Document heading doi: 10.21276/apjhs.2019.6.3.8 Review Article

Comparison of Duloxetine with Lidocaine infusion in the management of fibromyalgia: A review

Eze Onyegbule Okubuiro*, Longinus Ndubuisi Ebirim

Department of Anaesthesiology, College of Health Sciences, University of Port Harcourt, Port Harcourt, Nigeria

Received: 10-08-2019 / Revised: 20-8-2019 / Accepted: 22-09-2019

ABSTRACT

Background: Fibromyalgia is a complex poly-symptomatic condition. These symptoms include chronic widespread musculoskeletal pain. No one treatment has been found to address all the symptoms of this syndrome. Pharmacological interventions which have provided improvement in the symptoms of the disease include duloxetine, lidocaine infusion and tramadol. The aim of this essay is to compare the analgesic efficacy and quality of life of fibromyalgia patients following the use of duloxetine or lidocaine in their management. Evidence derived from analysis of existing literature will be used to decide a preference for either of the two interventions. **Methods**: An electronic search of Medline, EMBASE, Nice evidence, Trip database, Cochrane Library and Science Citation Index from inception to April 2016 and update to July 2018 was done using the key words below. Google scholar search engine and manual search of relevant studies from bibliographies in literature was also employed. Quality of included Randomized control trials (RCTs) were assessed using the JADAD score (I - V). Most relevant studies were included in this review. These were independently retrieved by the two investigators and were discrepancy existed, resolved by consensus. **Discussion**: Evidence abound on the safety and efficacy of duloxetine in the management of fibromyalgia and it promises to be the ideal pharmaco-therapeutic agent for the treatment of fibromyalgia. However, some cases may be refractory to it, necessitating the use of other agents like lidocaine. There is a dearth of good quality randomized control trials in literature to support the safety and efficacy of lidocaine monotherapy in the management of fibromyalgia patients. **Conclusion**: This article explores evidence regarding use of duloxetine and lidocaine infusion in management of fibromyalgia. Although the potentials of lidocaine infusion in the treatment of this condition is acknowledged, clinical evidence from this review is insufficient to fairly compare the efficacy of duloxetine with lidocaine infusion in the management of patients with fibromyalgia.Well-designed RCTs are required to compare the qualities of these 2 interventions in management of fibromyalgia

Key words: Fibromyalgia, management, comparison, duloxetine, lidocaine, infusion, analgesia, quality-of-life

INTRODUCTION

Pain is a subjective experience; it is what the patient says hurts[1]. It is a common cause of suffering, disability and economic loss in the community. The annual incidence of chronic pain was estimated at 8.3% according to the National Pain Audit in United Kingdom, concluded in 2012 [2]. That report also showed that 11% of adults and 8% of children in the United Kingdom suffer moderate to severe chronic pain.

*Corresponding Author
Eze Onyegbule Okubuiro
Department of Anaesthesiology, College of Health Sciences, University of Port Harcourt ,Port Harcourt, Nigeria.
E-mail: ezeokb@gmail.com

The prevalence of chronic pain in the United Kingdom, derived from 7 population studies in a meta-analysis by Fayaz et al. (2016) is43.5% (95% CI, 38.4-48.6%) [3]. Chronic pain is more prevalent with increase in age, female sex, poor housing and heavy manual employment [2].

Pain may manifest as a symptom of ongoing tissue pathology or injury. However, it may also represent a disease entity, serving no useful purpose; persisting beyond the healing period. As a disease, pain adversely affects the physical, psychosocial and spiritual well-being of patients. Fibromyalgia is a syndrome characterized by chronic widespread musculoskeletal pain, reduced pain threshold with hyperalgesia and allodynia affecting more than 65% of defined tender points (trigger points) in the body. Associated features include chronic fatigue, sleep disturbance, irritable bowel syndrome and cognitive dysfunction [4]. This condition is also commonly associated with

