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Treatment of fibromyalgia syndrome with gabapentin and pregabalin – A meta-analysis of randomized controlled trials

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ABSTRACT

The efficacy of gabapentin (GPT) and pregabalin (PGB) in the treatment of fibromyalgia syndrome (FMS) was assessed. We screened MEDLINE, PsycINFO, SCOPUS, www.clinicaltrials.org, the Cochrane Library (through October 2008), and the reference sections of original studies on GPT/PGB in FMS. Randomized controlled trials (RCTs) on the treatment of FMS with GPT and PGB were analyzed. Six out of 127 RCTs studying 2422 subjects on treatment with GPT (one study) or PGB (five studies) and 1056 subjects on placebo with a median treatment duration of 11 weeks were included into the systematic review. Five studies were suitable for meta-analysis. Effects were summarized using standardized mean differences (SMD). There was strong evidence for a reduction of pain (SMD -0.28, 95% CI −0.36, −0.20; $p < 0.001$), improved sleep (SMD −0.39, 95% CI −0.48, −0.39; $p < 0.001$), and improved health-related quality of life (HRQOL) (SMD −0.30, 95% CI −0.46, −0.15; $p < 0.001$), but not for depressed mood (SMD −0.12, 95% CI −0.30, 0.06; $p = 0.18$). There was strong evidence for a non-substantial reduction of fatigue (SMD −0.16, 95% CI −0.23, −0.09, $p < 0.001$) and of anxiety (SMD −0.18, 95% CI −0.27, −0.10; $p < 0.001$). The external validity of the studies was limited because patients with severe somatic and mental disorders were excluded.

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1. Introduction

The key symptoms of fibromyalgia syndrome (FMS) are chronic widespread pain, fatigue, and sleep disturbances/non-restorative sleep [23]. Most patients suffer from additional somatic and psychological symptoms. There is a high prevalence of comorbidities with inflammatory rheumatoid diseases [39], other functional somatic syndromes such as irritable bowel syndrome [17], and mental disorders like affective and anxiety disorders [13]. The etiology and pathogenesis of FMS are probably multifactorial: biological as well as psychosocial factors may predispose to and maintain FMS symptoms. Psychosocial stress and depressed mood have been identified in population-based studies to increase the risk of FMS [32].

Treatment of FMS is symptom based, aiming at alleviating pain, fatigue, sleep disturbances, and psychological symptoms as well as improving physical and social functioning. Until now neither pharmacological nor non-pharmacological treatment options can cure the entire range of FMS symptoms. Recently, evidence-based guidelines on the management of FMS were published to give patients and physicians an orientation within the continuously growing number of studies on the therapy of FMS [4,6,19]. In evidence-based medicine, systematic reviews and meta-analyses are considered to ensure the highest quality for specific recommendations [29]. Systematic reviews and meta-analyses are available for some treatment options of FMS, which were highly recommended by two guidelines [6,19]: aerobic exercise [5], antidepressants [16,37], and multicomponent therapy [15]. No systematic review or meta-analysis is available on pregabalin (PGB), the first drug licensed for FMS by the US Food and Drug Administration (FDA) [1].

PGB and gabapentin (GPT) are structural analogues of the neurotransmitter gamma-aminobutyric acid (GABA). These second-generation anticonvulsants are alpha-2-delta ligands that bind to and modulate voltage-gated calcium channels. By reducing calcium influx at nerve terminals PGB and GPT diminish the release of several neurotransmitters, including glutamate, norepinephrine, and substance P. This mechanism is assumed to be the basis for the drugs analgesic, anticonvulsant, and anxiolytic actions [33].

We saw the need for a systematic review and a meta-analysis aiming at two goals: first, to evaluate the effects of treatment with PGB and GBT on FMS-related symptoms; second, to examine the clinical relevance (efficacy, safety, and internal and external validity

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of randomized controlled trials) of treatment with these drugs in FMS.

2. Methods

Meta-analysis was performed according to the QUORUM-guidelines (quality of reporting meta-analyses) [25] and the recommendations of the Cochrane Collaboration [38] when appropriate. The clinical relevance of the RCTs analyzed was checked according to the recommendations of the Cochrane Collaboration [14].

2.1. Data sources and searches

The electronic bibliography databases screened included MEDLINE, PsycINFO, SCOPUS, and the Cochrane Library (through October 2008). The keyword (MESH-terms; all languages; limited to "human") "fibromyalgia" was used in combination with "anticonvulsants" or "GABA agents" or "pregabalin" or "gabapentin" and "randomized controlled trial". In addition, reference sections of original articles were screened manually and independently by two authors. We contacted Pfizer as the US-distributor of PGB and the former US and European distributor of GPT to enquire about published or unpublished studies. Furthermore, we searched the data-bases of the FDA (www.clinicaltrials.org) for unpublished studies on both drugs.

2.2. Study selection

To be included into the systematic review, studies needed to meet the following criteria:

1. Diagnosis of FMS based on the criteria of the American College of Rheumatology (ACR) [40].
2. A RCT design with a control group receiving pharmacological placebo.
3. Treatment with GPT or PGB.
4. Data published as full paper or data available on www.clinicaltrials.org.
5. To be included into meta-analysis, the results of the studies should be presented as continuous data with means or mean change scores with their standard deviations (SD) or as dichotomous outcome (absolute number or percentage). To create a more complete data set for analysis, we contacted the corresponding authors as well as Pfizer of those RCTs with incomplete presentation of outcomes (e.g. missing mean values, SD of pretest and posttest data or SD of change scores) and study design (e.g. details of randomization).

2.3. Assessment of internal validity

The methodological quality was assessed by the van Tulder score using 11 items. Based on the score of these items [38] we arbitrarily classified quality as high (score: 8–11), moderate (score: 5–7) or low (score: 1–4). Furthermore, we checked if an a priori power analysis for the sample size had been conducted and if a priori primary and secondary outcomes had been defined. Additionally, we analyzed the study design.

2.4. Assessment of external validity

The external validity or clinical relevance of RCTs can be checked by five questions [14]:

(a) Are the patients described in detail so that you can decide whether they are comparable to those that you see in your practice?
(b) Are the interventions and treatment settings described well enough so that you can provide the same for your patients?
(c) Were all clinically relevant outcomes measured and reported?
(d) Is the size of the effect clinically important?
(e) Do the expected treatment benefits outweigh potential harms?

For answering question (a) we analyzed the inclusion and exclusion criteria and the socio-demographic data of the study samples and checked if comorbidities were assessed and reported. For (b) we analyzed the settings and referrals of the RCTs and the co-therapies described. For (c) we checked if symptom specific outcomes of the key symptoms of FMS such as pain, fatigue, sleep disturbances, depressed mood, and health-related quality of life (HRQOL) [23] were assessed and reported. Anxiety is another frequent symptom in FMS patients and PGB is licensed by the European Medicines Agency for general anxiety disorders. Therefore, we also checked the assessment of anxiety. For (d) and (e) we calculated effect sizes of the outcomes and analyzed the percentage of patients who achieved a predefined reduction of pain (number needed to treat [NNT]); additionally, we calculated the percentage of patients who developed side effects under GPT/PGB treatment (number needed to harm [NNH]). We analyzed if these outcomes fulfilled the criteria of a clinically important change: $a \geqslant 30\%$ pain reduction on a 11-point numeric scale can be regarded as moderately important and $a \geqslant 50\%$ pain reduction as substantially important [11].

2.5. Data extraction (this section can be put online)

Two authors independently screened the titles and the abstracts of potentially eligible studies identified by the search strategy detailed above (KB, WH). The full text articles were then examined independently by two authors to determine if they met the selection criteria (CS, NÜ). For the preparation of the meta-analysis, two authors independently extracted data (study characteristics, study results) using standard extraction forms (CS, WH). All discrepancies were re-checked and consensus was achieved by discussion. If necessary a third author (NÜ) analyzed the discrepancies. We used kappa statistics to assess agreement between authors.

2.6. Data synthesis and analysis (this section can be put online)

We analyzed intention-to-treat (ITT) data whenever available. Descriptive data were analyzed using Winstat for Excel (Version 2001.1, R. Fitch Software, Germany). For the comparison of proportions the Chi^2-test was applied. Non-parametric tests (Mann–Whitney-U-test, Kruskal–Wallis-H-test) were used for the comparison of continuous variables. We did not use a post hoc correction method in case of multiple comparisons of NNTs and NNHs because missing a potential benefit or harm to a patient because of a corrected p-value seemed more critical to us than running the risk of a type-I-error. Therefore, a two-sided p-value of $\leqslant 0.05$ was considered significant.

