Adverse Events Attributable to Nocebo in Randomized Controlled Drug Trials in Fibromyalgia Syndrome and Painful Diabetic Peripheral Neuropathy

Systematic Review

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Objective: The objectives of the study were to determine the impact of nocebo effects on adverse events (AEs) in drug trials in fibromyalgia syndrome (FMS) and painful diabetic peripheral neuropathy (DPN).

Methods: MEDLINE, CENTRAL, SCOPUS, and the databases of the U.S. National Institutes of Health and the Pharmaceutical Research and Manufacturers of America were searched until December 31, 2010. Randomized controlled trials with a parallel design of any drug therapy compared with pharmacological placebo in patients with FMS and DPN were included. Pooled estimates of nocebo effects (number of patients with at least 1 AE and dropping out due AEs) were calculated for placebo and true drug groups by a random effects model.

Results: Fifty-eight FMS (62 DPN) trials included a total of 5065 (5095) patients in placebo groups. The quality of reporting the assessment strategy of AEs was poor in most trials. The pooled estimate of the event rate drop out rate due to AEs in placebo groups was 9.6 [95% confidence control (CI): 8.6-10.7] in placebo and 16.3 (95% CI: 14.1-31.2) in true drug groups of FMS trials and was 5.8 (95% CI: 5.1-6.6) in placebo and 13.2 (95% CI: 10.7-16.2) in true drug groups of DPN trials. Nocebo effects accounted for 72.0% (44.9) of the drop outs in true drug groups in FMS (DPN).

Discussion: Nocebo effects substantially accounted for AEs in drug trials of FMS and DPN. Standards to assess and report AEs should be defined by regulatory agencies. Strategies to minimize nocebo effects in both clinical trials and clinical practice should be developed.

Key Words: nocebo, fibromyalgia syndrome, painful diabetic peripheral neuropathy, systematic review, meta-analysis

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Valid information about adverse events (AEs) is crucial for determining the benefit-risk ratio for a given medication. Clinical decisions on drug use should depend not only on drug efficacy but also depend on drug safety and tolerability.[1] Safety implies AEs with organ damage such as hepatic toxicity assessed by objective tests. Tolerability involves AEs that are reported by the patient and are considered to be irritating such as dizziness and nausea but not associated with organ damage.[2] Irritating (subjective) AEs influence patient behavior in terms of medication adherence and drug discontinuation.[3]

Subjective AEs are examined in double-blind, randomized, controlled trials (RCTs) by comparing the symptoms reported by patients in "true" drug-treated groups with those reported by patients in placebo groups. The assumption is that symptoms found in true drug-treated groups result from a combination of specific pharmacological effects and nonspecific effects that also occur in the placebo groups. These nonspecific negative effects of placebos are termed the "nocebo effect."[1,4]

The nocebo effect is explained by patient-related psychological factors such as negative expectations, conditioning of adverse reactions on medication, and personality traits (eg, somatization, anxiety) and contextual factors such as negative suggestions of the physician.[4,5] Moreover, the ascertainment strategy of AEs influences the tolerability profile of drugs.[1,2]

To our knowledge, the question to which amount AEs in drug trials in pain medicine are determined by nocebo effects had not been studied. Only a few studies addressed the magnitude and putative predictors of nocebo effects in drug trials of migraine. In studies on acute migraine treatment in adults, a mean of about 23% patients reported at least 1 AE after placebo. The rate of AEs in placebo groups was higher in studies performed in North America than in Europe.[6] In migraine trials, the type of AEs in placebo arms depended on the AEs of true medication against which the placebo was compared. No associations between side effects in placebo groups and some study-related (sample size, publication year) and patient-related (sex, age, weight, race, type of migraine, migraine frequency) characteristics were found.[7,8] Migraine patients under triptans reported more AEs in a prompted questionnaire compared with an unprompted questionnaire.[2]

The impact of nocebo effects on AEs and its patient-related and study-related predictors in drug trials of other chronic pain conditions such as fibromyalgia syndrome (FMS) and painful peripheral diabetic neuropathy (PDN) had not been studied. The purposes of this review therefore were:

- To determine to which amount nocebo effects accounted for AEs in the true drug groups
- To test for patient-related and study-related characteristics associated with nocebo effects
- In RCTs of drug therapy in patients with FMS and painful PDN.

METHODS

Hypotheses

Patient Characteristics

Due to the limited findings in the literature, we had no a priori hypotheses on the impact of age, sex, and race on nocebo effects. We hypothesized that nocebo drop out rates will be higher in FMS than in painful diabetic peripheral neuropathy (DPN). Somatization had been assumed to be associated with nocebo effects [4] and had been described to be a main feature of FMS.[9]

Study-related Characteristics

We had no a priori hypothesis on the impact of year of study initiation on nocebo effects because of divergent results on nocebo effects in migraine[7] and multiple sclerosis[3] trials. We hypothesized that treatment duration would be associated with nocebo effects as shown in multiple sclerosis trials.[3] We expected higher rate of nocebo effects in studies with centrally acting agents (antidepressants, anticovulsants) than in studies with other medication.[10] We assumed that the incidence of nocebo effects would be higher in trials with structured assessment of side effects than in studies with spontaneously reported or observed side effects as shown in studies with statins, antidepressants, and migraine.[1,2,11]

Protocol

The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[12] and the recommendations of the Cochrane Collaboration.[13] Methods of analysis and inclusion criteria were specified in advance (review protocol available on request).

Data Sources and Searches

Painful DPN

We used the search strategy of the guideline of the National Institute for Clinical Excellence on pharmacological management of neuropathic pain[14] for MEDLINE. The search strategy was adapted to SCOPUS, the Cochrane Central Register of Controlled trials (CENTRAL), websites of the U.S. National Institutes of Health (www.clinicaltrials.gov) and the Pharmaceutical Research and Manufacturers of America (www.clinicalstudyresults.org). The search was conducted until December 31, 2010.

FMS

We expanded our searches used for the German interdisciplinary guideline on the management of FMS[15] in the electronic bibliography databases, detailed above, until December 31, 2010. Details of the search strategy had been outlined in a recent publication.[16] Both search strategies are presented in Supplemental Table 1 (Supplemental Digital Content 1, http://links.lww.com/CJP/A28).

For both conditions, we reviewed the reference lists of included studies. Two authors independently screened the titles and abstracts of potentially eligible studies identified by the search strategy detailed above. The full text studies were then examined independently by 2 authors to determine whether they met the inclusion criteria. Discrepancies were rechecked and resolved by consensus.

Selection

Types of Studies

Double-blind RCTs with a parallel design were included. Studies without randomization, single blind, and single session studies were excluded. Studies with an enriched enrollment and consecutive randomized withdrawal design were excluded because of the potential effects of the study design on placebo and thus potentially on nocebo effects.[17] 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.[7]

Types of Participants

Patients with painful PDN and FMS, diagnosed by defined criteria, were included. We excluded studies in which PDN was mixed with other neuropathic pain syndromes if no separate data for DPN were reported.