psychological states such as depression and anxiety; and stress-related psychiatric disorder (post-traumatic stress disorder[5]. It is seen in 1-3% of the population, affecting more females than males (ratio of 2:1)[6]. Fibromyalgia is commonly noticed between the 3rd and 6th decades of life. Fibromyalgia is a complex poly-symptomatic condition which lacks one treatment that addresses all the symptoms. The European league against rheumatism (EULAR), recommends that optimal treatment of fibromyalgia requires a multimodal approach comprising non-pharmacological and pharmacological modalities with active patient participation[7]. Evidence-based guidelines for the management of fibromyalgia (by EULAR, American pain society and German association of pain therapy) did not include lidocaine infusion therapy and some large randomized control trials that assessed duloxetine, pregabalin and milnacipran[7-9]. However, a Cochrane collaboration review suggests ''combination pharmacotherapy'' in the management of this condition [10]. Cognitive behavioural therapy (CBT), aerobic exercises, heated pool therapy (balneotherapy), relaxation techniques, and hypnotherapy have shown varying degrees of success in the treatment of fibromyalgia. Pharmacological interventions which have provided improvement in the symptoms of the disease include norepinephrine /serotonin re-uptake inhibitors, selective serotonin re-uptake inhibitors, tricyclic anti-depressants, serotonin antagonists, lidocaine infusion and tramadol [7-9,11].Duloxetine tablets are taken daily(per oral)by the patient on medical instruction and require strict compliance whereas, lidocaine may be administered as a monitored intravenous infusion in the hospital once every 2-3 months. Duloxetine is recommended for the treatment for fibromyalgia. [7-9] High attrition rates seen in studies that utilized duloxetine therapy (shown below) may be attributed to its undesirable side effects. This presents a risk of poor drug compliance by patients which could be addressed by periodic (monitored) administration of lidocaine infusion. In recalcitrant fibromyalgia that is refractory to duloxetine, or if a patient demonstrates adverse reaction to duloxetine, lidocaine infusion therapy (if shown to be as good or better than duloxetine) may be employed to achieve good clinical outcome. Therefore, this review will utilize evidence from clinical research to compare the analgesic efficacy and quality of life of patients following the use of duloxetine or lidocaine infusion in the management of fibromyalgia. The objective of this review is to decide from critical analysis of existing literature, a justification for the preference of either intervention in the management of this condition.

METHODOLOGY

Electronic search of NICE Evidence, Trip database, Cochrane Library, AMED, BNI, CINAHL, EMBASE, HBE, HMIC, MEDLINE, PsychoINFO, Google scholar and Science Citation Index from inception till 2016 and updated to July 2018 was done using the search key words above. Manual search of relevant studies from bibliographies in literature were also performed. Articles were excluded if they were ongoing trials or written in a language other than English. No article compared effects of Duloxetine with Lidocaine infusion in the management of fibromyalgia,this prevented any direct comparison of the two interventions. Quality of included studies were assessed using JADAD scale (I – V). [12] Most relevant studies with JADAD scores III and above were included in this review. These were independently retrieved by the two investigators and any discrepancy was resolved by consensus. The JADAD scale was adopted because it is easy to use, reliable and validated quality assessment tool that has good correlation with risk of bias of studies. [13]Forty-two RCTs assessed the qualities of Duloxetine alone or as combination regimen in the treatment of fibromyalgia. Only 10 placebo-controlled RCTs evaluated the effects of duloxetine as monotherapy for fibromyalgia. Seven of these RCTs assessed the analgesic efficacy of duloxetine or quality of life of the participants as primary outcomes (which are relevant to this review) and were therefore considered. The best 4 out of 6 placebo-controlled RCTs on Duloxetine monotherapy in fibromyalgia that had JADAD scores III and above (by consensus) were selected for detailed discussion. There was no placebo-controlled RCT on efficacy of lidocaine infusion monotherapy for fibromyalgia in literature. Three out ofthe 4 RCTs that employed lidocaine infusion as combined-therapy for fibromyalgia had JADAD score III and above and were discussed in this review. Because of dearth of RCTs evaluating lidocaine infusion monotherapy in treatment of fibromyalgia, two retrospective studies that employed this treatment regimen were also included in this review. Studies that employed lidocaine that were excluded include; case reports (n=2), case series (n=3), audit (n= 1) and surveys (n= 2).

