Placebo and nocebo responses in randomised controlled trials of drugs applying for approval for fibromyalgia syndrome treatment: systematic review and meta-analysis

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W. Haüser received one consultancy honorarium for study design from Daiichi Sankyo;
the other co-authors have declared no competing interests.

ABSTRACT

Objective. *The superiority of true drug treatment over placebo in reducing symptoms of fibromyalgia syndrome (FMS) is small and bought by relevant rates of drop-outs due to adverse events. Recent systematic reviews demonstrated that a substantial proportion of the beneficial and adverse effects of true drug is attributable to placebo in chronic pain trials. We determined the magnitude of the placebo and nocebo response and its impact on the benefits and harms of true drug in trials of drugs which were submitted for approval for treatment of FMS.*

Methods. *CENTRAL, MEDLINE and clinicaltrials.gov were searched from inception to June 30, 2012 for randomised double-blind placebo controlled trials with a parallel design for duloxetine, milnacipran, pregabalin and sodium oxybate in FMS-patients. The magnitude of placebo response was assessed by the pooled estimate of a 50% placebo pain reduction. The magnitude of nocebo response was determined by the pooled estimate of drop-out rates due to adverse events in placebo groups.*

Results. *18 studies with 3546 patients on placebo were included. The pooled estimate of a 50% pain reduction by placebo was 18.6% (95% CI 17.4 to 19.9%). The pooled estimate of drop-out due to adverse events in placebo groups was 10.9% (95% CI 9.9 to 11.9%).*

Conclusions. *The magnitude of placebo and nocebo response in trials of drugs applying for approval for FMS treatment was substantial. Study investigators aim to reduce placebo response. By contrast, clinicians often utilise placebo effects. Strategies to reduce nocebo responses in clinical trials and practice should be developed.*

Introduction

Evidence-based recommendations for the management of fibromyalgia syndrome (FMS) by drugs demonstrate small benefits from true drug compared to placebo, and considerable drop-out rates due to adverse events (1). The US Food and Drug Administration (FDA) approved three drugs (duloxetine, milnacipran and pregabalin) for FMS whereas the European Medical Agency (EMA) refused to license these drugs for FMS because the small benefits did not seem to outweigh the risks (2). Both agencies refused to approve sodium oxybate because of its considerable safety risks (3, 4).

The regulatory agencies did not consider separately the impact of placebo treatment on study results. Recent systematic reviews demonstrated that the efficacy differences between various types of drug treatment and placebo were limited by the magnitude of the response in the placebo group (placebo response) which accounted for approximately 50% of the treatment response in the active drug groups in FMS trials (5). On the other hand, the drop-out rate in placebo groups (nocebo response) in these trials was 13% and accounted for 72% of the drop-out rates in true drug groups (6).

The placebo response is defined to be the reduction in a symptom as a result of factors related to a patient's perception of the placebo intervention (7). The placebo response is determined by the placebo effect (psychological factors such as expectation of benefit, classical conditioning, verbal suggestions, and behaviours manifested by health care providers) as well as by the natural course of disease and by the study design (*e.g.* regression to the mean, uncontrolled parallel interventions). Accurate detection of the placebo effect requires comparison with

a no-treatment control group (8). The nocebo response is defined to be the deterioration of symptoms as a result of factors related to a patient's perception of the placebo intervention. The nocebo response is determined by the nocebo effect (psychological factors such as expectation of harm, classical conditioning, verbal suggestions, and behaviours manifested by health care providers) as well as by the natural course of disease (*e.g.* spontaneous symptom worsening), concurrent other diseases and by the study design (*e.g.* uncontrolled parallel interventions such as adverse events by rescue medication). Nocebo effects could be detected accurately in clinical trials only by means of comparison with a natural history control group (9).

If placebo and nocebo response represent the same or different biological and psychological mechanisms is one of the main questions of basic science (10). Whether placebo and nocebo response are associated in drug trials, and whether they are predicted by the same or different trial- and patient-related characteristics, has not been studied, to our knowledge.

Therefore, in we performed a systematic review to determine:

a. the magnitude of placebo response on pain;
b. the magnitude of nocebo drop-out rate;
c. the amount to which the placebo response accounts for the response in the true drug group for pain, and the amount to which nocebo response accounts for the drop-out rate in the true drug group;
d. the association of placebo response for pain with nocebo drop-out rate;
e. potential trial- and patient moderators of the placebo and nocebo response in randomised controlled studies of the four drugs which were proposed for approval for FMS-therapy: duloxetine, milnacipran, pregabalin and sodium oxybate.

Methods

Protocol

The review was performed according to the PRISMA-statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses (11). Methods of analysis and inclusion criteria were specified in advance.

Study selection

Types of studies. Double-blind randomised controlled trials (RCTs) with a parallel design were included. Studies without randomisation and single blind studies were excluded. Studies with a cross-over design were excluded if placebo response rates were not reported separately for the two stages of the trial. Studies with an enriched enrollment with randomised withdrawal design were excluded because of the potential effects of the study design on placebo effects (12). Crossover studies were excluded from analysis: If placebo is given as the first treatment, one is measuring the effects of suggestion only, whereas if placebo is given as a second treatment one is measuring the effects of both suggestion and conditioning (13).