Types of Interventions

RCTs comparing any type of pharmacological medication with pharmacological placebo were included. Studies with nonpharmacological placebos and with pseudoplacebos (pharmacodynamically active substance without evidence for effectiveness in the disease of interest) were excluded. Studies that combined pharmacological placebo with any other defined treatment, whose effects on pain were tested for, were excluded. Study duration should be at least 2 weeks.

Types of Outcomes Measures

The outcome measures for nocebo effects were the number of patients with at least 1 AE of any type (light, moderate, and severe) and the drop out rate due to AEs in placebo and true drug group for each study.[3] For inclusion, studies should report at least 1 of these 2 outcomes.

Data Abstraction

A structured coding plan was developed before the analysis. Two investigators independently extracted the data of all studies detailed below using standard extraction forms. Discrepancies were rechecked and consensus achieved by discussion. If needed a third investigator reviewed the data to reach a consensus. The coding plan included the following items.

Outcomes

We examined the incidence of the number of patients with at least 1 AE and drop out rates (total and due to AEs) in placebo and true drug groups of each trial. For trials with more than 1 dosage group of true drug, we chose the group with the highest dosage for comparison.

Patient Characteristics

Mean age, sex (percentage of females), and race (percentage of Caucasians) of the study participants were extracted.

Study Characteristics

The following variables were collected: year of initiation (if unavailable, estimated as 3 years before publication)[18] and publication of the study; sponsoring by pharmaceutical company (if support was not mentioned, we checked the acknowledgement sections and the affiliations of the authors for study support by pharmaceutical companies); continent in which the study took place (Europe, North America, Asia, mixed continent samples); number of study sites (if not reported, we chose the number of clinical institutions of the author list); type of active medication (antidepressants, anticonvulsants, other); application of medication (oral, topical, parenteral); approval by the Food and Drug Administration for FMS, respectively, painful DPN; total sample sizes in true drug and placebo group; treatment duration in weeks; publication status (peer reviewed journal versus only available in database); assessment strategy of AEs (structured assessment, observations, spontaneous reports, combination of assessment methods).

Validity Assessment

Two investigators independently collected the reported quality assessment of reports of randomized clinical trials in terms of Jadad scores, considering the description and sequence of randomization, the double-blind procedure, the appropriateness of randomization and double-blinding procedures, and the description of withdrawals and dropouts (range, 0 to 5).[19] Discrepancies were rechecked and resolved by consensus and if needed by a third investigator. Interrater reliability for study characteristics and validity characteristics were computed.

Dealing with Missing Data

Where details of study outcomes were missing, attempts were made to obtain these data through contacting 74 trial authors. Additional data were provided by 12 authors. We did not ask for not reported details of study design (eg, method of randomization, identity of active drug and placebo, type of AE assessment) because we were unable to receive these details of conducted before 2000 in previous systematic reviews on antidepressants in FMS.[20]

Risk of Bias in Individual Studies

The risk of bias in individual studies was assessed by summarizing the study quality in the Jadad score.[19]

Statistical Analysis

Descriptive statistics were used to characterize the features of the included trials. Nonparametrical tests were used for the comparison of continuous variables and χ^2 tests for the comparison of categorical variables. Correlations between continuous variables were calculated by Pearson correlation coefficients. A 2-sided P value of ≤ 0.05 was considered significant.

Pooled estimates of event rates of AEs in placebo and true drug groups and risk ratios for the combined studies were calculated using a random effects model.[20] Metaregression analyses were performed to determine whether linear relations exist between patient-related (mean age, percentage of women and of Caucasians of study participants) and study-related (incremental year of study initiation, study quality) characteristics (independent variables) and the logit rate of AEs in placebo groups (dependent variable). Metaregression used the random effects model. Tau square variance was calculated by the method of maximum likelihood.

To test the potential impact of categorical variables (types of assessment of AEs), a test of interaction with a predetermined 2-tailed α of 0.05 was used.[21] The I^2 statistics was used to estimate the percentage of total variation across studies because of heterogeneity, rather than by chance (ie, the percentage of variability of associations across studies that is not due to chance or random error, but rather due to real differences in study patients, design, or outcome definitions). I^2 values of $< 25\%$ represent low, 25% to 50% moderate, and $\geq 50\%$ substantial heterogeneity.[13]

Publication bias was assessed first by drawing a funnel of standard error of the relative risk of drop out due to AEs in true drug versus placebo group. In addition, the Egger intercept test[22] and the Begg rank correlation test[23] were performed at the significance level $P < 0.05$. We a priori decided to metaregress the relative risks of the pooled estimates of AEs in placebo group with the Jadad score. The statistical calculations were performed using SPPS version 17.0 (SPSS, Inc., Chicago, 2009) and Comprehensive Metaanalysis version 2.0 (Biostat, Englewood, 2010).

RESULTS

Search of Literature

One thousand two hundred fifty-one in FMS and 1034 studies in painful DPN different studies fulfilled the first level of inclusion criteria. After excluding studies based on information presented in study abstracts, 86 complete study reports were considered in more detail in FMS and 84 in

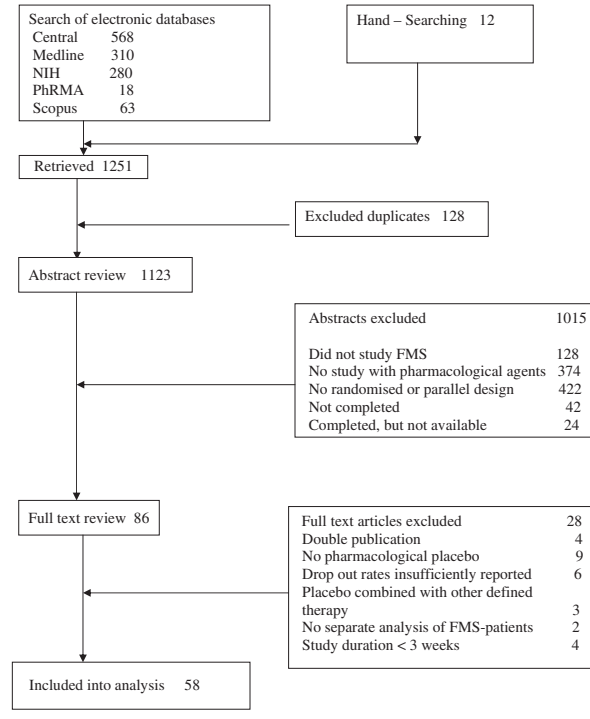

FIGURE 1. Flow diagram on numbers of publications screened and included (fibromyalgia syndrome). FMS indicates fibromyalgia syndrome; NIH, National Institutes of Health; PhRMA, Pharmaceutical Research and Manufacturers of America.