Literature review and critical analysis

There is no known cure for fibromyalgia [7].Treatment aims to relieve symptoms, improve function and quality of life. Pain relief following intervention in this condition, can be assessed by verbal rating scale (VRS), numerical rating scale (NRS), visual analogue scale (VAS) and brief pain inventory (BPI)[9]. Some studies have used an electronic pain diary which is

credited with a 'more accurate real-time measurement of pain'[14].A manual tender point assessment of pain threshold with dolorimetry has also been utilized to measure response to treatment. Similar uni-dimensional, self-administered tools have been used to generally evaluate fatigue and quality of life in some studies.[9] However, function and quality of life in the management of fibromyalgia are mostly assessed by a self-reported, validated fibromyalgia impact questionnaire (FIQ). The FIQ measures; physical functioning, work status, depression, anxiety, morning tiredness, pain, stiffness, fatigue and well-being during the preceding week [9]Although the pathogenesis of fibromyalgia remains poorly understood, evidence suggests central sensitization as an important pathophysiological mechanism[15]. Pain perception is a dynamic experience which results from a relationship between faciltatory and inhibitory endogenous modulation systems. The descending inhibitory systems involve the serotoninergic, noradrenergic and opioidergic pathways which are activated by higher centres in the brain.[16] Julien et al, showed a deficit of endogenous pain inhibitory systems in fibromyalgia but not in chronic back pain and therefore suggested that treatment of fibromyalgia should aim at stimulating the activity of those endogenous systems.[17]Duloxetine is recommended for the management of fibromyalgia. [7,9] Duloxetine is a balanced selective serotonin and noradrenergic reuptake inhibitor which was primarily licensed as an antidepressant. It gained approval for the management of fibromyalgia by the United States Food and Drug Agency in 2008.[18] Duloxetine inhibits the re-uptake of serotonin and nor-adrenaline in the central nervous system thereby enhancing the activities of these neurotransmitters via the descending spinal inhibitory pain pathway. The activation of this pathway hinders the transmission of nociceptive stimuli through the 'pain gates' at the dorsal horn of the spinal cord to the brain. It also exerts analgesia via sodium ion channel blockade in the CNS. It is usually administered orally at a dose of 60-120mg daily[18] Some associated side effects of duloxetine include nausea, dry mouth and dizziness; this is usually transient and reduced by graded increase in dosing of the drug. Arnold et al (2004) conducted a double-blind multi-centre randomized control trial which compared duloxetine with placebo in the treatment of fibromyalgiain 18 out-patient research centres including 207 patients with a mean age of 49 years in the United States of America. [19] Compared to the placebo-treated patients, duloxetine-treated patients showed significantly improved overall FIQ scores($p=0.027$), brief pain inventory (0.004), number of tender points (0.002) and better quality of life. While duloxetine-treated female patients (n=92/184) recorded significant improvement in most efficacy measures, their male counterparts (n=12/23) showed no significant improvement in any of the outcome measures. Although the female to male ratio in that study (8:1) suggests a higher female preponderance of this condition than earlier reported, the relatively insignificant number of the male participants (12%), impairs the generalizability of their findings to the male or entire population. The short duration of the study could not enable the determination of the long-term efficacy of duloxetine in the treatment of fibromyalgia. The study raises ethical concerns as placebo-treated patients received no other form of analgesia over the 12 weeks duration of the trial. Also, the FIQ which measured outcomes retrospectively may not have accurately represented the state of the patients after a period of one week. The power of the study (90%) was estimated to detect a treatment group difference of 1.4 points in pain severity; this may be considered much less than the general acceptable difference of 2.0 points and exposes the study to type 2 error. Although the study was powered to accommodate 200 patients, about 40% of the participants could not complete the trial. This grossly impairs the statistical power of the study and adversely affects its clinical significance. Another multi-centre randomized placebo controlled, double blind parallel group study confirmed the efficacy and safety of duloxetine 60mg daily and 60mg B.D in women with fibromyalgia.[20] The study showed that these two doses of duloxetine, provided significantly better brief pain inventory average pain severity score ($p<0.001$) than placebo. Patients in the duloxetine groups also had significantly better improvement in FIQ scores, patient global impression of improvement and quality of life measures. The effects of duloxetine on pain, mood and major depressive disorder were independent. A total of108 women (39%) withdrew from the study, this was greater than the attrition rate (30%) allowable in the design. This also adversely affects the power of the study to accurately detect response to the interventions. While a significantly greater number of patients withdrew in the duloxetine groups (n=52) due to adverse side effects, another great number from the placebo group did so due to lack of efficacy. Similar number of patients in the three groups were withdrawn from the study due to non-compliance. Also, side effects such as nausea, dry mouth, anorexia and constipation and somnolence were significantly greater in the duloxetine groups. These were more pronounced in the duloxetine 60mg B.D group, although this group benefitted from significant improvement in tender point assessments. The high