Continuous data were analyzed by RevMan Analyses software (RevMan 4.2.10) of the Cochrane collaboration [8]. Standardized mean difference (SMD) as effect measures were used by calculating SMD by means and SDs or change scores for each intervention. SMD used in Cochrane reviews is the effect size known as Hedges (adjusted) g. We used Cohen's categories [7] to evaluate the magnitude of the effect size, calculated by SMD, with $g > 0.2$–0.5 = small effect size, $g > 0.5$–0.8 = medium effect size, $g > 0.8$ = large effect size. I^2 statistics was used to measure heterogeneity of the RCTs. Examination of the combined results was performed by a random effects model, because this model is more

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conservative than the fixed-effects model and incorporates both within-study and between-study variances [21].

NNT and NNH were calculated with 95% confidence intervals using the pooled number of observations. We used the following definitions: when significantly more beneficial outcomes, defined as at least 30% pain reduction, occurred with GPT/PGB than with placebo, we used the term NNT. When significantly more adverse events, defined as withdrawal due to adverse events or frequency of specific adverse advents, occurred with GPT/PGB than with placebo, we used the term NNH.

We used the following levels of evidence descriptors to classify the results of the meta-analysis: strong = consistent findings in multiple (at least two) high or moderate quality RCTs; moderate = consistent findings in multiple low quality RCTs and/or one high or moderate quality RCT; limited = one low quality RCT; conflicting = inconsistent findings among multiple RCTs [38].

Because of the search strategy we suppose that we did not miss any RCTs with GPT or PGB in FMS. Therefore we did not perform funnel plots [12] and did not calculate fail-safe Ns [27] to check for a potential publication bias.

3. Results

3.1. Study selection

The literature search gave 127 citations involving FMS, GPT/PGB, and clinical trials. Of the 117 excluded articles 97 did not evaluate GPT/PGB in FMS, seven were double hits of controlled studies (study found in at least two data sources), and 13 were reviews. On more detailed review of the initially selected ten articles, further four papers were excluded because they had no placebo arm (long-term open-label studies). Five studies were published as full paper [2,3,9,10,24], one study was only published on file [28]. These six studies met our selection criteria and were systematically reviewed. One study applying an enriched enrollment with randomized trial design (EERW) was not suitable for meta-analysis, because study design and outcomes differed from the other studies [9] (see Fig. 1).

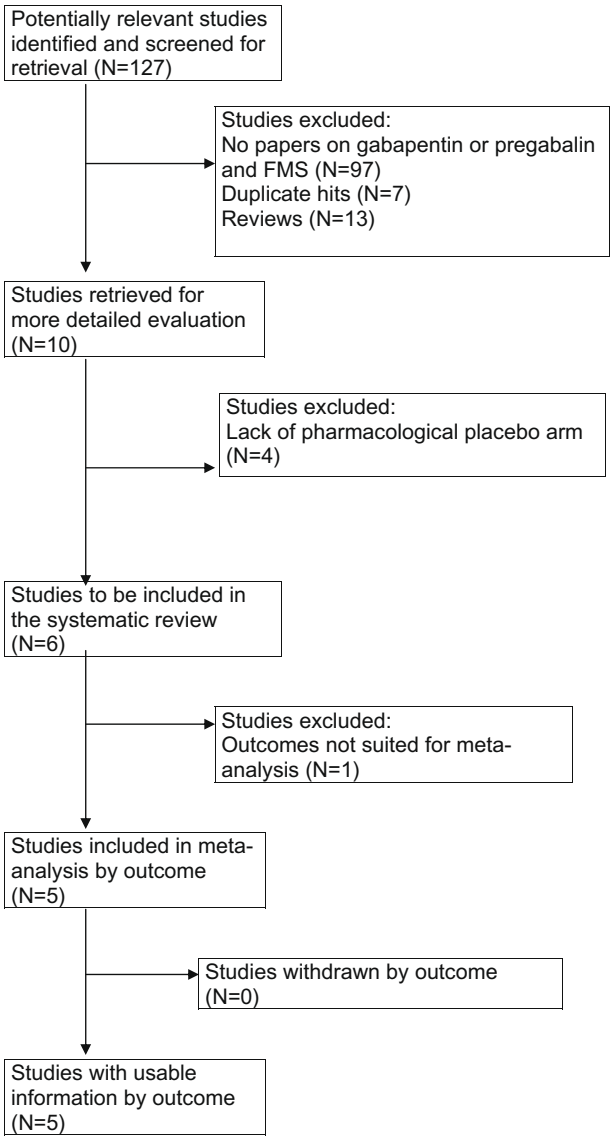

Fig. 1. QUORUM flow diagram.

3.2. Internal validity

3.2.1. Study characteristics

Some details of the methodological quality of the studies are outlined in Table 1. Interrater reliability for this assessment was $k = 0.92$. Five studies had a standard parallel design. One study had an EERW design: drug responders ($\geqslant$50% pain reduction) from a 6-week open-label run-in phase were selected for the subsequent double-blinded placebo-controlled trial during which half of the responders maintained their individual dose of the study drug while others switched to placebo on a random basis. The primary outcome was the time to loss of therapeutic response, defined as <30% pain reduction from open-label baseline [9]. The PGB studies with a parallel design used different fixed PGB dosages. One study used 150, 300, and 450 mg/d [10], the other three studies used 300, 450, and 600 mg/d [3,24,28]. The dose in the study with GPT was titrated over 6 weeks up to 2400 mg/d. If a patient could not tolerate this dose it was reduced to 1200 mg/d [2].

The median duration of the randomized phase of the trials was 11 weeks (range 8–26 weeks).

The median percentage of patients randomized was 60.9% (range 31.9–75.7%). 1507 patients completed treatment, 610 patients completed placebo. The median percentage of patients with placebo completing treatment was not different from the one with PGB/GPT (71.2 versus 60.9%; $p = 0.4$).

3.2.2. Methodological quality

Two studies used a single-blind placebo run-in phase [3,28], one study an open-label run-in [9]. These designs contributed to a moderate study quality according to the van Tulder score (3, 9, 28). Three studies had a high quality score (2, 10, 24). Interrater reliability for this assessment was $k = 0.90$. Only one study [24] reported non-pharmacological co-therapies at baseline; no study controlled for changes in non-pharmacological co-therapies during the study. Four studies reported the maximum dosage of co-medication allowed [3,9,10,24]. No study assessed the amount of co-medication and controlled the outcomes for the amount of co-medication. All studies performed a priori power analyses and ITT-analysis and a priori defined primary and secondary outcomes. I^2-statistics revealed a high homogeneity between the studies with PGB (see Fig. 2).

3.3. External validity

3.3.1. Exclusion and inclusion criteria and patient characteristics

Some study characteristics are presented in Table 2. Interrater reliability for this assessment was $k = 0.95$.

The study with GPT was supported by a grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases. All

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Table 1
Methodological quality and results of the studies.