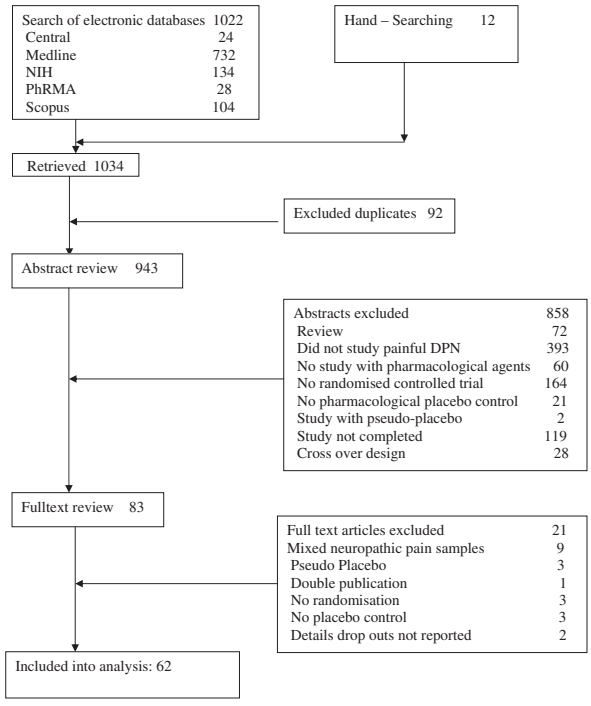

FIGURE 2. Flow diagram on numbers of publications screened and included (painful DPN). DPN indicates diabetic peripheral neuropathy; NIH, National Institutes for Health; PhRMA, Pharmaceutical Research and Manufacturers of America.

painful DPN. The final sample size consisted of 58 studies in FMS and 62 in painful DPN (Figures 1 and 2 and Supplemental Digital Content 2, http://links.lww.com/CJP/A29, and Supplemental Digital Content 3, http://links.lww.com/CJP/A30 [Reference lists of included and excluded studies by full-text review]).

Study Characteristics

Study Design and Patient Characteristics

A total of 5027 patients in placebo and 5065 patients in true drug group of FMS trials were included into analysis. A total 5086 patients in placebo and 5296 patients in true drug groups of DPN trials were included into analysis. There were no significant differences in the year of study initiation, publication status, approval status by the Food and Drug Administration for FMS painful DPN, respectively, types of application of medication, sample size in true drug group and baseline pain scores of patients on placebo between the 2 diseases. Trials with painful DPN significantly included more study sites and countries, were more frequently conducted in mixed continent samples, used more frequently anticonvulsants and less antidepressants, had greater sample sizes in placebo groups and included more older, male and non-Caucasians patients than FMS trials (Table 1). The characteristics of each study for which data were extracted are presented in Tables 2 and 3.

Assessment Strategy of AEs

Twenty-two of 58 (37.9%) of FMS-trials reported some details of the assessment strategy. In 10 studies, AEs were assessed by a combination of spontaneous reports and exploration and observation. Three of these studies indicated that the observation/exploration was performed by the investigator. Five studies relied on spontaneous reports, 6 on exploration (of which 2 reported the use of a checklist) and 1 on a structured interview.

Fourteen of 62 (22.6%) of the DPN trials reported some details of the assessment strategy. In 2 studies, AEs were assessed by a combination of spontaneous reports and exploration and observation. Nine studies relied on spontaneous reports, 2 on exploration, and one on a structured interview (Tables 2 and 3).

Reported Study Quality

The means of the Jadad score did not differ between FMS and painful DPN trials (Table 1).

Validity Assessments

The interrater reliability for the assessments of the study sample and outcome characteristics ranged from 0.86 to 0.92 and was for study quality $r = 0.94$.

Nocebo Effects

FMS Trials

The pooled estimate of the event of rate of patients with at least 1 AE in placebo groups was 59.9 (95% CI: 53.8-65.8) and in true drug groups was 73.3 (95% CI: 66.0-79.6). There was a high linear correlation between the event rates in placebo and active drug groups with $r = 0.83$ ($P < 0.001$). Nocebo effects accounted for 81.7% of the event rate of patients with at least 1 AE in true drugs.

The pooled estimate of the event rate of drop outs because of AEs accounting for total drop rate was 52.2 (95% CI: 46.3-57.9). The pooled estimate of the event rate of drop out due to AEs in placebo groups was 9.6 (95% CI: 8.6-10.7) and in true drug groups was 16.3 (95% CI: 14.1-31.2). There was a moderate linear correlation between the event rates in placebo and active drug groups with $r = 0.74$ ($P < 0.001$). Nocebo effects accounted for 58.9% of the event rate of drop out in true drugs. The forest plots of the event rates patients with at least one AE and dropping out due to AEs are presented in Supplemental Figure 3 (Supplemental Digital Content 4, http://links.lww.com/CJP/A31).

DPN Trials

The pooled estimate of the event rate of patients with at least 1 AE in placebo groups was 46.2 (95% CI: 36.5-56.1) and in true drug groups was 63.5 (95% CI: 53.6-72.4). There was a high linear correlation between the event rates in placebo and active drug groups with $r = 0.91$ ($P < 0.001$). Nocebo effects accounted for 72.8% of the event rate of patients with at least 1 AE in true drugs.

The pooled estimate of the event rate drop out because of AEs accounting for total drop rate was 54.7 (95% CI: 49.4-59.9). The pooled estimate of the event rate drop out rate due to AEs in placebo groups was 5.8 (95% CI: 5.1-6.6) and in true drug groups was 13.2 (95% CI: 10.7-16.2). There was a moderate linear correlation between the event rates in placebo and active drug groups due to AEs with $r = 0.62$ ($P < 0.001$). Nocebo effects accounted for 43.9% of the event rate drop out due to AEs in true drug groups. The forest plots of the event rates patients with at least 1 AE and dropping out due to AEs are presented in Supplemental Figure 4 (Supplemental Digital Content 5, http://links.lww.com/CJP/A32).

TABLE 1. Trial and Patient Characteristics in Fibromyalgia Syndrome and Painful Diabetic Neuropathy Studies

	FMS	Painful DPN	*P*
No. trials (N)	58	62	
Not published in peer-reviewed journals, N (%)	4 (6.9)	10 (16.1)	0.12
Study initiation year, mean (SD)	1998 (7.5)	1999 (5.9)	0.62
Industrial sponsoring, N (%)	45 (77.6)	52 (83.8)	0.38
Approved by the Food and Drug Administration for the given disease, N (%)	14 (24.1)	13 (21.0)	0.68
Continent			
Europe, N (%)	20 (34.5)	14 (22.6)	0.01
North America, N (%)	30 (51.7)	31 (50.0)	
Asia, Middle and South America and mixed continent, N (%)	8 (13.8)	17 (27.4)	
No. countries mean (SD)	1.8 (2.7)	2.5 (3.0)	0.05
No. study sites mean (SD)	18 (26.7)	26 (30.9)	0.005
Treatment duration (wk) mean (SD)	12.1 (7.2)	14.3 (12.3)	0.62
True drugs			< 0.001
Antidepressants, N (%)	25 (43.1)	7 (11.3)	
Anticonvulsants, N (%)	5 (8.8)	29 (47.8)	
Other, N (%)	28 (48.3)	26 (41.9)	
Application medication			0.90
Oral, N (%)	49 (84.5)	54 (87.1)	
Parenteral, N (%)	6 (10.3)	5 (8.1)	
Local, N (%)	3 (5.2)	3 (4.8)	
Jadad score	2.9 (1.6)	2.8 (1.8)	0.83
No. patients on placebo, mean (SD)	86.8 (106)	82.0 (65.7)	0.0003
No. patients on true drug (in case of multiple dosages: subgroup under highest dosage)	91.9 (113)	85.4 (63.6)	0.18
% Women, mean (SD)	93.1 (11.1)	43.5 (12.1)	< 0.001
% Caucasian, mean (SD)	91.0 (7.8)	77.8 (28.2)	< 0.001
Mean age, mean (SD)	48.0 (3.3)	58.3 (3.3)	< 0.001
Pain baseline (0-10), mean (SD)	6.6 (0.7)	6.3 (1.1)	0.07

DPN indicates diabetic peripheral neuropathy; FMS indicates fibromyalgia syndrome.