No language restrictions were made.

Types of participants. Adult (≥18 years) patients with FMS, diagnosed by defined criteria, were included.

Types of interventions. RCTs comparing duloxetine, milnacipran, pregabalin and sodium oxybate (true drug) with pharmacological placebo were included. Studies with non-pharmacological placebos and with pseudo-placebos (active drug without evidence for effectiveness in the disease of interest) were excluded. Studies which combined pharmacological placebo with any other defined treatment, whose effects on pain were tested for, were excluded.

Outcomes measures

Studies should assess patient's ratings of pain intensity. If more than one pain score was used, we preferred the following order for the inclusion into analysis: Pain VAS 0–100, pain NRS 0-100, pain VAS 0–10, pain NRS 0–10, any other pain VAS or NRS. We defined a substantial response by 50% pain reduction (14). We defined discontinuation of therapy because of placebo-attributed adverse events as outcome of nocebo response.

For trials with more than one dosage group of true drug, we pooled the results of the different dosage arms for comparison. If intention-to-treat (ITT) and completer analysis were reported, we used ITT-outcomes.

Literature search

We expanded the search of our systematic review on the magnitude of placebo and nocebo response in drug trials in FMS in the databases MEDLINE, the Cochrane Central Register of Controlled trials (CENTRAL) and the U.S. National Institutes of Health (NIH) (www.clinicaltrials.gov) up to June 31, 2012 (5, 6, 15). We reviewed the reference lists of included articles.

Data collection

Two authors independently screened the titles and abstracts of potentially eligible studies identified by the search strategy detailed above. The full text articles were then examined independently by two authors to determine if they met the inclusion criteria. Discrepancies were rechecked and resolved by consensus.

Two authors independently extracted the data using standard extraction forms developed prior to analysis. Discrepancies were rechecked and consensus achieved by discussion. If needed a third author reviewed the data to reach a consensus. The coding plan included the following items:

– *Trial characteristics*. Data on publication status, year of study initiation, types of recruitment of patients, number of continents and study sites, single blind placebo run-in phase with exclusion of placebo responder, study duration, number and ratio of patients in true drug and placebo arms

– *Patients' characteristics*. Mean age, mean percentage of women, mean percentage of Caucasians.

Where details of study outcomes were missing, attempts were made to obtain these data through contacting the trial authors and pharmaceutical companies who sponsored the trials. If the number of patients with a 50% pain reduction was not reported and not provided by request, they were calculated by the means and SDs of pain scores at baseline and post-treatment by an imputation method with worst case analysis (number of patients at baseline imputed) (16).

Statistical analysis

Descriptive statistics were used to characterise the features of the included trials. Pearson correlations between 50% pain reduction rates and between drop-out rates due to adverse events in true drug and placebo arms for all studies were calculated. Pooled estimates of the placebo response rates, true drug response rates and risk ratios for active drug *versus* placebo were calculated using a random effects model. To test the hypotheses of a subgroup effect, a test of interaction with a predetermined 2-tailed α of 0.05 was used (17).

The calculation of how much the improvement (drop-out rate) in the active drug group was attributed to the placebo (nocebo) response was performed based on the assumption, that the beneficial (harmful) effects of true drug are additive to placebo in case of high correlation between placebo and true drug pain reduction (drop-out rate) by dividing the pooled 50% pain reduction rate (drop-out rate) in placebo group by the ones of true drug group (15).

We decided *a priori* to perform the following subgroup analysis for categorical variables: studies with the four different drugs, studies conducted in North and Middle America *versus* studies conducted in other continents, studies with and without recruitment by media advertisement and studies with and without placebo-run-in excluding placebo responders. These analyses were designed to check potential sources of heterogeneity.

We decided *a priori* to perform the following meta-regression analyses of 50% pain response rates and drop-out rates due to adverse events with the following continuous variables: Study duration, incremental year of study initiation, number of countries and of continents and of study sites, randomisation rate[1] true drug *versus* placebo as study-related characteristics and mean age, mean percentage of women Caucasians as patient-related characteristics.

Meta-regression is a tool used in meta-analysis to examine the impact of moderator variables on study effect size using regression-based techniques. Meta-regression is more effective at this task than are standard regression techniques (18). We used a random-effects model. Tau^2 variance was calculated by the method of restricted maximum likelihood (REML).

The I^2 statistics was used to estimate the percentage of total variation across studies because of heterogeneity (real differences in study patients, design, or outcome definitions) rather than by chance. I^2 values <25% represent low, 25-50% moderate and ≥50% substantial heterogeneity (19).

Because of the exploratory nature of the study we did not adjust for multiple comparisons in subgroup- and meta-regression analyses.

The statistical calculations were performed using SPPS Version 17.0 (SPSS, Inc., Chicago, 2009), Review Manager Software Version 5.1 (The Nordic Cochrane Centre, Copenhagen: The Cochrane Collaboration, 2010) and Stata 12.1 (Stata Corp, College Station TX, 2012).