Author Year Country	Methodological quality score Tulder score	A priori primary outcome measure defined	Secondary outcomes Other outcomes	Outcome measures for meta-analysis	Outcomes reported Other outcomes
Gabapentin					
Arnold 2007 USA	8	Average pain severity score (BPI) response: ⩾30% reduction of score	Pain: BPI Fatigue: NA Sleep: MOS Sleep Problems index Depression: MADRS Anxiety: NA HRQOL: FIQ total score; SF-36 all subscales; BPI average pain interference score CGI Severity Tender Point pain threshold	Pain: BPI average pain severity score* Sleep: MOS sleep Problems score* Depression: MADRS* HRQOL: FIQ total score*	Pain: + Fatigue: NA Sleep: + Depression: – HRQOL: FIQ+; SF–36: NR BPI pain interference score: + CGI Severity: + Tender Point pain threshold: –
Pregabalin					
Crofford 2005 USA	8	Mean pain score at end point (diary)	Pain: mean pain diary NRS; SF-MPQ Fatigue: MAF Global Index Sleep: MOS Sleep Problems Score Depression: HADS Anxiety: HADS HRQOL: SF-36 PGIC CGIC MTPS	Pain: Mean pain diary Fatigue: MAF global Index*** Sleep: MOS Sleep Problems Score*** Depression: HADS**** Anxiety: HADS***** HRQOL: SF-36 subscales***	Pain: + (only in 450 mg) Fatigue: + (only in 300 and 450 mg) Sleep: + (only in 300 and 450 mg) Depressed mood: – Anxiety: – HRQOL: 450 mg: +4/8 SF-36 subscales; +150 and 300 mg:1/8 SF-36 subscales PGIC: + (300 and 450 mg) CGIC: + (300 and 450 mg)
Arnold 2008 USA	7	Mean pain score at end point (diary)	Pain: Mean pain diary NRS Fatigue: MAF Global Index Sleep: MOS Sleep Problems Score Depression: HADS Anxiety: HADS HRQOL: FIQ total score; SF-36 all subscales and two component scores PGIC	Pain: Mean pain diary* Fatigue: MAF Global Index* Sleep: MOS Sleep Problems Score* Depression: HADS* Anxiety: HADS* HRQOL: FIQ total score	Pain: + Fatigue: – Sleep: +(450 mg and 600 mg) Depression: – Anxiety: 300 and 450 mg-; 600 m:+ HRQOL: FIQ + (450 and 600 mg); –300 mg; SF-36: Not reported PGIC: +
Crofford 2008 USA	6	Time to loss of therapeutic response;<30% reduction in pain from open-label baseline: mean pain score (VAS)	Pain: VAS Fatigue: MAF Global Index Sleep: MOS sleep problems score Depression: NA Anxiety: NA HRQOL: FIQ total score and SF-36 component scores PGIC	Not possible due to study design	Pain: + Fatigue: + Sleep: + Depression: NA HRQOL (FIQ total and SF-36 component scores): + PGIC: +
Mease 2008 USA	9	Mean pain score at end point; % with <30% reduction in pain, PGIC, FIQ total	Pain: Mean pain diary NRS; SF-MPQ Fatigue: MAF global index Sleep: MOS sleep problems score; NRS 0–10 Depression: HADS Anxiety: HADS HRQOL: FIQ total score; SF-36;SDS PGIC	Pain: mean pain diary** Sleep: MOS sleep problems score** Depression: HADS*** Anxiety: HADS**** HRQOL: FIQ total score*****	Pain: + Fatigue: – Sleep: + Depression: – Anxiety: – HRQOL: – PGIC: +

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Table 1 (*continued*)

Author Year Country	Methodological quality score Tulder score	A priori primary outcome measure defined	Secondary outcomes Other outcomes	Outcome measures for meta-analysis	Outcomes reported Other outcomes
Pauer 2008	7	Mean pain score at end point; % with <30% reduction in pain	Pain: mean pain diary NRS; pain VAS Fatigue: MAF global index Sleep: MOS sleep problems score Depression: HADS Anxiety: HADS HRQOL: FIQ total score; SF-36 PGIC	Pain: Mean pain diary* Sleep: MOS sleep problems score**** Depression: HADS **** Anxiety: HADS**** HRQOL: FIQ total score****	Pain: + (only 450 mg) Fatigue: Not reported Sleep:+ Depression:– Anxiety: – HRQOL: Some FIQ-subscales + (only 450 mg); SF-36: Mental component score (all dosages) PGIC: + (450 and 600 mg)

Abbreviations: +, Treatment significantly superior to placebo; –, Treatment not significantly different to placebo; CGIC, Clinical Global Impression of Global Change; HADS, Hospital Anxiety and Depression Scale; HRQOL, Health-related quality of life; MADRS, Montgomery Asberg Depression Rating Scale; MAF, Multidimensional Assessment of Fatigue; MOS, Medical Outcomes Study; MTPS, Manual Tender Point Survey; NA, not assessed; NRS, Numeric Rating Scale; PGIC, Patient Global Impression of Change; SDS, Sheehan Disabilty Scale; SF-36, Short Form Health Survey; SF-MPQ, Short Form McGill Pain Questionnaire.
Data needed for meta-analysis: *included in original paper; **found in www.clinicaltrials.org; ***provided on request; ****not provided on request.

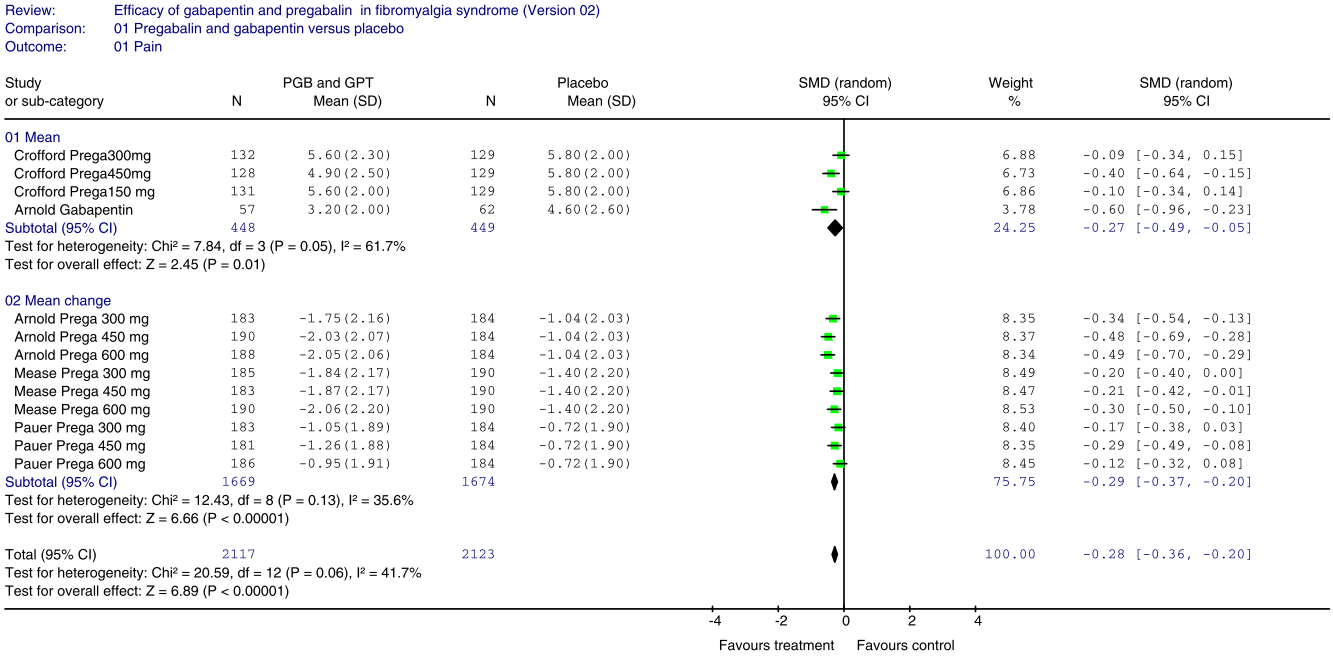

Fig. 2. Treatment effect of pregabalin and gabapentin on pain at posttreatment.

studies with PGB were sponsored by Pfizer. All studies included patients diagnosed with FMS according to the ACR criteria and with a mean average pain score of ⩾4/10 on a numeric rating or visual analogue scale. All studies excluded patients <18 years, with unstable somatic disease, and those applying for disability or engaged in litigation related to FMS. Two studies explicitly excluded patients with an inflammatory rheumatoid disorder [2,3]. All studies excluded patients with a creatinine clearance ⩽60 ml/min. All studies excluded patients with severe mental disorders, two studies [9,24] explicitly excluded patients with severe depression. One study [2] excluded patients who were refractory to treatment in the investigator's opinion.

Only two studies reported some comorbidities of the patients [2,9].

In one study patients were recruited from different continents (America, Europe, Asia, Australia) with US-Americans in the majority [28]. The other studies included only US-Americans. All studies were conducted in research centers. The median number of research centers enrolled was 76 (range 3–95). For all studies the patients were recruited by physicians' referral and journal advertisements.

Most patients were female (median 92.2%), white (median 90.6%), and middle-aged (median 48.7 years).

3.3.2. Clinical outcomes

The clinical outcomes of the studies are presented in Table 1. All studies assessed the key domains of FMS by applying mainly the same instruments. Pain was assessed by an 11-point rating-scale. Four studies used an electronic diary [3,10,24,28]. Fatigue was assessed by the Multidimensional Assessment of Fatigue (MAF) in all but one study [2]; sleep was assessed by the different scales of the Medical Outcomes study (MOS); depressed mood was assessed by the Hospital Anxiety and Depression Scale (HADS) [3,10,24,28] and the Montgomery Asberg Depression Rating Scale (MADRS) [2];

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Table 2
Main study characteristics.