Subgroup Analyses

Due to the poor quantity and quality of the reports on assessment strategies of AEs, we post hoc decided not to perform subgroup analyses of the different assessment strategies. The event rate of patients with at least 1 AE and dropping out due to AEs were higher in FMS than in DPN trials (P interaction 0.02 and < 0.001).

Metaregression Analyses

The regression coefficients for mean age and incremental year of study initiation on the logit of the event rates of patients with at least 1 AE were significant, indicating a strong linear correlation both in FMS and DPN trials. The regression coefficients of mean age, mean percentage of women, incremental year of study initiation, and study duration on the logit of event rates of patients dropping out to AEs were significant indicating a strong linear correlation both in FMS and DPN trials (Table 4).

Risks of Bias

Heterogeneity

I^2 of the pooled estimate of the event rate of patients with at least 1 AE was 60.5% and of drop out due to AE was 3.0% in the placebo groups of FMS trials. I^2 of the pooled estimate of the event rate of number of patients with at least 1 AE was 55.9% and of drop out due to AE was 0% in the placebo groups of DPN trials.

The relative risk of the event rate of patients with at least 1 AE comparing true drug versus placebo in FMS trials was 1.2 (95% CI: 1.1-1.3; $I^2 = 4.4\%$) and in painful DPN trials was 1.3 (95% CI: 1.2-1.5, $I^2 = 31.3\%$). The relative risk of the event rate of drop out due to AEs comparing true drug versus placebo in FMS trials was 2.1 (95% CI: 1.8-2.4; $I^2 = 0\%$) and in painful DPN trials was 2.8 (95% CI: 2.3-3.3, $I^2 = 0\%$).

Reported Study Quality

The Jadad score was not significantly associated with the logit pooled estimate of the event rate of at least 1 AE ($ß = 0.51$, $P = 0.20$, $df = 33$), but with the logit pooled estimate of the event rate of drop out due to AE in placebo groups of FMS trials ($ß = -2.16$, $P = 0 < 0.001$, $df = 58$). The Jadad score was not significantly associated with the logit pooled estimate of the event rate of at least 1 AE ($ß = -0.98$, $P = 0.09$, $df = 28$), but with logit pooled estimate of the event rate drop out due to AE in placebo groups of painful DPN trials ($ß = -3.02$, $P = 0 < 0.001$, $df = 59$).

Publication Bias

Visual inspection of funnel plots was not indicative for publication bias (details not shown). The Kendall tau of the Begg rank correlation test of the relative risk drop out due to AEs true drug compared with placebo was not significant in FMS (tau $= -0.13$, P 2-tailed $= 0.14$) and painful DPN trials (tau $= -0.02$, $P = 0.85$). The Egger intercept of the relative risk drop out due to AEs true drug compared with placebo was not significant in FMS (intercept = 0.12,

TABLE 2. Study and Patient Characteristics of Randomized Controlled Drug Trials in Fibromyalgia Syndrome Included Into Analysis

Author (References*)	Year Publication	Industrial Sponsoring	Active Drug Used for Comparison With Dosage	FDA Approval	Application	Continent	No. Countries	No. Study Sites	Duration Therapy
Ali	2009	No	Myers cocktail	No	Parenteral	North America	1	1	12
Anderberg	2000	No	Citalopram 20-40 mg/d	No	Oral	Europe	1	1	16
Andersson	1998	No	Staphylococcus toxid Increasing dosages of 0.001 to 1 mL vaccine/twice a week	No	Parenteral	Europe	1	3	12
Arnold	2004	Yes	Duloxetine 120 mg/d	Yes	Oral	North America	1	18	12
Arnold	2005	Yes	Duloxetine 120 mg/d	Yes	Oral	North America	1	21	12
Arnold	2007	Yes	Gabapentin 1200-2400 mg/d flexible	No	Oral	North America	1	3	12
Arnold	2008	Yes	Pregabalin 600 mg/d	Yes	Oral	North America	1	84	14
Arnold	2010a	Yes	Milnacipran 100 mg/d	Yes	Oral	North America	2	68	16
Arnold	2010b	Yes	Duloxetine 100-200 mg/d flexible	Yes	Oral	Mixed	2	48	12
Arnold	2010c	Yes	Esreboxetine 8 mg/d or maximum tolerated dosage	No	Oral	North America	1	56	8
Bell	2004	No	Homeopathic remedy individualized dosage	No	Oral	North America	1	2	16
Bennett	1988	Yes	Cyclobenzaprine flexible 10-40 mg	No	Oral	North America	1	2	12
Bennett	1998	Yes	Growth hormone dosage NR/daily	No	Parenteral	North America	1	1	36
Bennett	2003	Yes	Tramadol plus acetaminophen flexibel 75-300/650-260 mg	No	Oral	North America	1	27	13
Branco	2010	Yes	Milnacipran 200 mg/d	Yes	Oral	Other	13	89	15
Carette	1986	No	Amitriptyline 50 mg/d	No	Oral	North America	1	3	9
Carette	1994	Yes	Amitriptyline 50 mg/d: 75mg/d	No	Oral	North America	1	11	26
Caruso	1987	Yes	Dothiepin	No	Oral	Europe	1	1	8
Caruso	1990	No	5-Hydroxy-tryptophan 100 mg/d	No	Oral	Europe	1	1	4
Chappell	2008	Yes	Duloxetine flexible 100-200 mg/d	Yes	Oral	Other	5	36	27
Clauw	2008	Yes	Milnacipran 200 mg/d	Yes	Oral	North America	1	86	15
Crofford	2005	Yes	Pregabalin 450 mg/d	Yes	Oral	North America	1	40	8
Distler	2010	Yes	Terguride 3 mg/d	No	Oral	Europe	3	10	12
Ginsberg	1995	Yes	Amitryityline 25 mg/d	No	Oral	Europe	1	1	8
Ginsberg	1997	Yes	Moclomebid 150 mg/d: 20 mg/d	No	Oral	Europe	1	1	4
Glaxo	1995, not published	Yes	Paroxetine	No	Oral	Europe	1	1	8
Glaxo	2005, not published	Yes	Ropinirole 24 mg/d	No	Oral	Europe	9	22	12
Goldenberg	1986	Yes	Amitriptyline 25 mg/d	No	Oral	North America	1	1	6
Hannonen	1998	1	Amitriptyline flexibel 25-37.5 mg	No	Oral	Europe	1	1	12