incidence of side effects may have been due to the use of one dose of duloxetine in each of the treatment groups throughout the study duration, instead of a graded increase in dose over the same period. The small treatment group differencein pain scores, accepted as significant (1.2 points) may have yielded unreliable results. Finally, this study was conducted on women only therefore cannot be generalized to the male or entire population of both genders. With the aim to determine the long-term efficacy and safety of duloxetine in the management of fibromyalgia, Russel et al. (2008) conducted anothermulti-centre randomized double-blind control trial that primarily measured pain relief using brief pain inventory (BPI). [21] Compared to placebo, patients who received duloxetine 120mg/day reported significant analgesia at 3 and 6 months respectively. Both duloxetine 30mg/day and 60mg/dayprovided significantly greater improvements compared to placebo in FIQ total scores, clinical global impressions-severity scores and multi-dimensional fatigue inventory scores. Quality of life measured by EuroQoL questionnaire-5 dimension was significantly better in the treatment groups compared to placebo at 6 months. The insignificant difference in adverse events between the placebo and treatment groups is suggestive of the safety of these doses of duloxetine in the treatment of fibromyalgia. Reasons for the high drop-out rate (37.3%), which was comparable in all the groups (p=0.645) were mainly adverse effects (Duloxetine group) or lack of efficacy (Placebo group) and patient decision (both groups). This reduces the power of the study (80%), which was designed to evaluate 140 participants in each group. It would have been more appropriate to consider a drop-out rate of 40% in the study design based on similarly high attrition rates from previous studies[16, 17]. Although the study was meant to include both sexes diagnosed with fibromyalgia from 18 years and above, most of the participants were women (94.8%); also suggesting a higher female preponderance than estimated. Both sexes recorded similar improvements following treatment with duloxetine, however, the relatively insignificant number of males (5.2%), also implies that the findings of the study cannot be generalized to the male population. Number needed to treat (NNT) was mentioned in the study design but unfortunately, it was not calculated in any of the treatment groups. Although it could be assumed that duloxetine provided significantly better analgesia in fibromyalgia after 6 months of treatment, this cannot be categorically applied to the numerous secondary outcome measures since the study was not powered to assess such.Similarly, Murakami et al (2015) conducted another multi-centre RCT to assess the efficacy and safety of duloxetine among 393 patients diagnosed with fibromyalgia. [22]They reported significant improvement in pain relief (p=0.04) and quality of life measures (p= 0.02) among duloxetine group compared with placebo group. However, improvement in quality of life is not surprising as duloxetine is also licensed for treatment of depression, which is a condition often associated with fibromyalgia. Attrition rate of 15% noticed in the duloxetine group was mostly attributed to adverse drug reaction. This could explain the reports of poor drug compliance often noticed with use of duloxetine in this condition. [19, 20]Non-drug therapies are recommended as first line treatment for fibromyalgia [6] and participants on exercise therapy and cognitive behavioural therapy prior to this study were not excluded. The confounding effect of this inclusion on the final outcome could not be ascertained in this study. And, sponsorship of that trial by an interested party (Drug company) increases the risk of bias which impairs its credibility.A systematic review by Sultan et al.(2008) involving 6 clinical trials with 1,696 patients, confirmed the efficacy and safety of duloxetine in painful diabetic neuropathy and fibromyalgia pain[23]. NNT of 6 was reported using duloxetine in both conditions. They reported more withdrawals in the duloxetine groups (15%) than the placebo (8%). Side effects were significantly higher in the treatment groups than placebo and infrequent serious adverse events were noted. They also reported that doses greater than 60mg/day did not provide additional pain relief but caused more withdrawals due to side effects. However, the statistical significance of this review is challenged by few numbers of randomized clinical trials involved.Patients with fibromyalgia have lowered thermal and mechanical pain thresholds, high response and altered temporal summation to pain stimuli. Attempts at its pharmacological management are aimed at interference with the central processing of pain. Such interference may be achieved by pain inhibition modulatory drugs which activate serotoninergic and nor-adrenergic systems[17, 18]. Pain processing can also be altered by systemic administration of drugs which inhibit the excitatory pathway such as lidocaine[24]. Lidocaine is a local anaesthetic which is also used as an anti-arrhythmic agent. It is a sodium channel blocker which has been used successfully to treat neuropathic pain[21]. It exerts its membrane stabilizing effect by reversibly binding to intracellular sodium ion channels, obstructing influx of ions thereby preventing depolarization of such tissues. This effect is experienced by all excitable tissues and accounts for the side effects experienced following systemic administration. Lidocaine is administered at a dose of

