested in separate univariate linear meta-regression models as these indicators are highly correlated with each other. All meta-regression analyses were conducted with R and the ‘metafor’ package.37

The R-package ‘GLMulti’ was used to test the robustness of findings, namely whether World Bank indicators would still substantially predict endpoint depression severity when entered in a meta-regression model jointly with common predictors of antidepressant efficacy. Moderators suspected to have an effect on pre-post effect size or comparative effects included treatment type (only for pre-post effect size), whether data are IPD, depression rating scale, participant age, antidepressant dose (only for duloxetine) and depression symptom severity at baseline.

Applying the maximum-likelihood (ML) method, we used the Akaike information criterion corrected for small sample sizes (AICc) to select the most important predictors in terms of variance explanation. The ‘average importance across models’ was calculated with a threshold of 0.8. Sensitivity analyses were conducted using the alternative Bayesian information criterion (BIC). Influence case diagnostic statistics were used to identify cases extremely influential on effect sizes,38 which were then eliminated within additional sensitivity analyses of the corresponding model. The impact of estimated pre-post correlation coefficients on SMCR calculation was tested in sensitivity analyses with fixed correlation coefficients. Because we considered baseline depression severity a major predictor of SMCR, response and remission
rate, we also conducted sensitivity analyses that compared models where baseline severity is eligible vs. not eligible in the regression model according to GLMulti model selection, in order to assess potential effects of mathematical coupling.\(^3^9\) We also tested whether baseline depression severity. All sensitivity analyses were planned prior to data analysis and independent of results.

3 | RESULTS

3.1 | Characteristics of included studies

Of the group of 18 IPD studies requested from the manufacturer 15 were included in our analysis (see Figure 1). Only one of the original 18 trials was conducted in children, thus we restricted our analysis to adult samples. Two further studies were excluded because they did not meet inclusion criteria (studies either focused on medication switching or prevention of depression recurrence). The included studies comprised 6376 randomised participants who attended at least one post-baseline assessment after treatment onset. Six participants were excluded from the main analysis because they were arranged in subgroups with only two participants not permitting further analyses with these groups. Also, data from eight single-country studies were extracted from papers and trial reports providing non-IPD information for 2047 participants of whom all were US residents at the time of the trial.

In total, 8417 randomised participants from 29 countries receiving either duloxetine or placebo treatment entered data analysis. The sample contained several countries in Eastern and Western Europe, North America and Australia. Russia and Turkey were the only countries on the Asian continent, South Africa was the only African country, and Mexico and Puerto Rico were the only Latin-American countries included. The number of participants across countries ranged from six (Slovenia) to 4555 (USA). Of 23 included studies 18 contained a placebo treatment arm. In total, 5974 patients had been randomised to duloxetine and 2443 to placebo groups. The studies were conducted between 1993 and 2012. Characteristics of the included studies are detailed in Table S2.

3.2 | Pre-post changes

The primary meta-analysis revealed a mean SMCR for the duloxetine study arm of 3.07 (CI: 2.80 to 3.33; \(I^2 = 95.1\%\), \(p < 0.001\)) and for the placebo subgroup of 2.07 (CI: 1.82 to 2.30; \(I^2 = 89.7\%\), \(p < 0.001\)). The difference between duloxetine and placebo treatment effect sizes was 0.51 (CI: 0.36 to 0.67, \(I^2 = 43.5\%\), \(p < 0.001\)).

3.3 | Results of meta-regression analyses

Meta-regression analyses revealed a small but statistically significant proportion of outcome variance explained by GNI per capita (\(R^2 = 14.8\%\), \(p < 0.001\)) while the regression coefficient indicated a decrease of the SMCR with increase in GNI (\(\beta = -3.61\), \(p < 0.001\)). Accordingly, the correlation between GNI and SMCR was -0.38. Statistical heterogeneity was high (\(I^2 = 94.2\%\), \(p < 0.001\)). No data on HE per capita were available for Puerto Rico, so data from 5 studies had to be excluded (140 participants in duloxetine trial arms and 95 participants in placebo trial arms) from the respective meta-regression analyses. A relationship similar to the GNI-SMCR association was observed when health expenditure (HE) per capita was included in the model as single moderator of the pre-post differences (\(\beta = -4.72\), \(R^2 = 24.8\%\), \(I^2 = 93.8\%\), \(p < 0.001\)), the correlation was stronger with \(r = -0.50\).