(continued)

TABLE 2. *(continued)*

No. Study of Visits	No. Patients on Placebo	No. Patients on Active Drug	Percentage of Women on Placebo	Percentage of Caucasians on Placebo	Mean age of Patients on Placebo	Pain Base line 0-10	Jadad Score	Details of Type of Assessment of Side Effects
8	18	17	100	100	50.7	6.5	4	NR
6	19	21	100	100	48.6	6.5	3	Spontaneous reports and exploration by NR
NR	14	14	100	NR	47	6.5	1	NR
10	103	104	88.9	87	48.3	6.1	3	NR
8	120	118	100	89.5	49.6	6.5	1	NR
8	75	75	93.3	97.3	47.3	6	3	NR
8	184	557	91.8	91.8	49	6.6	5	Spontaneous reports and exploration by NR
10	509	516	93.7	90	48.7	6.4	5	NR
8	267	263	93.6	77.2	49.6	6.5	4	NR
6	133	134	90.2	89.5	50.1	6.8	5	Spontaneous reports and exploration by investigator
5	32	30	90.6	90.6	47.9	3.6	5	NR
6	58	62	94.8	NR	49.7	6.5	3	Spontaneous reports NR
4	25	25	100	NR	47.9	NR	5	NR
6	157	158	94.9	93.6	51	7.2	5	Spontaneous reports or in response to general, nonleading questioning by NR
9	449	435	93.5	NR	49.2	6.5	1	Spontaneous reports or in response to nonleading questioning by NR
3	32	27	91.5	NR	40.1	5.8	3	NR
7	42	84	92.9	NR	47.1	6.4	3	NR
4	30	30	93.5	NR	46.7	6.6	2	NR
3	25	25	24	NR	46.9	6.1	5	Exploration by NR
11	168	162	93.3	90.9	50.2	6.4	3	Spontaneous reports
8	401	806	94.8	93.5	50.7	6.6	5	Spontaneous reports or observed by the investigator
6	131	396	90.8	95.4	49.7	6.9	1	Spontaneous reports or observed by NR
13	34	65	88.2	100	49	7.2	3	NR
3	22	24	83	91.7	46	7.1	3	Spontaneous reports or observed by NR
3	28	28	82.2	NR	39.8	7.1	1	NR
NR	26	26	73.1	NR	46	6.9	1	NR
NR	91	90	92.3	99	47.4	6.8	3	NR
4	15	15	95.2	87.1	43.8	7.5	1	NR
4	45	42	100	NR	48.9	5.7	5	Spontaneous reports and exploration by NR

(continued)

TABLE 2. *(continued)*

Author (References*)	Year Publication	Industrial Sponsoring	Active Drug Used for Comparison With Dosage	FDA Approval	Application	Continent	No. Countries	No. Study Sites	Duration Therapy
Heymann	2001	Yes	Amitriptyline 25 mg/d	No	Oral	Other	1	1	8
Holman	2005	Yes	Pramipexole 4.5 mg/d	No	Oral	North America	1	1	14
Jacobsen	1991	Yes	S-adenosylmethionine 800 mg/d	No	Oral	Europe	1	1	6
Kendall	2004	Yes	Valacyclovir 1 g/d	No	Oral	Europe	1	1	6
Ko	2007	Yes	Essential oil 024 flexible dosage	No	Topical	North America	1	1	4
McCarty	1994	Yes	Capsaicin 0.025% cream	No	Topical	North America	1	1	4
Mease	2008	Yes	Pregabalin 600 mg/d	Yes	Oral	North America	1	79	12
Mease	2009	Yes	Milnacipran 200 mg/d	Yes	Oral	North America	1	59	27
Norregaard	1995	No	Citalopram flexible 20-40 mg/d	No	Oral	Europe	1	1	8
Olin	1998	Yes	Ritanserin 10 mg/d	No	Oral	Europe	1	NR	16
Patkar	2007	Yes	Citalopram 62.5 mg/d		Oral	North America	1	2	11
Pattrick	1991	No	Chormezanone 400 mg/d	No	Oral	Europe	1	1	6
Pfizer	2008, not published	Yes	Pregabalin 600 mg/d	Yes	Oral	Other	16	73	14
Quijada-Carrera	1996	Yes	Tenoxicam 20 mg/d	No	Oral	Europe	1	1	8
Quimby	1989	No	Cyclobenzaprine 10-40 mg/d	No	Oral	North America	1	1	6
Rossini	2007	Yes	Acetyl l-carnitine 1500 mg/d	No	Oral	Europe	1	7	10
Russell	2008	Yes	Duloxetine 120 mg/d	Yes	Oral	Other	2	38	27
Russell	2009	Yes	Sodium oxybate 4.5 g/d	No	Parenteral	Europe	1	21	8
Sadreddini	2008	No	Raloxifen 60 mg/d	No	Oral	Other	1	1	16
Skrabek	2008	Yes	Nabilone 0.5-1 mg/d	No	Oral	North America	1	1	4
UCB	2010	Yes	Rotigotine 8 mg/d	No	Topical	North America	1	35	13
Vaeroy	1989	Yes	Carisoprodol 600 mg/d plus acetaminophen 480 mg/d plus cafeeine 96 mg/d	No	Oral	Europe	1	1	8
Vitton	2005	Yes	Milnacipran 200 mg/d	Yes	Oral	North America	1	14	12
Vlainich	2010	No	Lidocain 240 mg/once a week	No	Parenteral	Other	1	1	4
Wahner-Roeder	2008	Yes	20 g of soy protein and 160 mg of soy isoflavone	No	Oral	North America	1	1	6
Wolfe	1994	Yes	Fluoxetine 20 mg/d	No	Oral	North America	1	1	6
Wyeth	2008, not published	Yes	Desvenlaxafine 400 mg/d	No	Oral	North America	1	58	30
Yunus	1989	Yes	Ibuprofen 1200 mg/d	No	Oral	North America	1	1	3
Zachrisson	2002	No	Staphylococcus toxid increasing dosages of 0.001 to 1 mL vaccine/twice a week	No	Parenteral	Europe	1	1	26

(continued)