2-5mg/kg body weight by intravenous infusion over 30-60 minutes[26, 27]. Its associated side effects include hypotension, hypertension, tachycardia, arrhythmia, headache and dizziness[26]. Tinnitus, circum-oral tingling, convulsion and coma are signs of avoidable local anaesthetic toxicity. This may be treated with intralipid emulsion infusion with cardiopulmonary resuscitation, if necessary. Lidocaine is contraindicated in persons with cardiac disease, abnormal ECG and electrolyte imbalance. Careful patient selection, strict adherence to safe doses and close patient monitoring are key to reduction of adverse side effects.Lidocaine has been used successfully in the management of fibromyalgia. In 2002, a retrospective study reported efficacy and adverse effects using intravenous lidocaine infusion in the management of 106 patients with fibromyalgia[28]. The results showed that pain and psychosocial measures (using numerical rating scale), improved significantly after treatment with5mg/kg of lidocaine. Two major (pulmonary oedema and supraventricular tachycardia) and 42 minor side effects were reported. Hypotension was mostly noticed (16%) amongst the patients who suffered adverse effects. None of the participants suffered any long-term sequalae. However, the sensitivity of the report is affected by the retrospective assessment methods employed. Absence of blinding exposed the study to bias thereby diminishing its credibility. Lack of control prevents a fair assessment of the true potentials of the intervention. Schafranski et al. (2009) confirmed the efficacy and safety of lidocaine infusion in the management of 23 fibromyalgia patients[11]. Significant improvement in FIQ scores was noticed on the 5^{th} ($p=0.020$) and 30^{th} ($p=0.01$) days post intervention. Pain relief (measured with visual analogue scale) also significantly improved on the 5^{th} $p=0.01$) and 30^{th} ($p=0.05$) days post treatment. No side effects were reported in this study. However, lack of randomization and control hampers the credibility of this report. Conversely, a randomized, double blind, comparative clinical trial which was conducted later, reported no difference in pain intensity or number of tender points between patients who had lidocaine infusion with amitriptyline and those who that received amitriptyline alone in the management of fibromyalgia[27]. However, compared to the baseline values, there was significant improvement in the two parameters earlier mentioned in the two treatment groups. They also reported no significant reduction in fatigue, subjective oedema or morning stiffness after treatment in both groups. But, there was no power calculation. The study did not state the allowable β-error (usually 0.2). There was no mention of the primary outcome; standard assessment of which would have been vital in the calculation of sample size. There was no mention of any pilot or similar studies from which significance of difference in outcome measures could have been derived. The small sample size (n=14 per group) and these methodological concerns arguably exposed this trial to a high probability of type 2 error. Amitriptyline has earlier been used for the treatment of fibromyalgia[7]. Its combination with lidocaine impairs a fair assessment of the true potentials of the later in the management of fibromyalgia. The credibility of the study is further eroded by non-mention of the statistical tools used in the analysis of the results. Ethical concerns are raised by non-exclusion of patients with cardiac/ECG abnormalities and lack of ECG monitoring of the patients who received lidocaine infusion. A similar study, later conducted by the same authors, found no improvement in pain intensity, no significant difference in plasma serotonin, norepinephrine or dopamine concentration following lidocaine infusion in fibromyalgia patients using the same regimen above[24]. Also, this study had no power calculation and the small sample size (n=15 per group), exposed it to high chances of β-error thereby diminishing its statistical relevance. This later study was also challenged by similar methodological controversies as its predecessor. Another RCT by Giraldes et al. (2016) comparing intravenous lidocaine injection combined with amitriptyline and intravenous injection of saline (placebo) combined with amitriptyline showed no meaningful impact of thefirst, compared to the later intervention in the treatment of fibromyalgia patients. [29] Patients who received lidocaine injection with amitriptyline reported similar reduction in pain intensity as those who had saline injection with amitriptyline and, there was no difference in their side effect profiles. However, amitriptyline is a tricyclic anti-depressant that is also used in treatment of fibromyalgia and other chronic pain conditions. It interferes with the true effects of lignocaine there by significantly confounding this study. Also, liberal consumption of paracetamol and tramadol by both groups (though comparable), hinders fair assessment of analgesic efficacy and side effects of the interventions in the two groups. Any effects noticed would be shared by these potent analgesics. These challenges the credibility of the study and diminishes acceptability of its findings. A retrospective study by Hung-Jun et al. (2013) affirmed the analgesic efficacy of lidocaine in patients with fibromyalgia.[30] This study reviewed 55 patients whose pains were mostly refractory to other treatments. Although significant difference in pain scores (measured with the visual analogue scale and brief pain inventory) were noted,