Author Year Study centers	Mean age Women % Caucasian %	Exclusion criteria	Comorbidities: assessed and reported	Study population		Treatment group		Placebo group	Co-medication allowed Other co-therapies
Referral	Mean disease duration			N screened/ Randomized (%)	N/ completing (%)	N/ completing (%)	Study design Duration treatment Dosage	N/ completing (%)	
Gabapentin									
Arnold 2007 3 US-American outpatient research centers Physician referral or advertisement	48.3 yrs 90 97 NR	Age < 18 yrs; unstable medical or psychiatric illness*; pain from other diseases incl. inflammatory rheumatoid disease; patients refractory to treatment in the investigator's opinion	Standardized psychiatric interview Partially: Major depression 18.7%; anxiety disorder: 10%	252/150 (59.5%)	150/119 (79.3%)	75/57 (76.0)	Standard parallel 12 wks 1200–2400 mg/d	75/62 (82.7)	Acetaminophen and over-the-counter NSAI; dosage NR Unconventional or alternative therapies allowed
Pregabalin									
Crofford 2005 40 US-Amercian study centers NR	48.6 yrs 91.5 93.2 9 yrs	Age < 18 yrs; clinically significant or unstable medical or psychological condition; creatinine clearance ⩽ 60 ml/min; applying for disability or engaged in litigation related to FMS	No No	825/529 (64.1)	529/410 (77.5)	398/313 (78.6)	Standard parallel 8 wks 150, 300, 450 mg/d	131/97 (74.0)	Acetaminophen ⩽ 4 g/d; Aspirin ⩽ 325 mg/d NR
Arnold 2008 84 US-American research centers Physician referral or advertisement for medication trial	50.0 yrs 94.5 91 10 yrs	Age < 18 yrs; unstable medical or psychiatric disorders incl. inflammatory rheumatoid disorder; creatinine clearance ⩽ 60 ml/min; applying for disability or engaged in litigation related to FMS	No No	1195/745 (62.3)	745/486 (65.2)	561/361 (64.3)	Standard parallel 14 wks 300, 450, 600 mg	184/125 (67.9)	Acetaminophen ⩽ 4 g/d; Aspirin ⩽ 325 mg/d NR
Crofford 2008 95 US-American centers NR	49.2 yrs 92,9 89,5 7.8 yrs	Age < 18 yrs; clinically significant or unstable medical or psychological condition including severe depression; creatinin clearance ⩽ 60 ml/min; applying for disability or engaged in litigation related to FMS	No Partially: depression 26%; hypertension28%	663/566** (85.0)	566/162 (28.6)	279/107** (38.4)	EERW parallel 6 wks open-label, then 26 wks 300, 450, 600 mg	287/55** (19.2)	Acetaminophen ⩽ 4 g/d NR
Mease 2008 USA 79 US-American research centers NR	48.8 yrs 94.4 90.2 9.3 yrs	Age < 18 yrs; clinically significant or unstable medical or psychological condition including severe depression; creatinin clearance ⩽ 60 ml/min; applying for disability or engaged in litigation related to FMS	No No	1328/748 (56.3)	748/485 (64.8)	558/355 (63.6)	Standard parallel 13 wks 300, 450, 600 mg	190/130 (68.4)	Acetaminophen ⩽ 4 g/d; Aspirin ⩽ 325 mg/d Physical therapy, massage, chiropractic care, psychological therapy allowed
Pauer 2008 73 centers in North-, Middle- and South America. Europe, Asia, and Australia NR	48.5 yrs 91 76% NR	Age < 18 yrs; no further information provided	No No	986/746 (75.7)	746/518 (70.5)	558/377 (69.4)	Standard parallel 14 wks 300, 450, 600 mg/d	184/141 (76.6)	NR NR

Abbreviations: EERW, Enriched enrollment with randomized withdrawal; NR, not reported; NSAI, non-steroidal anti-inflammatory; wks, weeks; yrs, years.
*Patients with major depressive and anxiety disorder included; **Data of responders randomized reported.
Note: The order of the presented studies is arranged according to drug, year of publication, and in alphabetic order for first author name.

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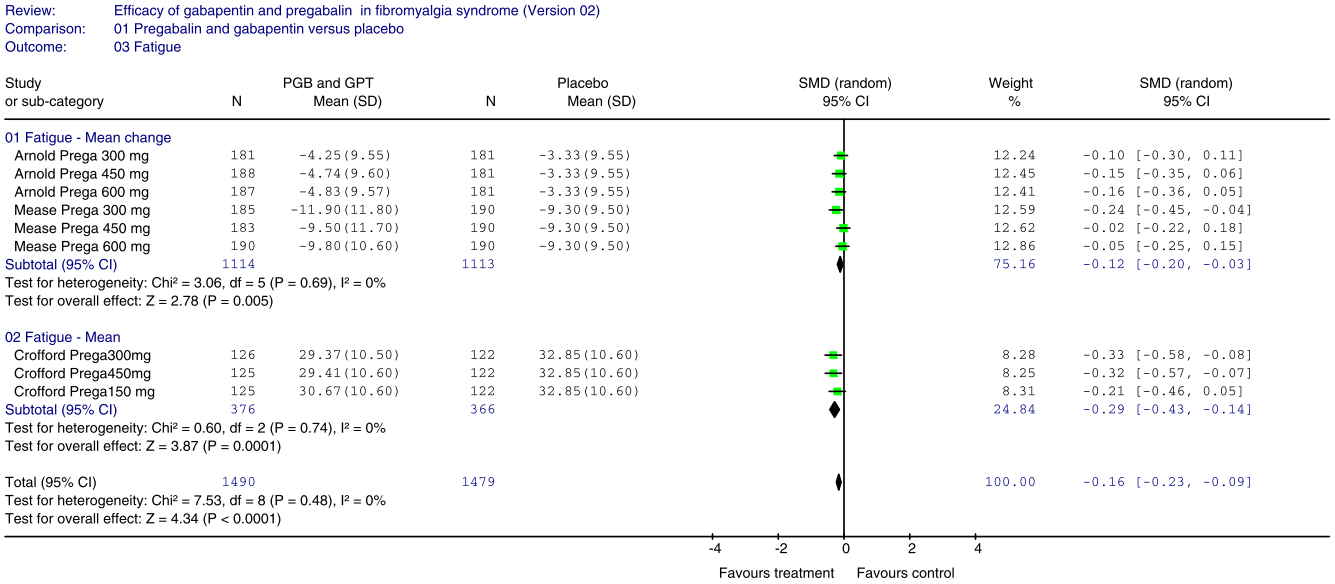

Fig. 3. Treatment effect of pregabalin on fatigue at posttreatment.

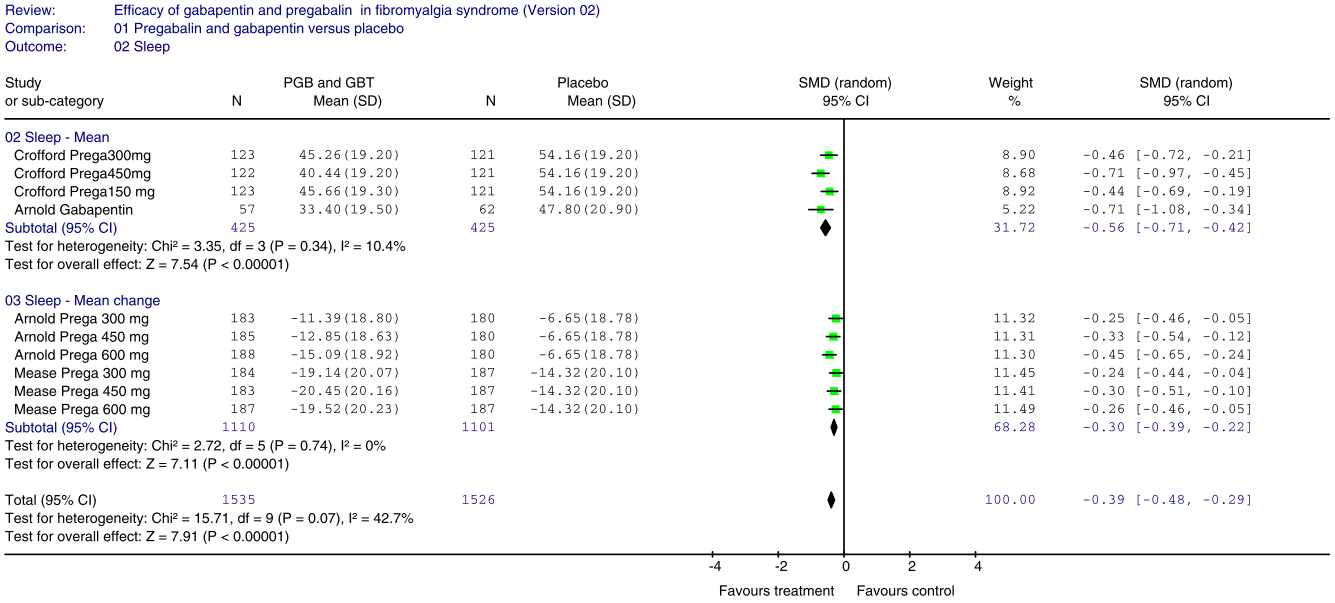

Fig. 4. Treatment effect of pregabalin and gabapentin on sleep at posttreatment.

anxiety was assessed by the HADS in four studies [3,10,24,28]; HRQOL was assessed by the disease specific Fibromyalgia Impact Questionnaire (FIQ) in five studies [2,3,10,24,28], and by the generic Short Form Health Survey F-36 in all studies. Furthermore all studies but one [2] measured the patient global impression of change (PGIC).