Both findings remained stable when depression severity at baseline, participant age and treatment dose were included as moderators (identified via best model selection, see Table 1 for details). Similar associations could be found for placebo treatment (see Table 1).

The relationship between GNI per capita and pre-post differences is comparable across treatment groups (see Figure 2).

3.4 | Comparative effect sizes

Comparative effect sizes could be calculated for 48 comparisons between duloxetine and placebo. The mean difference in pre-post changes of duloxetine and placebo treatment was 0.51 (CI: 0.36 to 0.67) with a small to moderate heterogeneity between data points \(I^2 = 43.5\%\) (\(p < 0.001\)). Neither per capita GNI nor health expenditure explained the variance of mean differences as moderator (GNI: \(\beta = -0.23\), \(R^2 = 0.0\%\), \(p = 0.82\); \(I^2 = 44.7\%\), \(p < 0.001\); see Figure 3, HE: \(\beta = -0.88\), \(R^2 = 0.0\%\), \(p = 0.38\); \(I^2 = 48.4\%\), \(p < 0.001\)).

3.5 | Results for response and remission rate

GNI and HE per capita were found to predict the rate of response to treatment significantly with a stronger relationship being observed for placebo compared to duloxetine treatment (Table 2). In contrast, GNI and HE per capita explained far less variance of the remission rate in the duloxetine group when no other predictors entered the meta-regression model.

3.6 | Dropout analyses

In total, 25.1% (27.1%) of participants prematurely discontinued study participation in the course of treatment any
time after being randomised into the duloxetine (placebo) group. Of these, 35.9% (20.5%) were excluded from participation because of one or more adverse events. Dropout analyses revealed a positive linear relationship of GNI or, respectively, HE per capita indices and dropout rates (GNI: \( \beta = 3.52, R^2 = 14.5\%, p < 0.001, I^2 = 92.6\%\); HE: \( \beta = 2.10, \))
Analyses in the placebo group showed similar results (GNI: \( \beta = 3.62, R^2 = 31.5\%, p < 0.001, I^2 = 84.5\% \)); and HE (\( \beta = 2.21, R^2 = 14.1\%, p < 0.05, I^2 = 87.2\% \)). Rates of dropout related to adverse events were positively linked to GNI (\( \beta = 4.31, R^2 = 29.3\%, p < 0.001, I^2 = 51.1\% \)) and HE (\( \beta = 4.16, R^2 = 30.0\%, p < 0.001, I^2 = 50.8\% \)) in the duloxetine but not the placebo group (GNI: \( \beta = -0.29, R^2 = 0.0\%, p = 0.77, I^2 = 33.4\% \); HE: \( \beta = -0.23, R^2 = 0.0\%, p = 0.82, I^2 = 33.5\% \)).

### 3.7 | Sensitivity analyses

Sensitivity analyses testing alternative imputation pre-post correlations did not result in substantial changes of results (see Table S6). Whenever influence diagnostics indicated highly influential cases the results changed only marginally and not in the direction of the effect after these cases had been removed from analysis. After the removal of four extreme outliers and highly influential cases, the negative linear relationship between GNI per capita and pre-post difference did not change substantially (\( \beta = -3.77, R^2 = 16.43\%, p < 0.001; I^2 = 93.7\% \)). Similarly, no substantial change could be found for the relationship of SMCR and HE having excluded one extreme outlier from the analysis (\( \beta = -4.78, R^2 = 24.4\%, p < 0.001; I^2 = 93.6\% \)). Sensitivity analyses revealed that regression models still explained substantial percentages of outcome variation, when baseline depression severity was excluded from eligibility as potential moderator in the model (see Tables S8–S13).