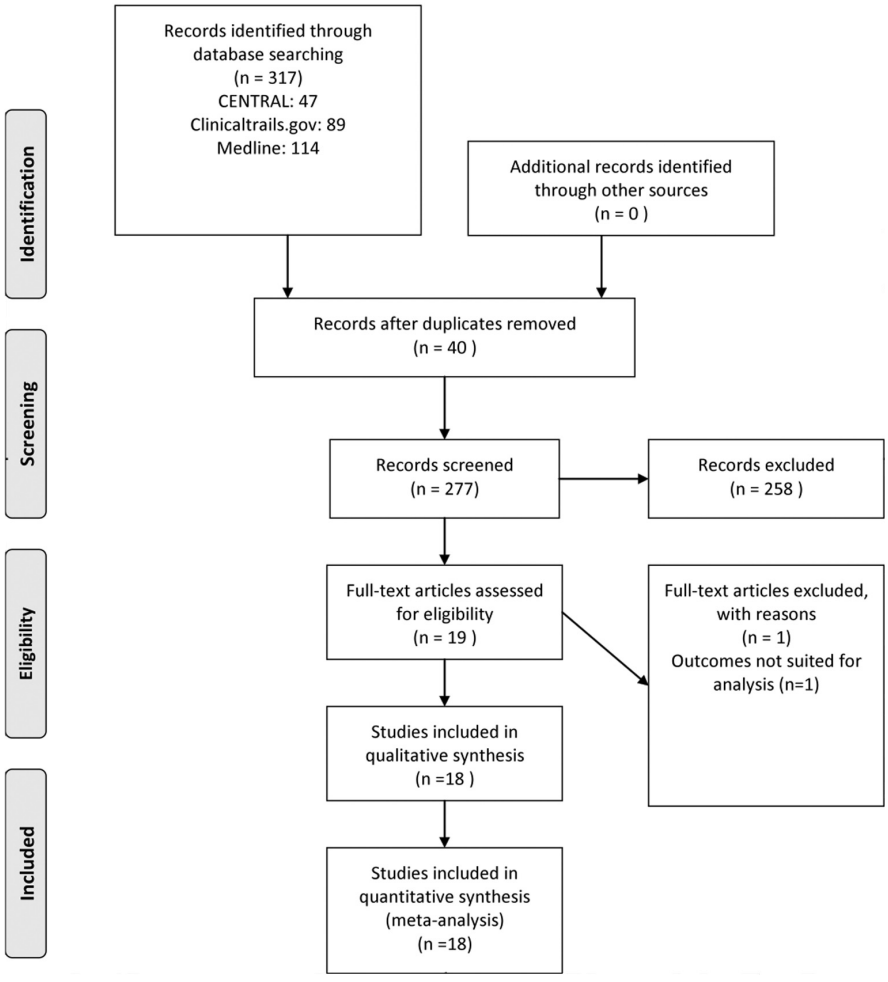

Fig. 1. PRISMA Flow diagram.

Results

Search of literature

317 studies fulfilled the first level of inclusion criteria. After excluding studies based on information presented in study abstracts, 19 complete study reports were considered in more detail. One study was excluded because no pain outcomes were reported. 18 studies met the inclusion criteria and were included into analysis (see Fig. 1 and appendix reference).

[1]Randomisation rate: Patients have to be informed in RCTs on the probability to receive the true drug. The chance to be treated by true drug in the studies analysed can be derived from the number of patients in all trued drug arms *versus* the number of patients in placebo arm. We assumed that placebo and nocebo responses will be higher in studies with higher probability than 50% to be treated with true drug.

Table I. Study and patient characteristics of included studies.