the p-values were not reported. The assessment of the effects of lidocaine based on data retrieved from patients' charts reduced the accuracy and sensitivity of the report. Lack of blinding and control precluded the objective assessment of the intervention and further erodes the clinical importance of the study.

CONCLUSION

Fibromyalgia is a complex poly-symptomatic condition of uncertain aetiology and pathogenesis.[4, 15] This enigmatic disease seems to have more female preponderance than previously reported.[6, 19] Its optimal management requires a multi-modal, multi-disciplinary approach involving pharmacological and non-pharmacological interventions.[7]Studies included in this review employed various pain assessment tools although most of them affirm the analgesic efficacy of duloxetine and lignocaine respectively, in treatment of fibromyalgia. Retrospective, patient-administered, investigator-administered and third-party data collection methods employed in different studies re-affirm marked methodological heterogeneity observed in this review. Duloxetine, a novel drug with dual mechanisms of action, is licensed for the management of fibromyalgia.[18] It is a sodium channel blocker which stabilizes neuronal membranes thereby reducing the cellular hyper-excitability observed in patients with fibromyalgia. It also acts centrally by activating the spinal and supra-spinal pain inhibitory pathways. With abundant evidence of its safety and efficacy in the management of fibromyalgia and few adverse effects, it promises to be the ideal pharmaco-therapeutic agent for the treatment of this condition.[23] However, some cases may be refractory to it necessitating the use of other agents like lidocaine. [26]Lidocaine, also a sodium channel blocker and neuronal cell membrane stabilizer, is recommended in the management of other neuropathies[25]. Controversies surrounding incidence of its side-effects and possible toxicity can be resolved by careful patient selection, close patient monitoring and strict adherence to safe doses[11, 26]. There is dearth of good quality randomized control trials in literature to support its safety and efficacy in the management of fibromyalgia patients. Evidence supporting its use in this condition is mainly derived from case reports and retrospective studies.[11, 28, 30] There is no study in current literature which directly compares duloxetine and lidocaine infusion in the management of fibromyalgia syndrome. Available clinical evidence from literature is insufficient to fairly compare the efficacy of duloxetine with lidocaine infusion in the management of patients with fibromyalgia.

