Meta-analysis on the Role of Pregabalin in Fibromyalgia

Andri Reza Rahmadi, MD,[1] Guntur Darmawan, MD,[2,3] and Laniyati Hamijoyo, MD[1]

Abstract

Background: Fibromyalgia is a difficult-to-treat chronic musculoskeletal pain and tenderness syndrome. It is considered due to augmented pain processing in central nervous system. Interest in antiepileptic drugs, included pregabalin, for treatment of fibromyalgia is currently growing. This study aimed to investigate the effectiveness of pregabalin for fibromyalgia.

Methods: We conducted the study according to the meta-analysis PRISMA guideline. Relevant randomized controlled trials (RCTs) were identified from a search of PubMed and Cochrane databases. Quality of selected studies was assessed using Jadad score for randomized placebo-controlled trials (RCT). Primary outcome was pain score reduction (30% and 50% reduction) and secondary outcome was patient global impression of change. Statistical analysis was performed using Review Manager 5.3.

Results: Six international, multicenter, high-quality RCTs with 8-15 weeks duration of treatment met inclusion criteria. Four studies used different fixed dose (300 mg/d, 450 mg/d, 600mg/d) and 2 studies used titrated dose in evaluating the efficacy of pregabalin. There was statistically significant benefit of pregabalin over placebo in mean pain score reduction [odds ratio (OR) 1.81, 95% confidence interval (CI) 1.56-2.10 p < 0.00001 in fixed dose pregabalin 30% pain reduction; OR 2.06 95% CI 1.66-2.56 p < 0.00001 in fixed dose pregabalin 50% pain reduction; OR 1.53 95% CI 1.10-2.13 p 0.01 in titrated dose pregabalin 30% pain reduction; OR 1.80 95% CI 1.12-2.88 p 0.01 in titrated dose pregabalin 50% pain reduction]. Pregabalin also demonstrated significantly better patient global impression of change than placebo. No heterogeneity was seen in most groups. No publication bias was observed.

Conclusion: Our study showed pregabalin monotherapy was effective for pain treatment associated with fibromyalgia. Further studies with longer treatment duration are needed to confirm the long-term effectiveness of pregabalin for fibromyalgia treatment.

Keywords: Fibromyalgia, pregabalin, meta-analysis

Introduction

Fibromyalgia is a worldwide common, chronic musculoskeletal pain disorder which is characterized by widespread pain and tenderness. It is frequently accompanied by insomnia, fatigue, depression, and anxiety. According to US National Health Interview Survey, the prevalence was 1.75% or 3.94 million persons in 2012.[1-4]

At present, treatment of fibromyalgia is symptom based, aiming to alleviate pain, increase restorative sleep, and improve physical function. Pharmacologic treatments include medications that have a neuromodulatory function, such as tricyclic compounds, selective serotonin reuptake inhibitor and serotonin/norepinephrine reuptake inhibitor antidepressants, analgesics, muscle relaxants, and hypnotics. Many trials performed to evaluate the most suitable medication for fibromyalgia, including gabapentin, several antidepressants. However, no single agent has demonstrated consistent efficacy across all symptom domains.[5-7] Several studies evaluating pregabalin as promising treatment in fibromyalgia.[1,2,5,8-11]

Our study aimed to evaluate the efficacy and safety of pregabalin in treatment of fibromyalgia in adult patient.

Methods

Study Search Strategy and Selection. We conducted systematic literature search of Cochrane and PubMed database (from 2000 to December 2019). We used following search terms for searching relevant literature with research subjects limited to humans and adults: "fibromyalgia" AND "pregabalin" AND "randomized controlled trial" OR "randomized, double blind, placebo-

[1] Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia
[2] Department of Internal Medicine, Faculty of Medicine, Krida Wacana Christian University, Jakarta, Indonesia
[3] Department of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia

Correspondence: Andri Reza Rahmadi, MD; rahmadiandri@yahoo.com

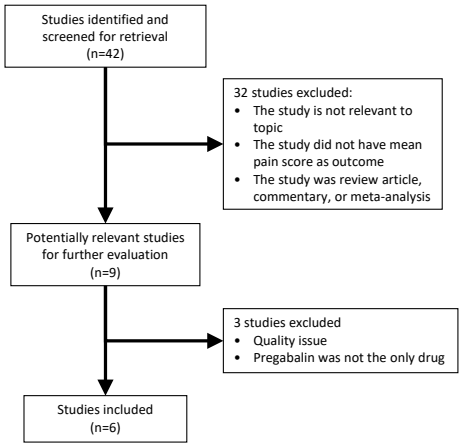


Figure 1. Flow chart of study selection

controlled trial" OR "RCT". Manual search was performed to look for additional relevant studies. Only article performed in human subject and published in English were included. All reviewers did article selection and assessment. The inclusion criteria were: (i) published randomized, double blind, placebo-controlled trial; (ii) studies were conducted in adult; (iii) pregabalin either fixed dose or titrated dose in the treatment group; (iv) the outcome was decrease in mean pain score, patient global impression of change; (v) study had adjusted odds ratio (OR) with 95% confidence interval (CI).

Each reviewer assessed the potential source of bias and quality of each selected study by Jadad score. Only studies with good quality were included in our final analysis review. Discrepancies and disagreements were resolved by consensus.

Statistical Analysis. We used the fully adjusted OR with 95% CI and pooled it. A fixed-effect model approach was

Table 1. Characteristic of included studies in association between pregabalin and fibromyalgia

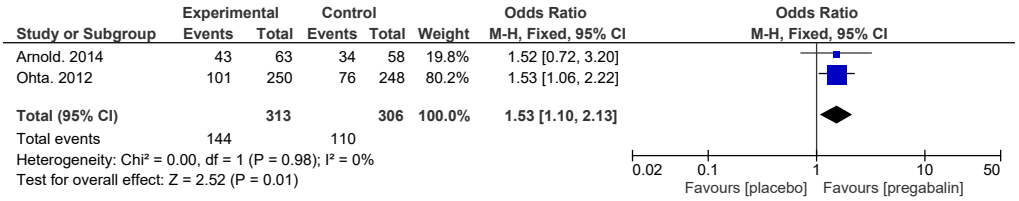
No	Author Year	Country	Subjects & age	Intervention	Duration	Outcome
1	Arnold 2008	United States	745 peoples Placebo 184 people Pregabalin 561 people >18 y o	Pregabalin 300 mg Pregabalin 450 mg Pregabalin 600 mg	14 weeks	30% decrease in mean pain score 50% decrease in mean pain score Patient global impression of change
2	Crofford 2005	United States	529 peoples Placebo 131 people Pregabalin 398 people >18 y o	Pregabalin 150 mg Pregabalin 300 mg Pregabalin 450 mg	26 weeks	30% decrease in mean pain score 50% decrease in mean pain score Patient global impression of change
3	Mease 2008	United States	748 peoples Placebo 197 people Pregabalin 558 people >18 y o	Pregabalin 300 mg Pregabalin 450 mg Pregabalin 600 mg	13 weeks	30% decrease in mean pain score Patient global impression of change
4	Pauer 2011	United States	736 peoples Placebo 184 people Pregabalin 552 people >18 y o	Pregabalin 300 mg Pregabalin 450 mg Pregabalin 600 mg	14 weeks	30% decrease in mean pain score 50% decrease in mean pain score Patient global impression of change
5	Arnold 2014	United States	320 peoples Placebo 58 people Pregabalin 63 people >18 y o	Titrated dose of pregabalin	13 weeks	30% decrease in mean pain score 50% decrease in mean pain score
6	Ohta 2012	Tokyo	498 peoples Placebo 248 people Pregabalin 250 people >18 y o	Titrated dose of pregabalin	15 weeks	30% decrease in mean pain score 50% decrease in mean pain score

M: male; F: female

Table 2. Risk of bias assessment for included trials

No.	Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Selective reporting
1.	Arnold 2008	+	+	+	+	+	+
2.	Crofford 2005	+	+	+	+	+	+
3.	Mease 2008	+	+	+	+	+	+
4.	Pauer 2011	+	+	+	+	+	+
5.	Arnold 2014	+	+	+	+	+	+
6.	Ohta 2012	+	+	+	+	+	+