First author (reference)	Drug	Study duration (weeks)	Year study initiation	Number of countries	Number of study sites	Recruitment	Exclusion of placebo responder	Mean age (placebo)	Percentage of females (placebo)	Percentage of Caucasian (placebo)	Patients on true drug	Patients on placebo
Arnold 2004	Duloxetin 120 mg/d	12	2001	1 (USA)	18	Referral and advertisement	NR	49,9	88,5	88,5	104	103
Arnold 2005	Duloxetin 60 or 120 mg/d	12	2002	1 (USA)	21	Referral and advertisement	No	50,5	100	89,6	118 (60 mg/d) 116 (120mg/d)	120
Arnold 2010	Duloxetine flexible 60 or 120mg/d	24	2008	2 (USA, Canada)	48	Referral and advertisement	No	50,7	92,8	89,3	263	267
Chappell 2008	Duloxetine flexible 60 or 120mg/d	27	2005	5 (USA, Germany, Spain, Sweden, UK	36	Referral and advertisement	No	50,8	91,9	92,6	162	168
Russell 2008	Duloxetine 20 to 60 or 60 mg/d or 120mg/d	26	2005	2 (USA, Puerto Rico)	38	Referral and advertisement	No	51,4	84,6	94,8	79 (20/60mg/d) 150 (60 mg/d) 147 (120mg/d)	144
Arnold 2010	Milnacipran flexible 60 or 120mg/d	24	2008	2 (USA, Canada)	48	Referral	No	49,1	96,9	91,9	263	267
Branco 2010	Milnacipran 200 mg/d	17	2006	13 West- and East European countries	89	Referral	No	48,3	95,1	98	430	446
Clauw 2008	Milnacipran 100 or 200 mg/d	15	2004	1 (USA)	86	Referral	No	50	97	93,5	399 (100mg/d) 396 (200mg/d)	401
Mease 2009	Milnacipran 100 or 200 mg/d	27	2003	1 (USA)	59	Referral	No	49,4	95,6	93	224 (100mg/d) 441 (200mg/d)	223
Vitton 2004	Milnacipran 200 mg/d (once or twice)	12	2001	1 (USA)	12	Referral	No	46,8	98	85,5	46 (once) 51 (twice)	28
Arnold 2008	Pregabalin 300 or 450 or 600mg/d	14	2005	1 (USA)	84	Referral and advertisement	Yes	50,4	90,2	91,2	183 (300mg/d) 190 (450mg/d) 188 (600mg/d)	184
Crofford 2005	Pregabalin 150 or 300 or 450mg/d	8	1999	1 (USA)	40	Referral and advertisement	No	48,2	91,8	92,6	132 (150mg/d) 134 (300mg/d) 132 (450mg/d)	131
Mease 2008	Pregabalin 300 or 450 or 600mg/d	13	2004	1 (USA)	79	Referral and advertisement	No	48,8	93,7	91	185 (300mg/d) 183 (300mg/d) 190 (600 mg/d)	190
Pfizer 2012	Pregabalin flexible 300 to 450 mg/d	14	2009	1 (Japan)	44	Referral and advertisement	Yes	47,9	90,4	0	251	250
Pauer 2011	Pregabalin 300 or 450 or 600mg/d	14	2006	18 (All continents)	73	Referral and advertisement	Yes	48,8	91,4	75,2	187 (200mg/d) 184 (450mg/d) 187 (600mg/d)	189
Russell 2009	Sodiumoxy-ate 4.5 or 6 g/d	8	2004	1 (USA)	21	Referral	No	46,9	94,4	94,6	58 (4.5g/d) 66 (6 g/d)	64
Russell 2011	Sodiumoxy-ate 4.5 or 6 g/d	14	2006	1 (USA)	74	Referral	No	47,5	91,3	94,6	182 (4.5g/d) 183 (6 g/d)	183
Späth 2012	Sodiumoxy-ate 4.5 or 6 g/d	14	2007	8 (USA and 7 European countries)	108	Referral	No	46,5	89,6	91,1	195 (4.5g/d) 190 (6g/d)	188

Study characteristics

Data are given as mean and range if not otherwise indicated. 5 studies each with duloxetin, milnacipran and pregabalin and 3 studies with sodiumoxybate were included. 12 studies were conducted in North America, two in North/Central America, two in North America/USA, one each in Asia (Japan) and in all continents. The study duration was 14 (8-27) weeks. The number of study sites was 48 (12-108).

Patients were recruited by referral and media advertisements in studies with duloxetine and pregabalin and by referral for studies with milnacipran and sodium oxybate. Three studies reported to have excluded placebo responders identified by single-blind placebo run in phase. The trials included a total of 3546 patients in placebo and 6589 patients in all arms of true drug groups. Studies included a total of patients as follows: Duloxetine 1941, milnacipran 4118, pregabalin 2987 and sodium oxybate 1308 patients. The average number of patients in all placebo groups was 186 (28 to 446) and in all arms of the true drug groups 370 (97 to 795). The mean age in the placebo groups was 49 (47 to 51) years. The mean percentage of females was 93.5 (89 to 100) and of Caucasians 91 (0 to 94) in placebo groups (Table I).

50% pain reduction rates

The pooled estimate of a 50% pain reduction by placebo was 18.6% (95% CI 17.4 to 19.9%). I^2 was 49.8% (95% CI 13.6 to 70.9). The pooled estimate of a 50% pain reduction by true drug was 31.6% (95% CI 30.5 to 32.7). I^2 was 86.9% (95% CI 80.7 to 91.1). The relative risk of a 50% pain reduction true drug *versus* placebo was 1.60 (95% CI 1.48 to 1.74). I^2 was 0 (95% CI 0 to 50) (Fig. 2). The Pearson correlation between the 50% pain reduction rates in true drug and placebo groups was small and not significant (r=0.37, p=0.07). Therefore we did not calculate how much placebo response accounted for pain reduction in true drug groups. After excluding the three studies which excluded placebo-responders by single-blind run in phase, Pearson correlation between the 50% pain reduction rates in true drug and placebo groups was medium and significant (r=0.55, p=0.02). 155/1053 (14.7%) of the patients reported a 50% pain reduction by placebo in the three studies which had excluded placebo-responders by single-blind run in phase. 599/3139 (19.1%) the patients reported a 50% pain reduction by placebo in the 15 studies without exclusion of placebo-responders by single-blind run in phase (χ^2=10.1, p=0.001).