All studies reported the percentage of patients who achieved *a* $\geqslant$ 30% pain reduction. Three studies [3,9,28] reported the percentage of patients who achieved *a* $\geqslant$ 50% pain reduction.

Except for one study [3] that did not report the results of the SF-36 and one study [28] that did not report the MAF data, all studies gave at least a global survey of all primary and secondary outcomes. Only the outcomes reported in the original papers of Arnold and co-workers [2,3] were suitable for meta-analysis. The data of the other studies published as full paper were not suitable for a meta-analysis [10,24]. We found the necessary data (means or mean changes with SD) for pain and sleep of one study [24] on www.clinicaltrials.org. Pfizer provided some other missing data of this study [24]. All necessary data except for anxiety and depressed mood of one study were provided by Pfizer on request [9]. One study available as a file [28] presented only the means and SDs of the outcome pain, but not of the other outcomes. The missing data were not provided by the authors and Pfizer despite requests. Thus the outcome pain could be meta-analyzed for five [2,3,10,24,28], sleep for four [2,3,10,24], depressed mood for three [2,3,24], fatigue for three [3,10,24], HRQOL [2,3], and anxiety for two studies [3,24] (Table 2).

3.3.3. Clinical importance of effect sizes

The effect sizes for GPT and PGB are shown in Figs. 2–7 (Figs. 2,4 and 7 in printed version, Figs. 3 and 5 online). There was strong evidence for a reduction of pain (SMD −0.28, 95% CI −0.36,

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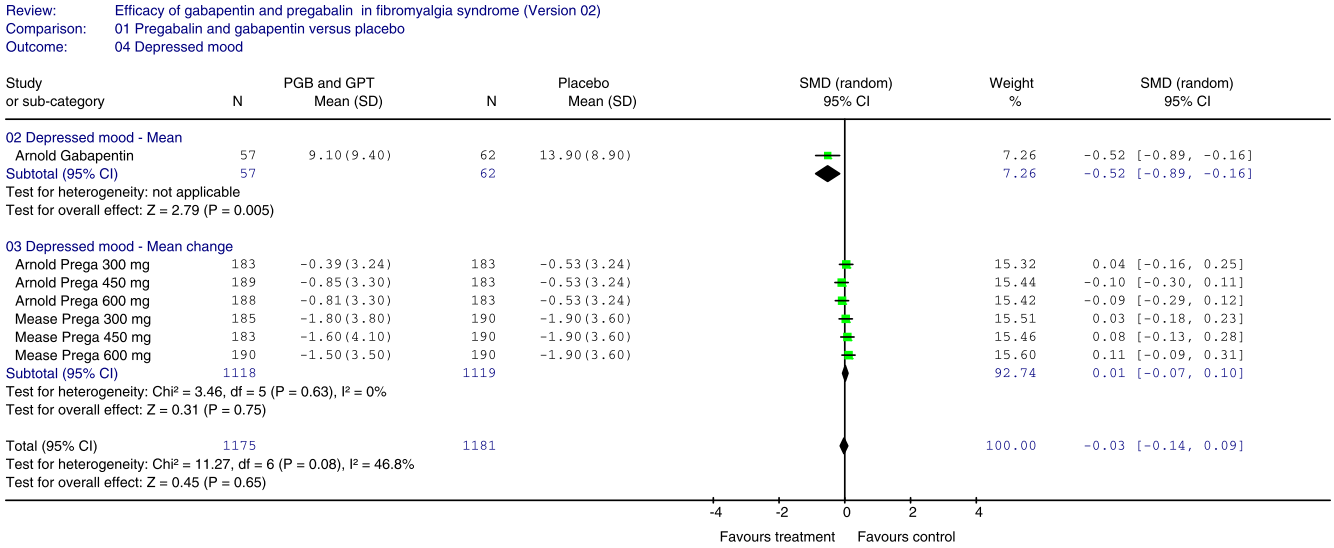

Fig. 5. Treatment effect of pregabalin and gabapentin on depressed mood at posttreatment.

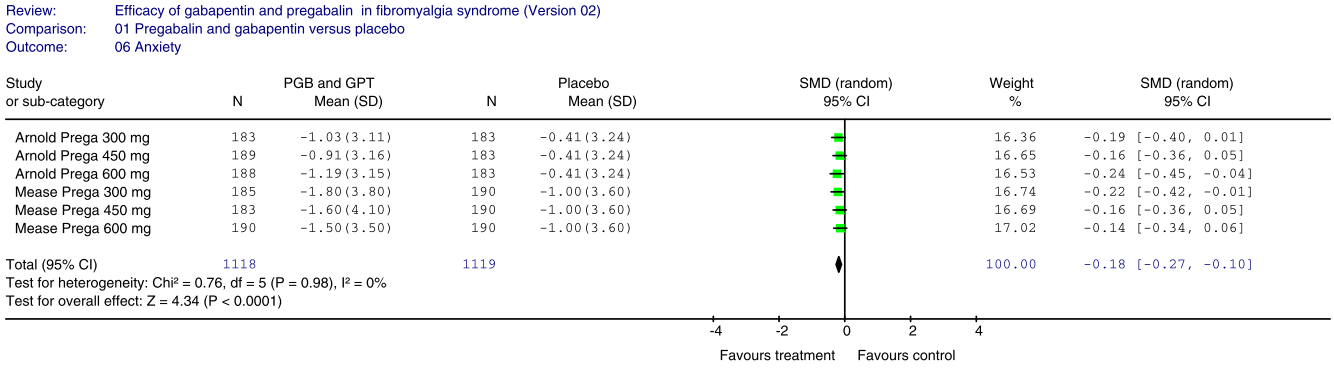

Fig. 6. Treatment effect of pregabalin on anxiety at posttreatment.

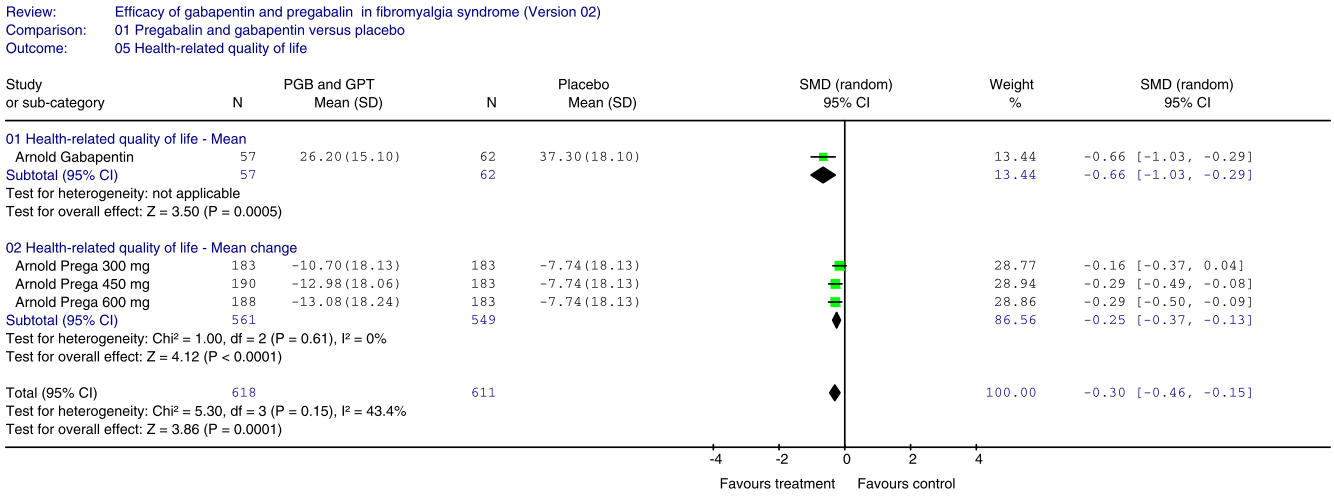

Fig. 7. Treatment effect of pregabalin and gabapentin on health-related quality of life at posttreatment.