Titrated pregabalin for the treatment > 30% decrease in mean pain score



Titrated pregabalin for the treatment > 50% decrease in mean pain score

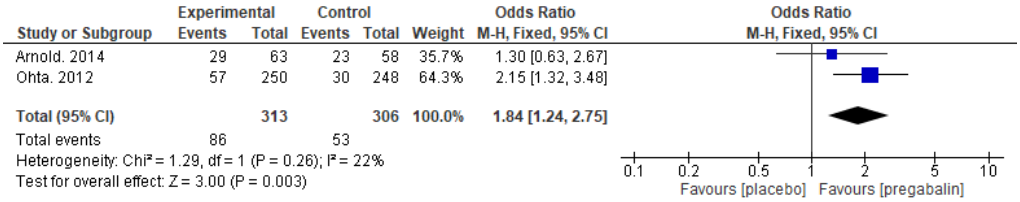


Figure 2. Titrated dose of pregabalin in mean pain score reduction

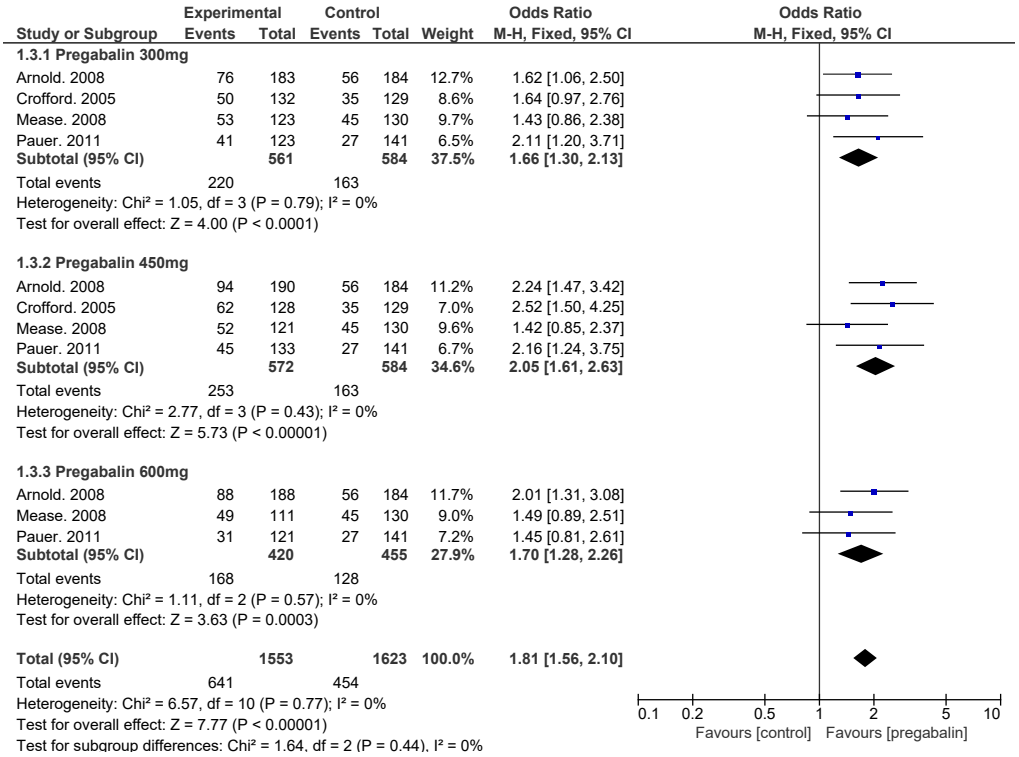


Figure 3a. Fixed dose of pregabalin in mean pain score reduction (> 30% decrease in mean pain score)

use if there was no heterogeneity; otherwise, a random-effect model was used. Heterogeneity was assessed using I^2. Negative value of I^2 was put equal to 0. I^2 values ranged from 0% (no observed heterogeneity) to 100%, and interpreted according to Cochrane Consumers and Communication Review Group.

Publication bias was assessed by funnel plot. Statistical analysis was performed using *Review Manager 5.3*.