### 4 | DISCUSSION

The aim of this study was to examine the relationship between gross national income as well as country healthcare expenditure and treatment outcome in countries in which duloxetine (vs placebo) RCTs were conducted. Meta-regression analyses indicated a significantly negative linear relationship between both indices and the pre-post difference for both duloxetine and placebo treatment. This indicates that duloxetine as well as placebo appeared to be less effective in improving depression with increasing...
national per capita income and healthcare expenditure. These results were independent of other predictors of pre-post change. Our estimate corresponds to a change of about 0.3 points on the HAMD scale per every 10 percentage points in GNI index. For countries in our sample, the GNI ranges from 29% below GNI world average (Romania) to 362% above (USA) in the year 2000 (Table S1), suggesting that there are meaningful differences across countries with an absolute range of 12 points on the HAMD scale.

The associations between pre-post differences and depression scores with country economic wealth and healthcare expenditure were stronger in the placebo than in the duloxetine study arms (cf. Ref. 40). This finding might be accounted for by unspecific factors affecting placebo effectiveness more than specific antidepressant effectiveness (eg treatment expectancy). 41

Sample selection might be another factor that contributes to these effects: study sites might differ in their rating of symptom severity leading to the inclusion of participants with weaker depression symptoms. Accordingly, lower symptom levels are more difficult to further alleviate which results in weaker duloxetine-placebo differences in countries with higher per capita income.

Our findings showed that comparative pre-post mean differences between duloxetine and placebo within a particular country failed to change significantly with gross national income or healthcare expenditure but remained unchanged regardless of trial country. The present results replicate findings in other publications that drug-placebo differences in antidepressant trials are similar across countries. 10 However, in addition to this, our study suggests that cross-national stability and trial comparability require a balanced sample composition in multinational trials with similar numbers of participants from a specific country in the experimental and placebo groups. Imbalance may contribute to variance in trial results of the overall comparative effect. In the present meta-analyses, only 48 of 87 duloxetine study arms were compared with placebo groups from the same study country. This finding supports the idea, that there may be an imbalance in cross-national sampling in original studies. Researchers should bear this in mind when planning (and assessing) multi-national trials.

Table 2: Main results of meta-regression analyses with response and remission rate as outcome and indicators for countries’ economic wealth and healthcare expenditure as predictors

|                      | Duloxetine |           | Placebo |           |
|----------------------|------------|-----------|---------|-----------|
|                      | β          | R² (p)    | I²      | β         | R² (p)    | I²      |
| **Response rate**    |            |           |         |           |           |
| Standardised GNI per capita |          |           |         |           |           |
| Single predictor model | −5.44     | 35.2% (<0.001) | 83.0% | −5.82     | 61.0% (<0.001) | 65.3% |
| GLMulti best model    | −6.05     | 43.9% (<0.001) | 80.5% | −6.87     | 73.7% (<0.001) | 54.2% |
| Standardised HE per capita |          |           |         |           |           |
| Single predictor model | −5.41     | 35.9% (<0.001) | 83.3% | −4.25     | 44.0% (<0.001) | 74.2% |
| GLMulti best model    | −5.86     | 43.2% (<0.001) | 81.2% | −5.13     | 59.7% (<0.001) | 65.6% |
| **Remission rate**   |            |           |         |           |           |
| Standardised GNI per capita |          |           |         |           |           |
| Single predictor model | −2.65     | 8.2% (<0.01) | 87.1% | −3.00     | 17.6% (<0.01) | 86.6% |
| GLMulti best model    | −2.90     | 15.8% (<0.01) | 85.8% | −3.67     | 39.0% (<0.001) | 81.8% |
| Standardised HE per capita |          |           |         |           |           |
| Single predictor model | −2.61     | 8.4% (<0.01) | 87.0% | −2.03     | 7.0% (<0.05) | 88.2% |
| GLMulti best model    | −2.82     | 16.4% (<0.001) | 85.7% | −2.76     | 29.7% (<0.001) | 83.9% |

GNI, gross national income; HE, health expenditure; β = z-standardised regression coefficient of World Bank predictor (GNI or HE); R² = percentage of variance explained by predictor(s); p = p-value of whole meta-regression model; I² = extent of data heterogeneity. GNI and HE were standardised by the respective year’s world average. Predictors were tested both in separate models and as one of several predictors selected the GLMulti model selection method.

aDose included as predictor in model.

bType of depression scale included as predictor in model.

cBaseline severity of depression included as predictor in model.