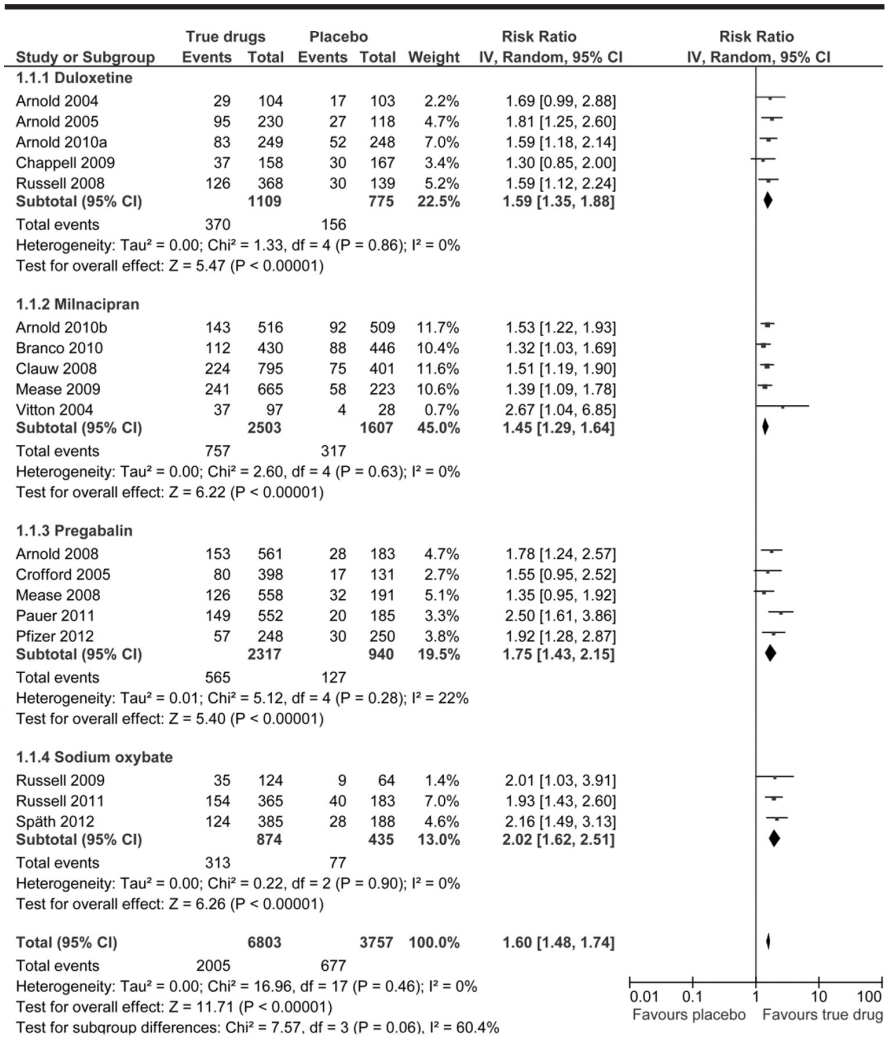

Fig. 2. Forest plot of relative risk 50% pain reduction true drug *versus* placebo.

Drop-out rate due to adverse events

The pooled estimate of drop-out due to adverse events by placebo was 10.9% (95% CI 9.9 to 11.9%). I^2 was 10.9% (95% CI 1.4 to 47.1). The pooled estimate of drop-out due to adverse events by true drug was 20.4% (95% CI 19.5 to 21.4%). I^2 was 72.0% (95% CI 55.2 to 82.6). The relative risk of a drop-out due to adverse events true drug *versus* placebo was 1.92 (95% CI 1.65 to 2.24). I^2 was 43% (95% CI 0-66) (Fig. 3). The Pearson correlation between the drop-out rates due to adverse events in true drug and placebo groups was small and not significant (r=0.26, p=0.14). Therefore we did not calculate how much of the nocebo response accounted for drop-out rates due to adverse events in true drug groups. After excluding the three studies which excluded placebo-responders by single-blind run in phase, Pearson correlation between the drop-out rates due to adverse events in true drug and placebo groups was still small and not significant (r=0.39, p=0.08).