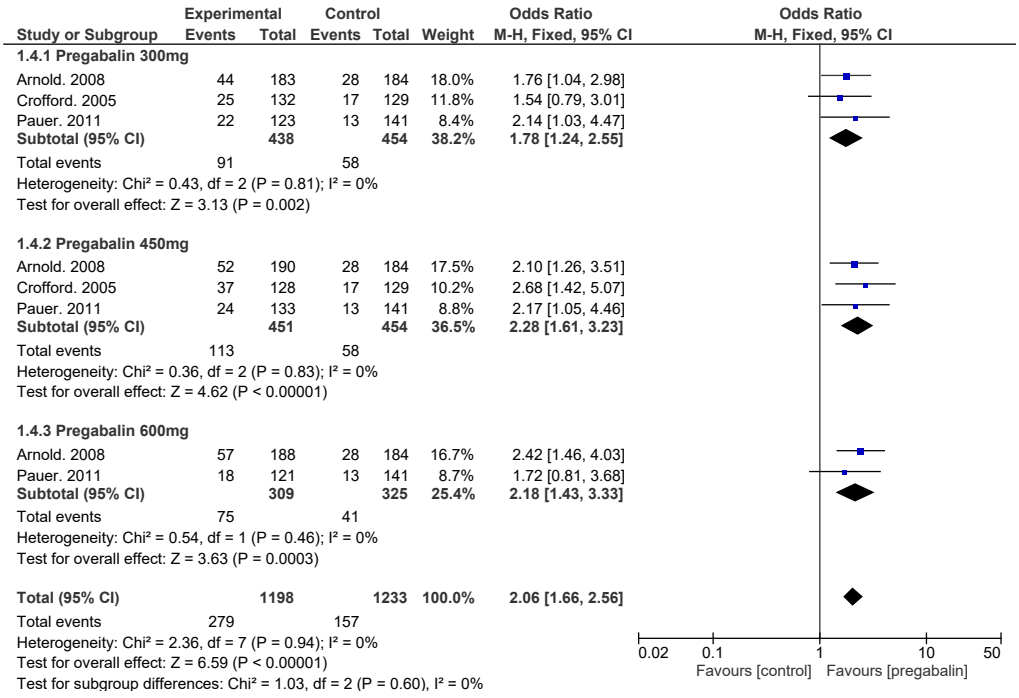


Figure 3b. Fixed dose of pregabalin in mean pain score reduction (> 50% decrease in mean pain score)

Results

Our initial search yielded 42 studies. After the final screening, 6 international, multi-center, high-quality RCTs met inclusion criteria. (*Figure 1*) The studies were published between 2005 and 2014, and the characteristics of which are summarized in *Table 1*. We assessed the risk of bias for each included study. (Table 2) Four studies used different fixed dose (300 mg/day, 450 mg/day, 600mg/day)[2,5,9,11] and 2 studies used titrated dose (150 mg/day titrated up to 300 mg or 450 mg/day and 165 mg/day titrated up to 495 mg/day).[8,10] in evaluating the efficacy of pregabalin. The outcome were > 30% mean decrease in pain score, > 50% mean decrease in pain score, and patient global impression of change.

Meta-analysis result. There was statistically significant benefit with low heterogeneity of pregabalin over placebo in mean pain score reduction in titrated dose of pregabalin [odds ratio (OR) 1.53 95% confidence interval (CI) 1.10-2.13 p 0.01 I^2=0% in > 30% mean pain reduction; OR 1.80 95% CI 1.12-2.88 p 0.01 I^2=22% in > 50% mean pain reduction]. (Figure 2) Such result also demonstrated in fixed dose pregabalin groups [OR 1.81, 95% CI 1.56-2.10 p < 0.00001 I^2=0% in > 30% pain reduction; OR 2.06 95% CI 1.66-2.56 p < 0.00001 I^2=0% in > 50% pain reduction] (Figure 3a and 3b). Moreover, pregabalin also demonstrated significantly better patient global impression of change than placebo. [OR 1.79, 95% CI 1.26-2.52 p = 0.001 I^2=0% in pregabalin 300 mg; OR 2.13 95% CI 1.43-3.16 p 0.0002 I^2=23% in pregabalin 450 mg; OR 1.70 95% CI 1.09-2.67 p 0.02 I^2=11% in pregabalin 600 mg]. (Figure 4) Death was reported in either treatment group or placebo, but was not considered to be associated with study drug. Small number of subjects experienced severe adverse events but none was related to study drug. Dizziness, somnolence, weight gain in mild to moderate intensity were the most common reported adverse events, which tended to be higher in pregabalin 600 mg group. Furthermore, no significant changes in vital sign, electrocardiogram were reported. No publication bias was observed. (Figure 5)