−0.20; $I^2 = 41.7\%$; $p < 0.001$), fatigue (SMD −0.16, 95% CI −0.23, −0.09; $I^2 = 0\%$; $p < 0.001$), and anxiety (SMD −0.18, 95% CI −0.27, −0.10; $I^2 = 0\%$; $p < 0.001$), as well as for improved sleep (SMD −0.39, 95% CI −0.48, −0.39; $I^2 = 42.7\%$; $p < 0.001$), and HRQOL (SMD −0.30, 95% CI −0.46, −0.15; $I^2 = 42.7\%$; $p < 0.001$). The test for overall effect on depressed mood was not significant (SMD −0.12, 95% CI −0.30, 0.06; $I^2 = 46.8\%$; $p = 0.18$). Based on Cohen's categories for evaluating the magnitude of effect sizes, the effect

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of GPT/PGB therapy was negligible for fatigue, depressed mood, and anxiety and was small for pain, sleep, and HRQOL. The reduction of pain fulfilled the criteria of a clinically important change of at least one point on an 11-point scale [11].

The results of the meta-analysis are mainly confirmed by a qualitative analysis of the outcomes of those studies which could not be meta-analyzed: one study [9] reported that PGB was not superior to placebo regarding depressed mood. One study found no superiority of all PGB arms over placebo for anxiety [10]. The outcomes on HRQOL were inconsistent: Crofford and co-workers [9] reported superiority of PGB over placebo in the FIQ total score as well as in the component scores of the SF-36. Two studies [10,28] reported superiority of PGB over placebo in some FIQ- and SF-36 subscales, whereas another study [24] did not find significant differences in both measures.

3.3.4. Treatment benefits and potential harms

The NNT to achieve at least a 30% pain reduction is presented in Table 3 (online).

The pooled NNT (all dosages) of five studies with a standard design [2,3,10,24,28] for an at least 30% pain reduction was 8.5 (95% CI 6.4, 12.6). In the study with an EERW design the NNT (all dosages) for a sustained $\geqslant$30% pain reduction at the end of treatment was 3.5 (95% CI 2.7, 4.8).

There was no significant difference regarding the percentages of patients with an at least 30% pain reduction between PGB 300, 450, and 600 mg/d and GPT 1200–2400 mg/d. There was a significant difference between PGB 300 and 450 mg for a sustained at least 30% pain reduction in the study with an EERW design ($p = 0.04$), but not for the other comparisons of dosages. Withdrawals due to lack of efficacy occurred significantly more often with placebo than with GPT and PGB in all studies ($p < 0.0001$) except PGB 150 mg/d.

Adverse events and resulting NNHs are presented in Table 4 (online). The pooled NNH of five studies [2,3,10,24,28] for a dropout because of lacking efficacy was −18.3 (95% CI −13.0, −30.5). Withdrawals due to adverse events occurred significantly more often with GPT and PGB than with placebo ($p < 0.001$) except PGB 150 mg/d. The pooled NNH of five studies [2,3,10,24,28] (all dosages) for a dropout due to treatment-related adverse events was 9.5 (95% CI 7.6, 12.8). There was a significant overall difference between placebo and PGB 300, 450, and 600 mg/d regarding the dropout rates ($p = 0.007$), treatment-related adverse events ($p = 0.005$), dizziness ($p = 0.001$), somnolence ($p = 0.04$), weight gain ($p = 0.02$), peripheral edema ($p = 0.03$), and negative neurocognitive effects ($p = 0.003$). PGB 600 mg/d and 450 mg/d led to significantly more dropouts due to drug-related adverse events ($p = 0.05$; $p = 0.02$) and serious treatment-related events (both $p = 0.03$) than 300 mg/d. GPT compared to placebo had more dropouts due to side effects ($p = 0.005$), dizziness ($p = 0.01$), and weight gain ($p = 0.01$). The frequency of drug-related adverse events was lower in the study with EERW design [9] during the double-blind phase than in the studies with a conventional design (all p-values < 0.01). Within the open-label phase of this study the

Table 3
Efficacy of gabapentin and pregabalin in pain reduction.

Author	Gabapentin 1200–2400 mg	P 150 mg	P 300 mg	P 450 mg	P 600 mg	Placebo
Drop out due to lack of efficacy (Standard design)						
Crofford, 2005		12/132 (9%)	6/134 (5%)	8/132 (6%)		18/131 (14%)
Arnold, 2007	1/75 (1%)					2/75 (3%)
Arnold, 2008			8/183 (4%)	6/190 (3%)	6/188 (3%)	20/184 (11%)
Mease, 2008			9/185 (5%)	6/183 (3%)	3/190 (3%)	22/190 (12%)
Pauer, 2008			6/183 (3%)	3/182 (2%)	5/186 (3%)	8/184 (4%)
Sum	1/75 (1%)	12/132 (9%)	29/685 (4%)	23/687 (3%)	14/564 (3%)	Pregabalin: 68/689 (10%)
NNT (95%CI)	−75.0 (−17.2,31.8)	−128.5 (−16.2,21.7)	−17.7 (−12.0, −33.9)	−15.3 (−11.0, −25.5)	−13.5 (−10.4, −20.8)	
$\geqslant$30% pain reduction (Standard design)						
Crofford, 2005		41/132 (31%)	51/134 (38%)	63/132 (48%)		36/131 (27%)
Arnold, 2007	38/75 (50.7%)					23/75 (31%)
Arnold, 2008			76/183 (42%)	94/190 (50%)	88/188 (47%)	56/184 (30%)
Mease, 2008			80/185 (43%)	79/183 (43%)	84/190 (44%)	67/190 (35%)
Pauer, 2008			59/183 (32%)	60/182 (33%)	48/186 (26%)	35/184 (19%)
Sum	38/75 (51%)	41/132 (31%)	266/685 (39%)	297/687 (43%)	220/564 (39%)	Pregabalin: 194/689 (28%)
NNT (95%CI)	5.0 (2.8;21.7)	34.4 (−17.6, 8.7)	9.4 (6.4, 17.5)	6.6 (5.0, 9.9)	9.2 (6.2, 17.7)	
Sustained $\geqslant$ 30% pain reduction (EERW design)						
Crofford, 2008			49/63 (78%)	45/73 (62%)	95/143 (66%)	113/287 (39%)
NNT (95% CI)			2.6 (2.0,3.7)	4.5 (2.9,10.0)	3.7 (2.7,5.7)	
$\geqslant$50% pain reduction (Standard design)						
Crofford, 2005		17/132 (13%)	25/134 (19%)	38/132 (29%)		17/131 (13%)
Arnold, 2007	NR					
Arnold, 2008			44/183 (24%)	52/190 (27%)	57/188 (30%)	28/184 (15%)
Mease, 2008			NR	NR	NR	NR
Pauer, 2008			33/183 (18%)	33/182 (18%)	28/186 (15%)	17/184 (9%)
Sum		17/132 (13%)	102/500 (20%)	123/504 (24%)	85/374 (23%)	62/499 (12%)
NNT (95%CI)		22.0 (−16.6, 14.6)	12.5 (8.0,29.3)	8.3 (6.0,13.8)	9.7 (6.5, 19.4)	
Drop out due to lack of efficacy						
Crofford, 2005		12/132 (9%)	6/134 (5%)	8/132 (6%)		18/131 (14%)
Arnold, 2007	1/75 (1%)					2/75 (3%)
Arnold, 2008			8/183 (4%)	6/190 (3%)	6/188 (3%)	20/184 (11%)
Crofford, 2008		NP	NP	NP	NP	NP
Mease, 2008			9/185 (5%)	6/183 (3%)	3/190 (3%)	22/190 (12%)
Pauer, 2008			6/183 (3%)	3/182 (2%)	5/186 (3%)	8/184 (4%)
Sum	1/75 (1%)	12/132 (9%)	29/685 (4%)	23/687 (3%)	14/564 (3%)	All: 70/764 (9%)
NNT (95%CI)	−75.0 (−17.2,31.8)	−128.5 (−16.2, 21.7)	−17.7 (−12.0, −33.9)	−15.3 (−11.0, −25.5)	−13.5 (−10.4, −20.8)	Pregabalin: 68/689 (10%)

Abbreviations: NNT, Number needed to treat; EERW, Enriched enrollment design; NP, Not possible due to study design; NR, Not reported.