Association between placebo and nocebo response

The Pearson correlation between placebo and nocebo response was not

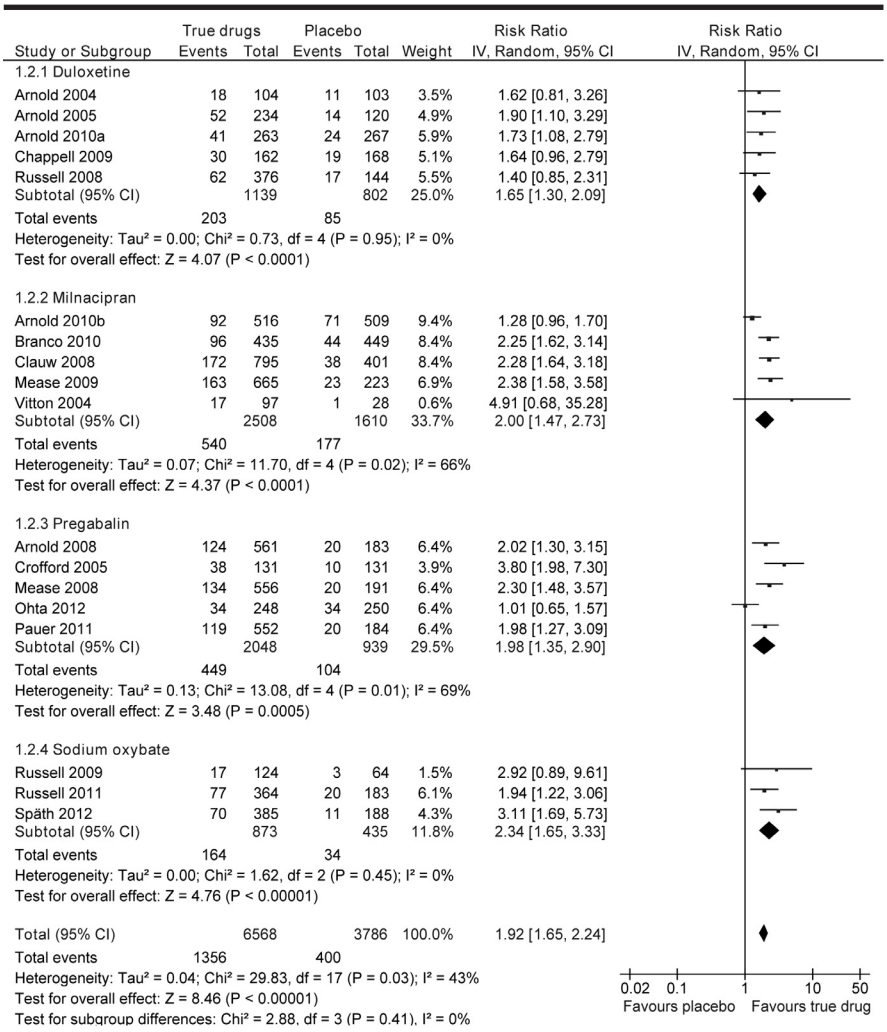

Fig. 3. Forest plot of relative risk of drop-out due to adverse events true drug *versus* placebo.

substantial (r=0.27) and not significant (p=0.13). After excluding the three studies which excluded placebo-responders by single-blind run in phase, the Pearson correlation between placebo and nocebo response was medium (r=0.61) and significant (r=0.009).

Subgroup analyses

Four drugs: 50 % pain reduction

There was no significant overall difference between the four drugs in the relative risk of a 50% pain reduction true drug *versus* placebo (p=0.06) (Fig. 2).

Four drugs: drop-out rates due to adverse events

There was no significant overall difference between the four drugs in the relative risk of drop-out due to adverse events for true drug *versus* placebo (p=0.41) (Fig. 3).

Single blind placebo run-in phase and by type of advertisement

The RR of a 50% pain reduction true drug *versus* placebo was higher in studies which excluded placebo-responders during single blind run-in phase than in studies without this procedure (p=0.03) (see Table II). There were significant differences between studies with and without recruitment by media advertisement in the relative risk of a 50% pain reduction true drug *versus* placebo. Studies with and recruitment by media advertisement and referral had a lower risk in the relative risk of drop-out due to adverse events true drug *versus* placebo than studies with recruitment by referral only (p=0.05) (Table II).

Metaregression analyses

By univariate meta- regression analysis, the log of the pooled estimate of a 50% placebo pain reduction was positively associated with study duration (p=0.003) and with mean percentage of women (p=0.001) and Caucasians (p=0.04) and negatively associated with number of continents (p=0.03) (Table III).

The logs of the pooled estimate of a 50% pain reduction by true drug and of drop-out due to adverse events in placebo and true drug groups were not significantly associated with any of the study- and patient-related variables (Tables III and IV).

Discussion

Principal findings

The meta-analysis of 18 studies with the four drugs that had applied for approval for FMS-treatment, namely duloxetine, milnacipran, pregabalin and sodium oxybate included 3 546 patients in placebo groups and 6 589 patients in true drug groups. The pooled estimate of a 50% pain reduction by placebo was 18.6% (95% CI 17.4 to 19.9%). The pooled estimate of drop-out due to adverse events in placebo groups was 10.9% (95% CI 9.9 to 11.9%). The pooled estimates of a 50% pain reduction and of drop-out due to adverse events by placebo and true drug were not significantly correlated. Placebo and nocebo responses were not significantly correlated. Placebo pain response was positively associated with study duration and percentage of Caucasian and women and was negatively associated with number of continents. Nocebo response was not significantly associated with study- and patient-related characteristics.