Discussion

Fibromyalgia is a common chronic pain condition affecting quality of life. The etiology of fibromyalgia has remained unknown, but newly emerging research suggests alterations in the regulation of neurotransmitters, particularly serotonin, norepinephrine, and substance-P, and abnormality of sensory processing within the central nervous system (CNS) are involved in its pathophysiology.[9]

Previous studies reported pregabalin and gabapentin were the most potential drugs for chronic neuropathic pain, compared with other antiepileptic drugs such as phenytoin, clonazepam, valproic acid, etc. Furthermore, pregabalin was superior to gabapentin in treating fibromyalgia according to previous systematic reviews.[12,13] Pregabalin was one of the most promising effective pharmacology treatment for fibromyalgia, as shown in study by Lee.[14] It is an α2δ ligand that has analgesic, anxiolytic-like, and anticonvulsant activity. The pharmacologic actions of pregabalin appear to be

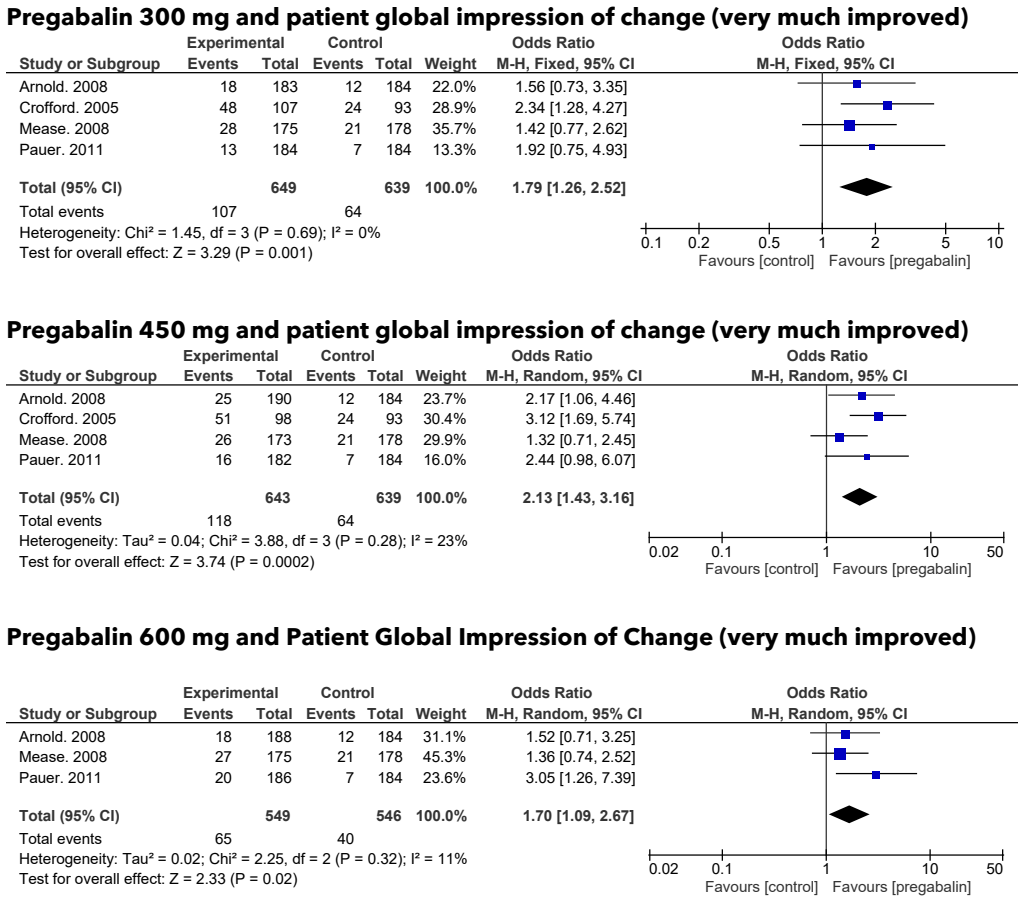


Figure 4. Fixed dose pregabalin and patient global impression of change

restricted to neurons. Potent binding of pregabalin at the α2δ ligand site reduces calcium influx at nerve terminals and, therefore, reduces the release of several neurochemicals, including glutamate, noradrenaline, and substance. The reduced neurotransmitter release caused by drug binding at the α2δ ligand site is presumed to account for the analgesic, anticonvulsant, and anxiolytic.[5,10]