The positive relationship between dropout rates and GNI or health expenditure per capita could be accounted for by improved access to treatment through participation in clinical psychopharmacological trials, making discontinuation and trial dropout less attractive to participants in countries with lower healthcare coverage.

Participating in a clinical trial conducted in countries with low standards of health care for mental disease entails better care even for participants randomised to the placebo group in the sense that they receive medical assessment.
Our results may help to better understand the perceived efficacy-effectiveness gap in clinical practice. Patients and clinicians in clinical practice are more interested in the improvement of psychopathology as indicated by pre-post symptom changes. Our findings suggest that, on the basis of international multi-country RCTs of antidepressants, expectations regarding medications effectiveness may be too high for patient populations in high-income countries.

These considerations are relevant for practitioners in routine care who have to make treatment decisions in their specific context.

4.1 Study limitations

Our method implied the aggregation of data at country level from original individual participant data (IPD). Although the quality of the data was high in terms of transparency and data processing our analyses have some limitations.

First, participants were distributed unevenly across countries with more than half the study participants residing in the United States. This limitation may be mitigated by the fact that most US residents centred on a low SMCR value and might have determined the average SMCR value in the upper end of the World Bank score range, but this does not affect the distribution of other data points. Excluding the US data from the analyses would still leave the influence of affluent Scandinavian countries.

Second, only sparse data were available for African, Asian and South-American countries. Having had more data from these regions of the world would have provided a picture of duloxetine efficacy in LAMICs with a much higher level of resolution.

Third, GNI per capita and health expenditure are rather generic indicators of the national economic situation. The health expenditure index does not provide specific information on mental healthcare spending. Considering that the within-country gap between poor and rich varies across countries and can be expected to be particularly harsh in LAMICs, other indicators of social inequality and access to healthcare infrastructure (eg GINI index, number of psychiatrists) may be better suited to the search for moderators of antidepressant efficacy and effectiveness. Furthermore, the economic moderators studied do not allow for conclusions on individuals. Data on individual-level socio-economic status were not available but could contribute to a better understanding of the impact of socio-economic factors on outcome variance in antidepressant drug trials.

Fourth, we cannot exclude some risk of an ecological bias arising from inferences made from data sets based on data of a higher level aggregation. This may be because of using national level data to differences on an individual level.

Finally, only trials of duloxetine were analysed in this study, limiting the transferability to other antidepressant treatments.

Nevertheless, our findings challenge views that psychopharmacologic treatment yields similar effects around the globe and imply that treatment context may play an important role which is not well understood. Treatment outcome of antidepressant drugs may be affected by economic circumstances, but the underlying mechanism is still unclear. More proximal predictors than gross national per capita income and health expenditure may help elucidate the relationships between economic status, psychotropic drug treatment and treatment outcome. The relocation of clinical trials to LAMICs needs to be reviewed not just ethically but also with a view to limited-between-country transferability of study results. These findings may also have consequences for network meta-analyses, as differences between countries may affect the transitivity of trials. Future research needs to shed light on the importance of the economic, social and infrastructural context for treatment effectiveness. In a globalised world, this context is important as there are dramatic differences in both living circumstances and access to mental health services.

ETHICS STATEMENT

Our analyses use anonymised patient-level data which is publicly available upon request. The research protocol was reviewed by an independent review panel at https://www.clinicalstudydatarequest.com. An ethical approval was judged not to be necessary for this secondary data analysis.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to declare.

ACKNOWLEDGEMENT

Open Access funding enabled and organized by Projekt DEAL.

AUTHORS’ CONTRIBUTIONS

All authors were involved in developing the study design and methods. TK and MK conceptualised data analyses. MK and TK conducted the data collection. TK extracted, cleaned and processed the data. TK and MK performed the statistical analysis. TK was responsible for writing the first draft of the manuscript. MK supervised the analyses and the writing of the manuscript. All authors read, critically revised and approved the final manuscript.