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Table 4
Adverse events with numbers needed to harm of gabapentin and pregabalin.

Author	Gabapentin 1200–2400 mg	P 150 mg	P 300 mg	P 450 mg	P 600 mg	Placebo
Drop out due to treatment-related adverse events						
Crofford, 2005		11/132 (8%)	10/134 (8%)	17/132 (13%)		10/131 (8%)
Arnold, 2007	12/75 (16.0%)					7/75 (9%)
Arnold, 2008			31/183 (17%)	43/190 (23%)	50/188 (27%)	20/184 (11%)
Crofford, 2008			12/63 (19%)	13/73 (18%)	22/143 (15%)	20/287 (7%)
Mease, 2008			35/185 (19%)	41/183 (22%)	62/190 (33%)	19/190 (10%)
Pauer, 2008			36/183 (20%)	38/182 (21%)	47/186 (25%)	23/184 (13%)
Sum	12/75 (16%)	11/132 (8%)	124/748 (17%)	152/760 (20%)	181/707 (26%)	All: 99/1051 (9%) Pregaba-lin: 92/976 (9%)
NNH 95% CI	7.5 (4.5;23.4)	−91.5 (−16.2, 25.2)	14.0 (9.6, 25.5)	9.5 (7.2, 13.9)	6.2 (5.0, 8.0)	
Serious treatment-related adverse events						
Crofford, 2005		NR	NR	NR	NR	NR
Arnold, 2007	No details					No details; no significant difference
Arnold, 2008			15/183 (8%)	18/190 (10%)	26/188 (14%)	6/184 (3%)
Crofford, 2008			6/63 (10%)	8/73 (11%)	16/143 (11%)	3/287 (1%)
Mease, 2008			15/185 (8%)	14/183 (8%)	24/190 (13%)	13/190 (7%)
Pauer, 2008			19/183 (10%)	17/182 (9%)	19/186 (10%)	6/184 (3%)
Sum			55/551 (10%)	57/628 (9%)	85/707 (12%)	Pregabalin: 28/845 (3%)
NNH 95% CI			15.0 (10.8, 25.7)	17.3 (12.0, 31.1)	11.5 (8.8, 16.0)	
Selected adverse events						
Dizziness						
Crofford, 2005		30/132 (23%)	42/134 (31%)	65/132 (50%)		14/131 (11%)
Arnold, 2007	19/75 (25%)					7/75 (9%)
Arnold, 2008			51/183 (28%)	71/190 (37%)	79/188 (42%)	14/184 (8%)
Crofford, 2008			NR	NR	NR	NR
Mease, 2008			60/185 (32%)	80/183 (44%)	88/190 (46%)	16/190 (8%)
Pauer, 2008			67/183 (37%)	70/182 (39%)	90/186 (48%)	23/184 (13%)
Sum	19/75 (25%)	30/132 (23%)	220/685 (32%)	286/687 (42%)	257/564 (46%)	All: 74/764 (10%) Pregabalin: 67/689 (10%)
NNH 95% CI	6.3 (3.6, 24.1)	7.7 (4.9, 18.1)	4.5 (3.8, 5.5)	3.1 (2.8, 3.6)	2.8 (2.5, 3.2)	
Somnolence/sedation						
Crofford, 2005		21/132 (16%)	37/134 (28%)	37/132 (28%)		6/131 (5%)
Arnold, 2007	14/75 (19%)					6/75 (8%)
Arnold, 2008			23/183 (13%)	37/190 (20%)	41/188 (22%)	7/184 (4%)
Crofford, 2008			NR	NR	NR	NR
Mease, 2008			39/185 (21%)	44/183 (24%)	53/190 (28%)	10/190 (5%)
Pauer, 2008			36/183 (20%)	23/182 (13%)	33/186 (18%)	10/184 (5%)
Sum	14/75 (19%)	21/132 (16%)	135/685 (20%)	141/687 (21%)	127/564 (23%)	All: 39/764 (5%) Pregabalin 33/689 (5%)
NNH 95% CI	9.4 (4.7, 1269.6)	9.0 (5.7, 21.4)	6.7 (5.5, 8.7)	6.4 (5.2, 8.1)	5.6 (4.7, 7.2)	
Fatigue/asthenia						
Crofford, 2005		7/132 (5%)	12/134 (9%)	11/132 (8%)		8/131 (6%)
Arnold, 2007	6/75 (8%)					5/75 (7%)
Arnold, 2008			15/183 (8%)	11/190 (6%)	17/188 (9%)	8/184 (4%)
Crofford, 2008			3/63 (5%)	2/73 (3%)	3/143 (2%)	3/287 (1%)
Mease, 2008			13/185 (3%)	10/183 (2%)	11/190 (5%)	5/190 (3%)
Pauer, 2008			11/183 (6%)	26/182 (14%)	14/186 (8%)	10/184 (5%)
Sum	6/75 (8%)	7/132 (5%)	54/748 (7%)	60/760 (8%)	45/707 (6%)	All: 39/1051 (4%) Pregabalin: 34/976 (3.5%)
NNH 95% CI	75.0 (10.3, 14.3)	NA	26.8 (16.9, 64.4)	22.7 (15.0, 46.0)	34.7 (19.9, 134.1)	
Weight gain						
Crofford, 2005		10/132 (8%)	13/134 (10%)	9/132 (7%)		2/131 (2%)
Arnold, 2007	6/75 (8%)					0/75 (0%)
Arnold, 2008			22/183 (12%)	24/190 (13%)	26/188 (14%)	4/184 (2%)
Crofford, 2008			1/63 (2%)	3/73 (4%)	6/143 (4%)	1/287 (0.3%)
Mease, 2008			15/185 (8%)	16/183 (9%)	26/190 (14%)	5/190 (3%)
Pauer, 2008			23/183 (13%)	23/182 (13%)	24/186 (13%)	6/184 (3%)
Sum	6/75 (8%)	10/132 (8%)	74/748 (10%)	75/760 (10%)	82/707 (12%)	All: 18/1051 (2%) Pregabalin: 18/976 (2%)
NNH 95% CI	12.5 (7.1, 53.8)	17.5 (9.7, 87.8)	12.4 (9.7, 17.4)	12.5 (9.7, 12.4)	10.3 (8.2, 13.8)	
Peripheral edema						
Crofford, 2005		7/132 (5%)	9/134 (7%)	14/132(11%)		1/131 (1%)
Arnold, 2007	12/75 (16%)					6/75 (8%)
Arnold, 2008			12/183 (7%)	12/190 (6%)	23/188 (12%)	5/184 (3%)
Crofford, 2008			2/63 (3%)	3/73 (4%)	3/143 (2%)	2/287 (1%)
Mease, 2008			5/185 (3%)	4/183 (2%)	10/190 (5%)	2/190 (1%)
Pauer, 2008			16/183 (9%)	12/182 (7%)	22/186 (12%)	5/184 (3%)
Sum	12/75 (16%)	7/132 (5%)	44/748 (6%)	45/760 (6%)	58/707 (8%)	All: 21/1051 (2%) Pregabalin: 15/976 (2%)

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Table 4 (*continued*)

Author	Gabapentin 1200–2400 mg	P 150 mg	P 300 mg	P 450 mg	P 600 mg	Placebo
NNH	12.5 (5.5, 43.1)	NA	23.0 (16.1, 40.1)	22.8 (16.1, 39.4)	15.0 (11.3, 22.2)	
Negative neurocognitive effects						
Crofford, 2005*		1/132 (1%)	5/134 (4%)	7/132 (5%)		0/131
Arnold, 2007	NR					
Arnold, 2008**			9/183 (5%)	12/190 (6%)	14/188 (7%)	2/184 (1%)
Crofford, 2008			NR	NR	NR	NR
Mease, 2008***			15/185 (8%)	12/183 (7%)	17/190(9%)	2/190 (1%)
Pauer, 2008**			10/183 (6%)	11/182 (6%)	15/186 (8%)	3/184 (2%)
Sum		1/132 (1%)	39/685 (6%)	42/687 (6%)	46/564 (8%)	Pregabalin: 7/689 (1%)
NNH		NA	21.4 (15.2, 35.9)	19.6 (14.2, 31.7)	14.0 (10.5, 21.0)	

Abbreviations: All, Gabapentin and pregabalin studies; NNH, Number needed to harm; NR, Not reported.
*Confusion; **Disturbed attention; ***Thinking abnormal.

frequency of drug-related adverse events was reported for all dosages of PGB pooled together and was as high as in the studies with a parallel design. PGB 150 mg/d did not differ significantly from placebo regarding specific side effects.