Relation to other studies

In a previous systematic review which searched the literature until December 2010 and included all types drug trials in FMS with a parallel design and study duration ≥12 weeks, the pooled estimate of a 50% pain reduction by placebo was 18.8 (95% CI 17.5 to 20.1) %. 30 studies with 3846 patients on placebo were analysed (5). The placebo response rate was comparable to the one of this review.

In a previous systematic review which searched the literature until December

Table II. Subgroup analysis of the pooled relative risk of the 50% pain reduction rate and of the drop-out rate due to adverse events true drug *versus* placebo groups in fibromyalgia syndrome (FMS).

Outcome: RR 50% pain reduction				
Moderator	Number of studies	Pooled % (95% CI)	Heterogeneity I^2 % (95% CI)	*p*-value of test of interaction
Exclusion of placebo responder by single blind run-in phase				
Yes	3	2.01 (1.59 to 2.53)	82.6 (46.7 to 94.3)	**0.03**
No	15	1.56 (1.43 to 1.70)	0 (0 to 53.1)	
Recruitment				
Advertisement and referral	10	1.66 (1.47 to 1.88)	0 (0 to 67.6)	0.56
Referral	8	1.59 (1.40 to 1.80)	14.3 (0 to 55.6)	
Outcome: RR drop-out rate due to adverse events				
Recruitment				
Advertisement and referral	10	1.80 (1.47 to 2.20)	0 (0 to 62.4)	**0.05**
Referral	8	2.07 (1.68 to 2.54)	71.7 (41.7 to 86.2)	

Table III. Study- and patient-related predictors of a ≥50% pain reduction in placebo and true drug groups in drug trials of fibromyalgia syndrome by univariate metaregression analyses.

	Placebo		True drug	
Predictor	Coef. (B)	Unad-justed *p*	Coef. (B)	Unadjusted *p*
Study duration	0.20	**0.003**	0.005	0.53
Incremental year study initiation	- 0.11	0.61	0.60	0.83
Number of continents	- 0.14	**0.03**	0.67	0.23
Number of countries	- 0.01	0.23	0.51	0.26
Number of study sites	- 0.006	0.80	-0.005	0.82
Randomisation rate true drug *vs*. placebo	- 0.005	0.94	0.905	0.40
Mean age	0.07	0.06	0.001	0.98
Mean percentage of women	0.06	**0.001**	0.008	0.60
Mean percentage of Caucasians	0.05	**0.04**	0.002	0.44

2010 and included all types drug trials in FMS with a parallel design the pooled estimate of drop-out due to adverse events in placebo groups was 9.6 (95% CI 8.6-10.7) %. 58 studies with 5065 patients were analysed (6). The nocebo drop-out rate was similar to the one of this review.

The Pearson correlation between the 50% pain reduction rates in true drug and placebo groups of this review was small (r=0.37). In contrast the Pearson correlation between average pain reduction in true drug and placebo groups of a previous review was moderate (r=0.69) (15). We conclude that placebo response accounts more for average pain reduction than for substantial pain reduction. The results of this review support the assumption of Rappaport *et al*. (20) that placebo responders differ from drug responders, therefore indicating that the mechanisms of improvement under placebo might differ from the mechanisms of improvement under active treatment. In addition, the moderators of placebo and nocebo response might be different (10) because the correlation between placebo and nocebo responses were not significant in this systematic review.

Our previous review did not find a significant association between patient-related predictors (mean age, mean percentage of women and Caucasians) and placebo response on pain (5). This review found a significant association between placebo response in pain and female sex.

Most notably, placebo response in duloxetine-, milnacipran-, pregabalin- and sodium oxybate was positively associated with study duration. A review on postherpetic neuralgia and pain diabetic peripheral neuropathy clinical trials found no decrease of placebo response over time (21). We conclude that long-lasting pain reductions can be achieved in the context of a randomised controlled trial by placebo in some patients.

Mean age, mean percentage of women and incremental year of study initiation were associated with nocebo drop-out in our previous review including all drugs tested (6). We did not find these associations in duloxetine-, milnacipran-, pregabalin- and sodium oxybate trials. The differences in the year of study initiation and composition of study samples might explain these differences: The previous review included studies which had been conducted between 1980-2000 (5). The studies with duloxetine, milnacipran, pregabalin and sodium oxybate were conducted between 2000-2010 and included more male patients than the studies of the previous review (5) (no details reported).

Of note, neither placebo response nor nocebo drop-out were associated with randomisation rate true drug *versus* placebo in this review. We had expected higher placebo response and nocebo drop-out in trials in which the patients had a chance of >50% to receive true drug.

The benefits and harms of placebo treatment (placebo and nocebo responses) gained increasing attention by clinical researchers, drug companies and by clinicians, but for divergent reasons. Clinical researchers and drug companies wish to reduce the placebo response, because negative results of some placebo-controlled trials in chronic neuropathic pain syndromes had been attributed to unexpectedly large reductions of pain intensity in placebo groups that compromised the ability to show significant greater improvements with active medication (23). Drug companies try to identify modifiable trial characteristics to enhance the ability to detect benefits of pharmacological treatments, *e.g*. by excluding placebo responders identified in a single-blind placebo run-in phase. This review demonstrated that

single blind placebo run-in phases over 1–2 weeks with the exclusion of placebo responders reduce the rates of placebo responder.