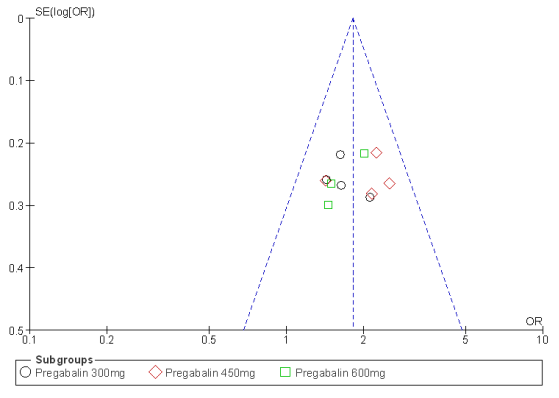


Figure 5. Funnel plot

Our study demonstrated the efficacy of pregabalin in decreasing mean pain score. The dose in fixed dose study was equal or higher than 150mg/day of pregabalin and only 1 study started titration dose from 150 mg/day. According to study by Moore, et.al. and Lee, pregabalin at 150 mg daily was not effective.[14,15] In the fixed dose studies, pregabalin showed efficacy in reducing both > 30% and > 50% mean pain score, with 450 mg pregabalin placed as the most effective dose. The finding was in line with study by Argoff, et. al. analyzing 3 RCTs demonstrated significant improvement in pain intensity score in 450 mg dose of pregabalin irrespective of comorbid osteoarthritis.[16] Pregabalin, especially at 450mg/day showed improvement in patient global impression of change. Moreover, pregabalin was associated with improvement in sleep.

As, reported by other studies, most common side effects were dizziness, somnolence with mild to moderate in severity, demonstrated in both fixed dose and titrated dose studies, depending on treatment dose.[9] Overall,

pregabalin was considered to be safe and generally well tolerated.

Meta-analysis by Straube, et. al. reported that improvement in pain intensity related with greater improvement in work interference.[17] Also, 2 previous meta-analysis using fixed dose of pregabalin demonstrated efficacy of pregabalin in treating fibromyalgia with good safety profile.[18,19] Our study evaluated the efficacy of pregabalin in fibromyalgia in two different treatment methods: titrated dose dan fixed dose. There were some limitations in our study. First, pregabalin was used as monotherapy in studies included and excluded patients with combination of drugs. Patients with fibromyalgia might also have other comorbidities which might affect health-related quality of life and the outcome measured. Second, all studies did not include active comparator; therefore, we could not compare efficacy of pregabalin to other drugs in treatment of fibromyalgia. Hence, it could compromise its' generalizability to daily clinical practice. Third, most studies having studies duration of 13-15 weeks. Therefore, future studies with longer treatment duration, comparing with active comparator including cost-effectiveness analysis are warranted to be done.

Conclusion

Pregabalin monotherapy showed effectiveness in reducing mean pain score in fibromyalgia in both fixed and titrated dose. It was also relatively safe and generally well tolerated.

Acknowledgement

The authors would like to thank Dr. Rachmat Gunadi for his advice on this research work.

Ethical approval:

This study does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest and source of funding: all authors declare no conflict of interest. The study received no external funding.