INFORMATION ON DATA SUPPLY AND AVAILABILITY

The manufacturers of Duloxetine (Eli Lilly & Co., Boehringer Ingelheim International GmbH) provided individual participant data that allowed the authors of this contribution to
aggregate duloxetine trial data on a country level. The data that support the findings of this study are not publicly available and were used for this study with the permission of Eli Lilly & Co. and Boehringer Ingelheim International GmbH. The authors of this article were only authorized to use these data in the scope of this research project. Beyond providing data, the manufacturers did not have any influence on data collection, data extraction, statistical analysis or the interpretation of the present findings and were not involved in designing this study, nor in creating this manuscript.

CONSENT STATEMENT
The analysis is a secondary analysis of anonymised participant-level data which was retrieved via https://www.clinicalstudydatarequest.com, therefore, it was impossible to seek informed consent for our analysis. But informed consent has been sought for the primary studies.

PEER REVIEW
The peer review history for this article is available at https://publons.com/publon/10.1111/acps.1337.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from https://www.clinicalstudydatarequest.com. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of https://www.clinicalstudydatarequest.com.

ORCID
Thomas Klein © https://orcid.org/0000-0002-9545-4480
Markus Koesters © https://orcid.org/0000-0001-7018-6021

REFERENCES
1. Rettig RA. The industrialization of clinical research. Health Aff. 2000;19:129-146.
2. Glickman SW. Ethical and scientific implications of the globalization of clinical research. New England J Med. 2009;360:2792.
3. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. Nat Rev Drug Discov. 2008;7:13-14.
4. Strüver V, Fneish F, Muche R, Fortwengel G. The temporal development of clinical research in emerging countries. Am J Clin Exp Med. 2021;9:1-7.
5. Alemayehu C, Mitchell G, Nikles J. Barriers for conducting clinical trials in developing countries- a systematic review. Int J Equity Health. 2018;17:37.
6. Ana J, Koehlmoos T, Smith R, Yan LL. Research misconduct in low- and middle-income countries. PLoS Med. 2013;10:e1001315.
7. da Silva RE, Amato AA, Guilhem DB, Novaes MRCG. Globalization of clinical trials: ethical and regulatory implications. Int J Clin Trials. 2016;3:1.
8. Fuertes N. GSK malpractice case raises questions about trial standards. Lancet. 2012;379:508.
9. Panagiotou OA, Contopoulos-Ioannidis D, Ioannidis JPA, Rehnborg CF. Comparative effect sizes in randomised trials from less developed and more developed countries: meta-epidemiological assessment. BMJ. 2013;346:f1707.
10. Khin NA, Yang P, Hung HMJ, et al. Regulatory and scientific issues regarding use of foreign data in support of new drug applications in the United States: an FDA perspective. Clin Pharmacol Ther. 2013;94:230-242.
11. Vieta E, Pappadopulos E, Mandel FS, Lombardo I. Impact of geographical and cultural factors on clinical trials in acute mania: lessons from a ziprasidone and haloperidol placebo-controlled study. Int J Neuropsychopharmacol. 2011;14:1017-1027.
12. Ioannidis JPA. Why most published research findings are false. PLoS Med. 2005;2:e124.
13. Khin NA, Chen Y-F, Yang Y, Yang P, Laughren TP. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J Clin Psychiatry. 2011;72:464-472.
14. Lesser IM, Myers HF, Lin K-M, et al. Ethnic differences in antidepressant response: a prospective multi-site clinical trial. Depression and Anxiety. 2010;27:56-62.
15. Lesser IM, Zisook S, Gaynes BN, et al. Effects of race and ethnicity on depression treatment outcomes: The CO-MED trial. Psychiatric Services. 2011;62:1167-1179.
16. Kirmayer LJ, Minas H. The future of cultural psychiatry: an international perspective. Can J Psychiat. 2009;62:112-152.
17. Pi EH, Simpson GM. Cross-cultural psychopharmacology: a current clinical perspective. Psychiatric Services (Washington, D.C.). 2005;56:31-33.