Table IV. Study- and patient-related predictors of drop-out rate due to adverse events in placebo and true drug groups in drug trials of fibromyalgia syndrome by univariate meta-regression analyses.

	Placebo		True drug	
Predictor	Coef. (B)	Unadjusted *p*	Coef. (B)	Unadjusted *p*
Study duration	0.01	0.19	0.005	0.60
Incremental year study initiation	0.04	0.06	0.005	0.83
Number of continents	-0.02	0.80	0.07	0.23
Number of countries	-0.007	0.51	0.008	0.48
Number of study sites	-0.003	0.13	-0.0004	0.82
Randomisation rate true drug *vs*. placebo	-0.06	0.29	0.05	0.40
Mean age	-0.03	0.40	0.001	0.98
Mean percentage of women	-0.002	0.94	0.008	0.60
Mean percentage of Caucasians	-0.003	0.18	0.002	0.44

Limitations

How much regression to the mean and spontaneous improvement contributed to placebo response and how much spontaneous deterioration contributed to nocebo response could not be assessed, because the studies did not include an observation (no treatment) arm. However, an analysis of 30 RCTs (1414 patients) of diverse non-pharmacological treatments of FMS demonstrated that the change from baseline to final treatment of the outcome pain in study arms with usual care was nearly zero (Häuser *et al*. submitted). Therefore regression to the mean or spontaneous improvements are unlikely to happen in FMS-patients participating in clinical studies.

We used study-level variables for the meta- regression analysis. Thus the sensitivity of the analysis may be lower than it should be. An analysis of individual patient data was not possible.

Our data on placebo and nocebo response rates are restricted to RCTs with a parallel design.

We might have underestimated nocebo response, because we did analyse only nocebo drop-out rates and not the frequency of specific adverse events in placebo groups (*e.g*. dizziness) without dropping out the study.

We could not assess the potential impact of patients' treatment expectations and of the quality of verbal suggestions manifested by healthcare providers because these contextual factors affecting placebo and possibly nocebo response (22) were not assessed in the studies analysed.

Implications for clinical practice and trials

Clinical investigators wish to reduce placebo response. In contrast, clinicians are interested in using placebo effects. The use of placebo treatment had been promoted by editorials (24, 25). Most physicians confess to use placebo in clinical practice (26). However, we do not know if placebos will work as well outside the context of a RCT in FMS. In addition, ethical concerns had been raised on the use of placebo in clinical practice (27). Regardless of these uncertainties and controversies, unspecific (placebo) effects of communication such as a warm and empathic interaction style should be used in every type of medical treatment (28).

Both clinicians and principal investigators are interested to reduce the nocebo response because both wish patients to adhere to medication. Nocebo responses can be induced by the informed consent disclosure relating to the side effects of study treatments (10). Systematic reviews on adverse events in trials with migraine medication (13) and antidepressants (29) demonstrated that the types and frequency of adverse events depended of which type of adverse events patients and clinicians expected to happen. Dizziness and somnolence were the most frequent adverse events in the studies with duloxetine, milnacipran, pregabalin and sodium oxybate (details not shown). If a patient reports dizziness in a drug trial of FMS it is difficult to decide if this symptom is due to the drug tested, to the use of co-medication (*e.g*. oxycodone was used as rescue medication in milnacipran trials), to comobidity (*e.g*. depression) or to "fibro fog". Using a structured assessment for identifying symptoms frequently reported by patients and general population controls (*e.g*. dizziness) at baseline and during treatment (30, 31) could help to differentiate potential causes of adverse events. In a study with St. John's Wort and citalopram in minor depression both drugs were associated with a significant number of new or worsening adverse events during treatment. A structured assessment prior to the administration of study compound revealed that 60% of subjects endorsed items that would be characterised as adverse events once study compound was administered (30).

The full information of patients on all potential adverse events is inevitable for clinical trials. Recent recommendations on improving assay sensitivity in chronic pain trials (32) and structured assessment of adverse events (21) could at least minimise the high heterogeneity of nocebo drop-outs which we found in this review.

Recently, a discussion has been started how to reduce nocebo effects in clinical practice during information on drug therapies (10, 33). In general, medical interventions should be accompanied by a reassuring, empathetic, and supportive communication. Potentially promising methods of reducing nocebo effects include strategies of framing information (by focussing on tolerability), authorised concealment of side effects by the patient, educating patients about the possibility of nocebo responses and rapid consultation on bothersome symptoms, *e.g*. by a telephone or e-mail hotline (10, 33).

Adequate and continuous communication with FMS-patients during drug therapy is advisable to increase their placebo responses and to reduce their nocebo responses. This approach might contribute to cost-effectiveness of FMS-drug treatment. A recent observational prospective Spanish multicentre study

demonstrated that treated patients improved their clinical status which was accompanied by a significant reduction in the cost of the illness. The extra cost of drugs was substantially compensated for by less use of other healthcare resources and fewer days off work (34).

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