References

1. L. M. Arnold, D. L. Goldenberg, S. B. Stanford, J. K. Lalonde, H. Sandhu, P. E. Keck, et. al. (2007). Gabapentin in the treatment of fibromyalgia: A randomized, double-blinded, placebo-controlled, multicenter trial. *Arthritis & Rheumatology*. 56(4): 1336-44.
2. L. M. Arnold, I. J. Russell, E. Diri, W. R. Duan, J. P. Young, U. Sharma, et. al. (2008). A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *The Journal of Pain*. 9(9): 792-805.
3. B. Walitt, R. L. Nahin, R. S. Katz, M. J. Bergman, F. Wolfe. (2015). The prevalence and characteristics of fibromyalgia in the 2012 National Health Interview Survey. *PloS one*. 10(9): e0138024
4. L. P. Queiroz. Worldwide epidemiology of fibromyalgia. (2013). *Current Pain and Headache Reports*. 17(8):356.
5. L. J. Crofford, M. C. Rowbotham, P. J. Mease, I. J. Russell, R. H. Dworkin, A. E. Corbin, et. al. (2005). Pregabalin for the treatment of fibromyalgia syndrome: Results of a randomized, double-blinded, placebo-controlled trial. *Arthritis & Rheumatology*. 52(4):1264-73.
6. D. J. Clauw. (2014). Fibromyalgia: A clinical review. *JAMA*. 311(15):1547-55.
7. D. L. Goldenberg, C. Burckhardt, L. Crofford. (2004). Management of fibromyalgia syndrome. *JAMA*. 292(19): 2388-95.
8. L. M. Arnold, P. Arsenault, C. Huffman, J. L. Patrick, M. Messig, M. L. Chew, et. al. (2014). Once daily controlled-release pregabalin in the treatment of patients with fibromyalgia: A phase III, double-blind, randomized withdrawal, placebo-controlled study. *Current Medical Research and Opinion*. 30(10):2069-83.
9. P. J. Mease, I. J. Russell, L. M. Arnold, H. Florian, J. P. Young, S. A. Martin, et. al. (2008). A randomized, double-blind, placebo-controlled, phase III trial of pregabalin in the treatment of patients with fibromyalgia. *The Journal of Rheumatology*. 35 (3):502-14.
10. H. Ohta, H. Oka, C. Usui, M. Ohkura, M. Suzuki, K. Nishioka. (2012). A randomized, double-blind, multicenter, placebo-controlled phase III trial to evaluate the efficacy and safety of pregabalin in Japanese patients with fibromyalgia. *Arthritis research & therapy*. 14(5):217.
11. L. Pauer, A. Winkelmann, P. Arsenault, A. Jespersen, L. Whelan, G. Atkinson, et. al. An international, randomized, double-blind, placebo-controlled, phase III trial of pregabalin monotherapy in treatment of patients with fibromyalgia. (2011). *The Journal of Rheumatology*.2:11.
12. T. Tzellos, K. Toulis, D. Goulis, G. Papazisis, V. Zampeli, A. Vakfari, et. al. (2010). Gabapentin and pregabalin in the treatment of fibromyalgia: A systematic review and a meta-analysis. *Journal of Clinical Pharmacy and Therapeutics*. 35(6):639-56.
13. P. J. Wiffen, S. Derry, R. A. Moore, D. Aldington, P. Cole, A. S. C. Rice, et. al. (2013). Antiepileptic drugs for neuropathic pain and fibromyalgia: An overview of Cochrane reviews. *Cochrane Database Syst Rev*. 11: CD010567.
14. Y. H. Lee, G . G. Song. (2016). Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: A Bayesian network meta-analysis of randomized controlled trials. *Rheumatology International*. 36(5):663-72.
15. R. A. Moore, S. Straube, P. J. Wiffen, S. Derry, H. J. McQuay. (2009) Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 8(3): CD007076.
16. C. E. Argoff, B. Emir, E. Whalen, M. Ortiz, L. Pauer, A. Clair. (2016). Pregabalin improves pain scores in patients with fibromyalgia irrespective of comorbid osteoarthritis. *Pain Medicine*. 17 (11): 2100-8.
17. S. Straube, R. A. Moore, J. Paine, S. Derry, C. J. Phillips, E. Hallier, et. al. (2011). Interference with work in fibromyalgia-effect of treatment with pregabalin and relation to pain response. *BMC Musculoskeletal Disorders*. 12 (1):125.
18. S. Derry, M. Cording, P. J. Wiffen, S. Law, T. Phillips, Moore RA. (2016). Pregabalin for pain in fibromyalgia in adults. *Cochrane Database Syst Rev*. 9(9): CD0011790.
19. S. Straube, S. Derry, R. A. Moore, H. J. McQuay. (2010). Pregabalin in fibromyalgia: Meta-analysis of efficacy and safety from company clinical trial reports. *Rheumatology*. 49(4):706-15.