18. Desjarlais R, Eisenberg L, Good B, Kleinman A. World mental health: problems and priorities in low-income countries. New York, NY: Oxford University Press; 1995.
19. Thompson JJ, Ritenbaugh C, Nichter M. Reconsidering the placebo response from a broad anthropological perspective. Cult Med Psychiatry. 2009;112-152.
20. Bhugra D, Ventriglio A. Do cultures influence placebo response? Acta Psychiatr Scand. 2015;132:227-230.
21. Bhugra D, Mastrogiani A. Globalisation and mental disorders. Br J Psychiatry. 2004;184(1):10-20.
22. World Health Organization. The World Health Report 2001. Mental Health: New Understanding, New Hope. WHO; 2001.
23. Patel V, Kleinman A. Poverty and common mental disorders in developing countries. Bull World Health Organ. 2003;69:615-619.
24. Saxena S, Thornicroft G, Knapp M, Whiteford H. Resources for mental health: scarcity, inequity, and inefficiency. Lancet. 2007;370:878-889.
25. Schneider C, Breilmann J, Reuter B, Becker T, Kösters M. Systematic evaluation of the ‘efficacy-effectiveness gap’ in the treatment of depression with venlafaxine and duloxetine. Acta Psychiatr Scand. 2021:https://doi.org/10.1111/acps.13293.
26. Koesters M. The relationship of treatment effects and per capita income of study countries in duloxetine trials in the treatment of depressed patients [Proposal 1250], 2016 [cited 2021 Mar 22]. Available from: https://www.clinicalstudydatarequest.com/Posting.aspx?ID=14402&GroupId=SUMMARIES
27. Stewart LA, Clarke M, Rovers M, et al. Preferred reporting items for systematic review and meta-analyses of individual participant data: the PRISMA-IPD statement. JAMA. 2015;313:1657-1665.
28. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiat. 1960;56-61.
29. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry. 1979;134:382-389.
30. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry. 1961;561-571.
31. GNI, PPP (constant 2011 international $) | Data [cited 2018 Oct 10]. Available from: https://data.worldbank.org/indicator/NY.GNP.MKTP.PP.KD
32. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Chichester, UK: John Wiley & Sons; 2008.
33. Borenstein M. Introduction to meta-analysis. Chichester, UK: John Wiley & Sons; 2009.
34. Becker BJ. Synthesizing standardized mean change measures. Br J Math Stat Psychol. 1988;41(2):257-278.
35. Morris SB, DeShon RP. Combining effect size estimates in meta-analysis with repeated measures and independent-groups designs. Psychol Methods. 2002;7:105-125.
36. Morris SB. Estimating effect sizes from pretest-posttest-control group designs. Organizational Res Methods. 2008;2:364-386.
37. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Soft. 2010;36:1–48.
38. Viechtbauer W, Cheung MW-L. Outlier and influence diagnostics for meta-analysis. Res Synthesis Methods. 2010;1:112-125.
39. Tu Y-K, Maddick IH, Griffiths GS, Gilthorpe MS. Mathematical coupling can undermine the statistical assessment of clinical research: illustration from the treatment of guided tissue regeneration. J Dent. 2004;32:133-142.
40. Li F, Nasir M, Olten B, Bloch MH. Meta-analysis of placebo response in adult antidepressant trials. CNS Drugs. 2019;33:971-980.
41. Leuchter AF, Hunter AM, Tartter M, Cook IA. Role of pill-taking, expectation and therapeutic alliance in the placebo response in clinical trials for major depression. Br J Psychiatry. 2014;205:443-449.
42. Gini C. Variabilità e Mutuabilità: Contributo allo Studio delle Distribuzioni e delle Relazioni Statistiche, C. Cuppini. 1912.
43. Breilmann J, Furukawa TA, Becker T, Koesters M. Differences in the placebo response in duloxetine and venlafaxine trials. Acta Psychiatr Scand. 2018;137:472-480.
44. Rücker G, Schwarzer G. Differences in the placebo response between trials do not necessarily preclude network meta-analysis. Acta Psychiatr Scand. 2018;138:615.

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Klein T, Weinmann S, Becker T, Koesters M. Antidepressant treatment effects and country income: meta-regression analysis of individual participant data from duloxetine trials. Acta Psychiatr Scand. 2021;00:1–11. https://doi.org/10.1111/acps.13337