TABLE 2. *(continued)*

No. Study of Visits	No. Patients on Placebo	No. Patients on Active Drug	Percentage of Women on Placebo	Percentage of Caucasians on Placebo	Mean age of Patients on Placebo	Pain Base line 0-10	Jadad Score	Details of Type of Assessment of Side Effects
2	40	40	100	65	49.4	NR	3	NR
8	21	39	95	95	46	7.7	5	NR
3	22	22	90.9	NR	49	6.8	5	NR
2	30	30	96.6	NR	50.2	7.8	5	NR
4	68	65	94.1	98.5	55.5	6.6	5	Exploration by NR
3	24	21	100	83.3	48.6	6.1	1	NR
8	190	458	96.3	87.9	48.6	7.2	1	Spontaneous reports and exploration by investigator
10	223	665	95.5	94.6	49.4	7.4	1	Spontaneous reports and observation by investigator
3	21	21	NR	NR	50	6.7	3	Exploration by NR
3	27	27	100	NR	44	NR	1	NR
12	58	58	94.8	NR	49.1	7.5	5	Exploration by NR according to systematic assessment for treatment emergent events exploration
4	21	21	100	NR	49	6.5	1	
8	184	551	91	NR	48.5	6.7	1	NR
2	41	41	NR	NR	43	NR	3	NR
3	22	23	100	NR	45	NR	3	NR
5	52	50	NR	NR	46.3	7.3	5	NR
12	144	79	94.8	84.2	50.3	6.6	3	Spontaneous reports
7	64	66	95.3	89.1	47.3	6.6	3	Spontaneous reports and observation by NR
3	50	50	100	100	58.8	6.5	3	NR
4	20	20	85	NR	50.1	6.2	3	Spontaneous reports
10	82	74	92.7	NR	46.4	7	1	NR
2	23	20	100	NR	48.3	7.1	3	NR
7	28	97	97.6	84	48	6.7	3	Spontaneous reports
4	15	15	100	NR	44.7	7	1	NR
6	25	25	NR	NR	47.7	NR	3	NR
7	21	21	100	95.2	52.9	5	1	Structured interview by NR
NR	174	174	NR	NR	NR	NR	1	NR
6	24	22	96	NR	39.1	8	1	NR
NR	50	50	100	100	47	6.2	5	NR

*References available in Supplemental Digital Content 2, http://links.lww.com/CJP/A29.
FDA indicates Food and Drug Administration; NR, not reported; Other, Asia, Middle and South America, and mixed continent.

TABLE 3. Study and Patient Characteristics of Randomized Controlled Drug Trials in Fibromyalgia Syndrome Included Into Analysis

Author (References*)	Year of Publication	Industrial Sponsoring	Active Drug Used for Comparison with Dosage	FDA Approval	Application	Continent	No. Countries	No. Study Sites	Duration Therapy
Agrawal	2009	No	Valproat and glyceriltrinitrat spray (20 mg/kg/d)	No	Oral	Other	1	2	12
Arezzo	2008	Yes	Pregabalin (600 mg/d)	Yes	Oral	North America	1	23	12
Atli	2005	Yes	Zonisamide (540 mg/d)	No	Oral	North America	1	1	12
Backonja	1998	Yes	Gabapentin (3600 mg/d)	No	Oral	North America	1	20	8
Beydoun	2006	Yes	Oxcarbazepin (1800 mg/d)	No	Oral	North America	1	37	16
Boulton	1990	Yes	Tolrestat (200 mg/d)	No	Oral	Europe	2	19	52
Capsaicin group	1991	Yes	Capsaicin 0.08% 4 times/d	No	Topical	North America	1	12	8
Cohen	1991	No	Pentoxifylline (400 mg/d)	No	Oral	North America	1	3	24
De Grandis	2002	Yes	Levacecarnine (2000 mg/d)	No	Parenteral	Europe	1	20	51
Dogra	2005	Yes	Oxcarbazepine (1800 mg/d)	No	Oral	North America	2	22	16
Eisenberg	2001	Yes	Lamotrigin (400 mg/d)	No	Oral	Other	1	1	8
Eli Lilly NC-T00408993	2009	Yes	Duloxetine (flexible 60-120 mg/d)	Yes	Oral	Other	1	NR	12
Eli Lilly NC-T00552175	Not published, 2010	Yes	Duloxetine (60 mg/d)	Yes	Oral	Other	1	NR	12
Freeman	2007	Yes	Tramadol (37.5 mg/d)	No	Oral	North America	1	46	9.5
Gill	1990	No	Ponalrestat (300 mg/d)	No	Oral	Europe	1	2	16
Gimbel	2003	Yes	Oxycodone (60 mg/d)	No	Oral	North America	1	15	6
Goldstein	2005	Yes	Duloxetine (120 mg/d)	Yes	Oral	North America	1	4	12
Grosskopf	2006	Yes	Oxcarbazepin (1200 mg/d)	No	Oral	Other	3	22	16
Hanna	2008	Yes	Oxycodone (5 mg/d)	No	Oral	Other	12	70	12
Harati	1998	Yes	Tramadol (210 mg/d)	No	Oral	North America	1	9	6
J&J NC-T00455520	Not published 2010	Yes	Tapentadol (500 mg/d)	No	Oral	North America	2	NR	12
Jensen	2006	Yes	Oxycodon (120 mg/d)	No	Oral	North America	1	15	6
Kochar	2002	Yes	Valproat (1200 mg/d)	No	Oral	Other	1	1	4
Kochar	2004	No	Valproat (500 mg/d)	No	Oral	Other	1	1	12
Krentz	1992	Yes	Ponalrestat (600 mg/d)	No	Oral	Europe	1	1	52
Lesser	2004	Yes	Pregabalin (600 mg/d)	Yes	Oral	North America	1	45	5
Malik	1998	Yes	Trandolapril (2 mg/d)	No	Oral	Europe	1	1	52
Oskarsson	1997	Yes	Mexiletine (675 mg/d)	No	Oral	Europe	2	11	3
Pfizer A9451008	Not published, 2005	Yes	Gabapentin (3600 mg/d)	No	Oral	North America	1	43	15
Pfizer A0081030	Not published, 2007	Yes	Pregabalin (flexible 150-600 mg/d)	Yes	Oral	Other	19	47	12
Pfizer 1008040	Not published, 2007	Yes	Pregabalin (600 mg/d)	Yes	Oral	Other	10	49	9
Pfizer A0081060	Not published, 2007	Yes	Pregabalin (600 mg/d)	Yes	Oral	Europe	1	23	13

(continued)

TABLE 3. *(continued)*

No. Study of Visits	No. Patients on Placebo	No. Patients on Active Drug	Percentage of Women on Placebo	Percentage of Caucasians on Placebo	Mean Age of Patients on Placebo	Pain Baseline 0-10	Jadad Score	Details of Type of Assessment of Side Effects
4	21	20	NR	NR	59.2	7.4	3	NR
10	85	82	47	71.8	58.3	6.6	5	NR
8	12	13	7	66.6	61.5	6.4	5	NR
18	81	84	38.3	82.7	53	6.5	5	NR
6	89	88	43.8	NR	62.1	7.1	5	Spontaneous reports
10	107	112	NR	NR	55		−1	Spontaneous reports
5	139	138	51.1	NR	60	7.6	3	NR
6	20	20	NR	NR	59	7.3	3	NR
8	166	167	39.8	NR	65	6.5	5	NR
4	77	69	62	NR	60.5	7.4	3	Spontaneous reports
4	30	29	38.5	NR	57.8	6.6	5	NR
4	109	106	54	NR	59.9	5.5	1	Spontaneous reports
4	167	172	22.8	NR	60.8	5.8	1	NR
5	153	160	42.1	76.3	55.1	7.1	5	Spontaneous reports and nondirected questioning by NR
5	13	17	38.5	30.8	58.6	4.6	2	NR
4	77	82	50.6	80.5	58.8	6.8	5	Exploration by NR
15	115	113	48.7	77.4	60.4	5.8	3	Spontaneous reports
3	70	71	45.7		61.4	7.1	1	Spontaneous reports
11	169	169	33	99	60.7	6.5	3	NR
5	66	65	41	NR	59	5.7	5	NR
5	193	196	39.9	NR	60.6	6.5	1	NR
4	77	82	NR	NR	58.9	7.8	5	NR
3	24	28	45.8	NR	53.8	4.9	3	Exploration by NR
4	21	22	50	NR	56.2	5.7	1	NR
52	25	25	NR	NR	NR	NR	1	NR
4	97	82	39.2	93.8	57.8	6.6	5	NR
3	23	23	0		48.7		3	NR
2	31	95	77.4	100	57	5	3	Spontaneous reports
6	189	200	NR	NR	58.5	6.5	1	NR
12	135	271	NR	31.9	57.3	6.4	1	NR
7	81	86	NR	NR	60	6.3	1	NR
10	85	82	47	NR	58	6	3	Nonleading questioning and observation by NR