There were some minor and transient deviations in laboratory tests, which were not considered relevant by the investigators.

3.3.5. Sensitivity analysis (can be put online)

There were no significant differences (overlapping 95% confidence intervals) of the effect sizes between studies with moderate and high methodological quality (details not presented). Due to the predefined criteria only a subgroup analysis of the 300, 450, and 600 mg/d doses of PGB on pain was possible. The effect of the different doses of PGB on pain was small: Cohen's g was −0.24 (95% CI −0.36; −0.12) for 300 mg/d, −0.33 (95% CI −0.48, −0.17) for 450 mg/d, and −0.30 (−0.51, −0.09) for 600 mg/d.

4. Discussion

The aim of this systematic review and meta-analysis was to determine the clinical relevance of GPT/PGB for the treatment of FMS. We found strong evidence for the efficacy of GPT and PGB in reducing pain and sleep disturbances, however, with small effect sizes. The pooled NNT to achieve a moderately important clinical change in pain (at least 30% reduction) was eight. We found strong evidence against a favorable effect on depressed mood, anxiety, and fatigue. There was conflicting evidence on the improvement of HRQOL by both drugs. The dosages 300, 450, and 600 mg/d PGB did not differ in pain reduction as to the small effect size. The NNT to reach an at least 30% pain reduction. The incidence of some adverse events (dropout rates due to drug-related adverse events; side effects like dizziness and somnolence) increased with the dose of PGB. We found limited evidence that the efficacy and side effects of PGB 150 mg/d did not differ from placebo.

Because only one study was available on GPT with a rather small number of patients, this meta-analysis does no allow a conclusive comparison of GPT and PGB.

The internal validity of the RCTs analyzed was limited for the following reasons: First, serum levels were not measured to assess patients' adherence to the treatment scheme. Second, no study controlled the outcomes for the dosage of concomitant analgesic medication. Only one study compared the amount of co-medication between verum and placebo [9]. The influence of this co-medication on study outcomes is unclear. Third, the internal validity of EERW designs in chronic pain trials is discussed controversially. Staud and Price argue that unblinding may have occurred during the withdrawal phase after open-label treatment, and that this may have contributed to incorrect estimates of the difference between drug and placebo conditions [30, 34]. However, Crofford [9] conducted multiple sensitivity analyses and found no evidence that such unblinding occurred. Fourth, some studies did not report the results of all outcomes and side effects assessed.

The external validity of the RCTs analyzed was limited by the following: Although the studies lasted up to 26 weeks, the lack of follow-up after treatment cessation leaves the question unanswered whether GPT and PGB have long-term beneficial effects on FMS symptoms and which is the optimal treatment duration. Second, despite evidence of higher prevalences of mental disorders in FMS [13], only one study performed a standardized psychiatric interview. No study performed subgroup analyses among participants with and without depressive disorders. Third, no statements are possible on the efficacy of GPT and PGB in men, non-Caucasians, and patients older than 65 years, because these subgroups were not analyzed. Fourth, since most studies excluded patients with severe somatic diseases like inflammatory arthritic diseases, it is unknown whether GPT and PGB are effective in these patients with FMS. Fifth, because of the incomplete reporting of patient recruitment, it remains unclear if the results will also apply for FMS patients in primary care. The median percentage of randomized patients was only 64% of all patients screened, which also indicates that the study samples may not represent the general population of patients with FMS. Especially those patients who are "difficult to be treated" in clinical practice (e.g. severely depressed patients; patients applying for a disability pension) were excluded. Sixth, the benefits of GPT and PGB do not clearly preponderate their risks. NNTs of 7–9 for the effective dosages to achieve an at least 30% pain reduction are contrasted with NNHs of 6–14 for discontinuation of treatment due to adverse events. There are relevant side effects with NNHs of 3–4 for dizziness and 6–7 for somnolence. Moreover, central nervous system side effects such as confusion, disturbed attention, euphoric mood, and anxiety were inconsistently reported in the trials with a pooled NNH of 14–21. These neurocognitive side effects are of special relevance, because they can increase the "fibrofog" which is prevalent in many patients [18]. Moreover, these side effects can interfere with daily functioning such as driving a car. The NNHs of 10–12 for weight gain and 15–23 for peripheral edema might be relevant for obese patients. The NNHs calculated are in favor of PGB because we included the low frequency of adverse events in the double-blind phase of the study with an EERW design. The data of the study with the EERW design indicate that the frequency of side effects diminishes after 6 weeks.

Our findings are partially consistent with current reviews on the pharmacological treatment of FMS with PGB. We agree with a recent review which concluded that PGB has a multidimensional effect in the treatment of FMS and is associated with a clinically significant improvement in several outcome measures related to core symptoms of the syndrome [22]. Our systematic review

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including meta-analysis shows that GPT and PGB reduce pain and sleep disturbances, but not other key symptoms such as fatigue, depressed mood, and anxiety. We only partially share the optimism of Späth on the safety of PGB [33]. Our results of a higher frequency of side effects of PGB 600 mg/d compared to lower dosages are in line with the results of a recent meta-analysis which pooled the data of RCTs with PGB in neuropathic pain (eight studies) and FMS (one study; [10]). The limitations of only one study with an EERW design in FMS given in our results confirm the conclusion of the pooled analysis [35]: The EERW design favored a positive outcome for PGB, because the NNTs to maintain an at least 30% pain reduction were smaller than the ones to reach an at least 30% pain reduction in a conventional design. In contrast to neuropathic pain [35], we found no superiority of 600 mg compared to 300 mg PGB.

This review has limitations. First, since demographics and comorbidities of study participants and the amount of co-medication were not reported, these possible sources of heterogeneity could not be examined. Second, the outcomes for fatigue, depressed mood, and HRQOL of two published studies could not be included into meta-analyses because the necessary data were not given in the publication and not provided by the authors and Pfizer upon request. Third, there is no gold standard of the methods used in meta-analyses. There are limitations of some methods used in this paper such as the use of I^2 for assessing the amount of heterogeneity in random-effects meta-analysis [20,26]. Cohen's categories of effect sizes are relative not only to each other, but particularly to the specific content and research method being employed in any given investigation [7].

In conclusion, the alpha-2-delta-ligands GPT and PGB have enriched the scope of pharmacological therapy and study designs in FMS. As to the number of patients included into studies, PGB is the best-studied drug in the treatment of FMS. For clinical practice we recommend to consider concomitant diseases and patients' preferences before treatment is initiated. Non-pharmacological therapies whose efficacy had been demonstrated by systematic reviews and meta-analysis [15] such as multicomponent therapy (aerobic exercise and psychological therapy) should be offered to the patient as alternatives or add-on therapies [36]. The usage of GPT and PGB can be considered for the treatment of pain and sleep disturbances in FMS patients. Because of some dose-dependent relevant side effects of both drugs the that is to say that treatment should start with low dosage and the dosage should be increased slowly with small dosages [31]. The patient should be titrated to dosages of 300 mg/d. Since evidence for a long-term effect of GPT and PGB in FMS is still lacking and relevant side effects are associated with the treatment with alpha-2-delta-ligands, their effects should be re-evaluated at regular intervals to determine whether benefits outweigh side effects. To patients with additional symptoms like depressed mood, anxiety, and fatigue, treatments which are effective in reducing these symptoms like antidepressant or multicomponent therapy should be offered [15,16].

The following issues should be addressed in future trials: It should be tested whether the beneficial effect of GBT and PGB on FMS symptoms persists after cessation of therapy and if the drugs reduce FMS-related costs. The identification of patient characteristics associated with positive and negative therapeutic outcomes are needed to better target pharmacological therapy of FMS. Future studies should include patients with somatic and mental comorbidities. We hope that the study group of PGB will use the possibilities of a pooled analysis of the studies to perform subgroup analysis of male and non-white patients and patients with elevated depression and/or anxiety scores of the HADS. Because of the importance of meta-analysis in evidence-based medicine, reviewers of scientific journals should guarantee that all outcomes of RCTs are reported in an appropriate manner.

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