(continued)

TABLE 3. *(continued)*

Author (References*)	Year of Publication	Industrial Sponsoring	Active Drug Used for Comparison with Dosage	FDA Approval	Application	Continent	No. Countries	No. Study Sites	Duration Therapy
Pfizer A0081071	Not published, 2007	Yes	Pregabalin (600 mg/d)	Yes	Oral	North America	1	50	13
Pfizer A0081163	2010	Yes	Pregabalin (600 mg/d)	Yes	Oral	Other	1	62	13
Raskin	2004	Yes	Topiramate (400 mg/d)	No	Oral	North America	1	39	12
Raskin	2005	Yes	Duloxetine (120 mg/d)	Yes	Oral	Other	12	26	12
Rauck	2007	Yes	Lacosamide (400 mg/d)	No	Oral	North America	1	36	10
Richter	2005	Yes	Pregabalin (600 mg/d)	Yes	Oral	North America	2	29	6
Ropper	2009	No	Vascular endothelial growth factor (flexible 1-4 mg/injections/ 24 weeks)	No	Parenteral	Other	2	2	24
Rosenstock	2004	Yes	Pregabalin (300 mg/d)	Yes	Oral	North America	1	25	8
Rowbotham	2004	No	Venlaxafine (225 mg/d)	No	Oral	North America	1	12	6
Rowbotham	2009	Yes	ABT 594 (neuronal nicotinic acetylcholine receptor) (300 mg/d)	No	Oral	North America	1	29	7
Scheffler	1991	Yes	Capsaicin 0.08% 4 times/d	No	Topical	North America	1	1	8
Selvarajah	2010	No	Cannabis-based product (0.26 mg/ml 4 times/d)	No	Oral	Europe	1	1	12
Shaibani	2009	Yes	Lacosamide (600 mg/d)	No	Oral	North America	1	84	18
Simpson	2001	No	Gabapentin/Venlaxafine (2700 mg/d)	No	Oral	North America	1	1	8
Sindrup	2005	No	TKA 731 (NK1 receptor antagonist) (150 mg/d)	No	Oral	Europe	5	12	2
Stracke	1992	Yes	Mexiletine (450 mg/d)	No	Oral	Europe	1	7	5
Stracke	2008	Yes	Benfotiamine (600 mg/d)	No	Oral	Europe	1	10	6
Tanan	1991	Yes	Capsaicin 0.08% (4 times/d)	No	Topical	North America	1	1	8
Thienel	2004	Yes	Topiramate (400 mg/d)	No	Oral	Other	11	195	18
Tölle	2008	Yes	Pregabalin (600 mg/d)	Yes	Oral	Other	6	58	12
Valk	1996	No	ORG2766 (neurotrophic peptide) (5 mg/d)	No	Parenteral	Europe	1	4	52
Vinik	2007	Yes	Lamotrigin (400 mg/d)	No	Oral	North America	1	62	19
Wernicke	2006	Yes	Duloxetine (120 mg/d)	Yes	Oral	North America	2	28	12
Wright	1997	Yes	Mexiletine (600 mg/d)	No	Oral	North America	1	1	3
Wyeth NC-T00283842	Not published, 2010	Yes	Desvenlaxafine (400 mg/d)	No	Oral	North America	1	NR	13
Wymer	2009	Yes	Lacosamide (400 mg/d)	No	Oral	North America	1	53	18
Ziegler	1995	Yes	Alpha-lipoidic acid (1200 mg/d)	No	Parenteral	Europe	1	38	3
Ziegler	2006	Yes	Alpha-lipoidic acid (1800 mg/d)	No	Oral	Other	2	5	5
Ziegler	2009	Yes	Actovegin (2000 mg/d)	No	Parenteral	Other	3	26	23
Ziegler	2010	Yes	Lacosamide (600 mg/d)	No	Oral	Europe	12	50	18

(continued)

TABLE 3. *(continued)*

No. Study of Visits	No. Patients on Placebo	No. Patients on Active Drug	Percentage of Women on Placebo	Percentage of Caucasians on Placebo	Mean Age of Patients on Placebo	Pain Baseline 0-10	Jadad Score	Details of Type of Assessment of Side Effects
7	151	152	43	NR	59.9	NR	1	NR
7	135	45	NR	NR	60	6.5	1	NR
4	109	214	46.8	86.2	58.9	6.9	5	NR
10	116	116	54.3	100	59.2	5.5	5	NR
12	59	60	54.2	89.8	55.3	6.5	5	NR
5	85	82	45.8	78.8	57.1	6.9	3	NR
6	11	39	90.9	NR	65.6	4.5	1	NR
6	70	76	42.9	91.4	60.3	6.1	1	NR
9	81	82	41	NR	60	6.9	3	NR
7	65	67	42	88	60.2	6.5	3	NR
6	26	28	68	57.7	62	7.3	1	NR
	14	15		NR	54.4	6.9	3	Standardized forms
7	65	137	40.9	74.2	59.5	6.2	5	NR
3	30	30	40	NR	52	6.5	1	NR
4	42	44	57	NR	61.1	6.7	5	Spontaneous reports or questioning (type of questioning NR)
7	48	47	35	100	57	7.1	1	NR
4	53	57	27.9	NR	61	3.9	3	NR
5	11	11	54.5	100	53.3	8.6	1	NR
5	384	260	40	NR	59	5.8	5	NR
5	96	101	46.9	99	58.9	6.4	1	NR
4	25	25	60	NR	48.9	2.6	5	NR
6	90	90	36.4	82	59.8	6.3	1	NR
11	108	112	36.1	79.6	60.8	5.9	3	NR
3	16	15	75	50	50	8.4	5	Listed spontaneous reports
5	90	69	27.7	NR	59	6.5	1	NR
6	93	91	54	76	58.3	6.6	5	NR
4	82	65	98.5	99.7	60.2	4.7	5	NR
7	43	46	65	NR	57	7	1	NR
10	286	281	44.4	93	55.6	6.3	3	NR
7	74	133	55.5	100	58.3	5	−1	NR

*References available in Supplemental Digital Content 2, http://links.lww.com/CJP/A29.
FDA indicates Food and Drug Administration; NR, not reported; Other, Asia, Middle and South America, and mixed continent.

TABLE 4. Metaregression Analyses of Patient-related and Study-related Predictors of Pooled Estimates of Patients With Nocebo Effects in Placebo Groups of Drug Trials in Fibromyalgia Syndrome and Painful Diabetic Polyneuropathy

	FMS			Painful DPN		
Predictor	**df**	ß	***P***	**df**	ß	***P***
Logit pooled estimate of the event rate of patients with at least one adverse event						
Mean age	32	−5.90	**0.03**	26	−15.7	**0.006**
Mean percentage of women	31	2.10	0.67	26	1.41	0.22
Mean percentage of White	20	1.27	0.64	19	0.67	0.48
Incremental year of study initiation	33	−1.10	**0.005**	28	−2.25	**0.0001**
Study duration	33	−0.31	0.39	28	0.80	**0.04**
Logit pooled estimate of the event rate of patients with drop out due to adverse events						
Mean age	52	−3.75	**0.03**	54	−4.02	**0.03**
Mean percentage of women	51	−2.10	**0.04**	51	−2.63	**< 0.0001**
Mean percentage of White	29	−1.84	0.08	38	−1.27	0.12
Incremental year of study initiation	**57**	**−2.76**	**< 0.0001**	59	−3.34	**< 0.0001**
Study duration	57	−2.41	**< 0.0001**	59	−2.67	**< 0.0001**

ß is the regression coefficient of each regression representing the slope of each model. Significant results ($P < 0.05$) are marked as bold.

P 2-tailed = 0.77) and painful DPN trials (intercept = −0.01, *P* 2-tailed = 0.98).

DISCUSSION

Summary of Main Results

Nocebo effects accounted for 82% of the event rate of patients with at least 1 AE in FMS and for 73% painful DPN trials. Nocebo effects accounted for 72% of the drop out rate to AE in FMS and for 44% painful DPN trials. The magnitude of nocebo effects was associated in both diseases with higher incremental year of study initiation and with longer duration of the study.

Agreement With Other Studies on Nocebo Drop Out Rates in Clinical Drug Trials

Incidence of Nocebo Effects

The pooled event rate of patients with at least 1 AE in placebo groups in FMS and in painful DPN was higher than the one of migraine trials with 23%.[6] The pooled event rates of drop out due to AEs in placebo groups in FMS and painful DPN were higher than the ones reported in multiple sclerosis with 2.1% in disease modifying and 2.3% in symptomatic treatment trials.[3] Rief et al[1] found a great variability of drop out rates (4% to 20%) in placebo groups in statin therapies of randomized controlled trials in atherosclerosis diseases.[1] The migraine studies did not analyze drop out rates due to AEs in placebo groups.[6,7]

Trial and Patient Characteristics Associated With Nocebo Effects

Nocebo drop out rates exhibited an association with the year of study publication in multiple sclerosis[3] trials likewise in our study. On the basis of the expectancy theory of nocebo,[5] we hypothesize that the number of patients with former negative experience with drugs and lower tolerance to adverse effects increased over the years. Information regarding trial medications made increasingly available by the media and other sources including the internet may have contributed to patients discontinuing trial medications more easily today than 20 years ago. The decline in tolerance to unspecific symptoms may also reflect the greater availability of therapeutic options or even the increasing possibilities for participating in clinical trials seen in the last 20 years.[3]

In accordance with our findings, side effects in placebo groups were not associated with race in migraine medication,[6,7] statins,[2] and oral drug challenge trials.[24] In contrast to these studies,[2,6,7,24] we found a positive association of female sex with drop out due to AEs. Our results confirm pharmacovigilance observations that medication side effects occur more frequently in older than in middle-aged patients.[25] We speculate that the higher nocebo drop out rates in FMS are due to higher levels of anxiety and somatization compared with painful DPN patients although we do not know direct comparisons of these psychological variables in both diseases.

Limitations

Methods

The inherent difficulty in attributing non-specific symptoms to be drug-related has to be recognized as a source of clinical heterogeneity between the trials. The decision to register a drug-related AE might depend if the exploration was performed by study nurse or medical doctor, if leading or nonleading questions and prompted or unprompted questionnaires were used. These details of assessment strategy of AE were not reported by nearly half of the studies and insufficiently outlined by the reporting studies. Moreover, the types of assessment differed in the reporting studies. As a result of the lacking or insufficient data, we were unable to test for the impact of the assessment strategy on the incidence of nocebo effects. Therefore, the pooled estimates of the nocebo effects must be handled with extreme caution. However, heterogeneity of the drop out rates due to AEs in placebo group and the relative risks of the event rates of patients with at least 1 AE and dropping out due to AEs were low. Therefore, pooling of estimates of nocebo effects and metaregression analyses were justified from a methodological point of view. The high amount to which nocebo effects accounted for drop out due to AEs does likely not depend on the assessment strategy of AEs of the studies analyzed.

Further major limitations of systematic reviews are publication bias, quality of the included studies, and insufficient data. We did not find indicators for publication bias. We found that the magnitude of nocebo effects was associated with higher reported study quality. We had to exclude some studies because of insufficient data from analysis. These studies were mainly studies with small sample sizes that had been conducted before 2000. Their

results—if available—would probably not have substantially changed the results. The total sample size and the number of studies included in our meta-analysis were sufficiently high for the outcome variable. Some of the studies included did not report in detail the characteristics of their study samples, especially demographic characteristics of the patients such as race limiting the validity of the results of the metaregression analysis. There is an ecological bias in the metaregression analyses performed, as the analysis was conducted at the study level and did not include the underlying patient-level variation.[26]

Variables Analyzed

To reduce errors to due multiple testing, we did not assess other potential moderators of nocebo effects such as type and frequency of drug application. Meta-analyses are limited in providing understanding of factors that contribute to nocebo effects because they do not systematically vary factors that affect its magnitude. We could not assess putative patient-related predictors of nocebo response such as anxiety and somatization.[1] Verbal suggestions and behaviors manifested by healthcare providers are likely to vary greatly across research contexts and may consequently generate considerable variability in nocebo effects.[27]

CONCLUSIONS

Reliable data on the tolerability and safety of a drug are necessary for clinical decision making. Regulatory agencies should define standards of the assessment of AEs in drug trials applying for approval. A recent study suggested to use a combination of sophisticated approaches for expected side effects, systematic screening for general side effects, and open question methods for spontaneous reports.[10] Reviewers and editors of peer-reviewed journals should demand a detailed report of the assessment strategy of AEs.

Awareness of nocebo effects is a prerequisite for enabling clinical investigators and practitioners to better recognize AEs. Better elucidation of patient characteristics such as anxiety, somatization and previous negative experiences with drugs and of contextual factors such as content and style of communication potential AEs would allow the development of strategies to prevent or minimize nocebo effects in both clinical trials and clinical practice.[4]

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