RECOMMENDATIONS

Following the dearth of standard clinical research on the use of lidocaine infusion in the management of fibromyalgia, more randomized controlled trials that are sufficiently powered (80%,β-error: 0.02) are required to assess its effects on patients. Adequate sample size for such robust studies may be derived from pilot studies of previous clinical trials with good methodologies. Some patients may show resistance or intolerance to the side effects of some recommended drugs. Therefore, comparative studies of duloxetine and lidocaine infusion in the treatment of this condition are recommended to determine their relative safety and potency and widen the treatment options. Such double-blind studies should be meticulously designed with adequate statistical power and sample size estimation. The results obtained should be analysed with standard statistical tools to ensure its credibility.

In designing studies which use duloxetine in the management of this condition, sample size estimation should accommodate up to 40% attrition rate. High drop-out rates previously experienced might also be reduced by provision of incentives to the participants. More hospital-based assessments of the interventions are recommended to reduce the error of improper assessment which may occur in patients' self-administered assessments. Validated, 'real-time' outcome measures such as visual analogue scale should be encouraged in the assessment of analgesic efficacy of the interventions to ensure uniformity and more accurate representation of the effects of the treatments.

LIMITATIONS

Inclusion of only studies reported in English language might have inadvertently excluded relevant clinical trials that might have been performed on the subject but in other languages. Dearth of good quality clinical trials comparing duloxetine versus lidocaine or lidocaine alone versus placebo, adversely affects direct or indirect comparison of effects of the two interventions in management of fibromyalgia.

REFERENCES

1. Smith BH, Hopton JL, Chambers WA.Chronic pain in primary care. Family Practice 1999; 16(5): 475-482.
2. http://www.nationalpainaudit.org/final-report/ 2010-2012. Accessed on 10.09.2018.
3. Fayaz A, Croft P, Langford RM, et al. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. BMJ Open 2016; 6: e010364.
4. Glass JM. Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: new trends and future directions. CurrRheumatol Rep 2006; 8 (6):425-429.
5. Buskila S, Cohen H. Comorbidity of fibromyalgia and the psychiatric disorders. Curr Pain Headache Rep 2007; 11(5):333-338.

6. Chakraborty S,Zoorob R. Fibromyalgia. American Family Physician 2007; 76(2): 247-254.

7. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017; 76: (2): 318-328.

8. Choy E, Marshall D, Zahava L, et al. a systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Semin Arthritis Rheum 2011; 41: 335-345.

9. Goldenberg DL, Burckhardt C,Crofford L. Management of fibromyalgia syndrome. JAMA 2004; 292 (19): 2388-2395.

10. Gilron I, Shum B,Wiffen PJ. Combination pharmacotherapy for treatment of fibromyalgia (protocol). Cochrane 2013; 6: CD010585.

11. Schafranski MD,Malucelli T, Machado F,et al. Intravenous lidocaine for fibromyalgia syndrome: an open trial. ClinRheumatol 2009; 28: 853-855.

12. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996,17:1-12.

13. Halpern SH, Douglas MJ (EDs) (2005). Jadad scale for reporting randomised control trials. In, Evidence-Based Obstetric Anaesthesia. Blackwell, Oxford.

14. Gendreau RM, Thorn MD, Gendreau JF, et al. Efficacy of milnacipran in patients with fibromyalgia. The Journal of Rheumatology 2005; 32: 1975-1985.

15. Staud R, Spaeth M. Psychophysical and neurochemical abnormalities of pain processing in fibromyagia. CNS Spectr 2008; 13 (3 suppl 5): 12-17.

16. Basbuam AI, Fields HL. Endogenous pain control mechanisms; review and hypothesis. Ann Neurol 1978; 4: 451-462.

17. Julien N, Goffaux P, Arsenault P, Marchand S. Widespread pain in fibromyalgia is related to a deficit of endogenous pain inhibition. Pain 2005; 114: 295-302.

18. Mease PJ, Russel IJ, Kajdasz DK, et al. long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. Semin Arthritis Rheum 2010; 39: 454-464.

19. Arnold LM, Lu Y, Crofford LJ, et al. A double blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. Arthritis Rheumatism 2004; 50(9): 2974-2984.

20. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebocontrolled trialof duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. Pain 2005; 119: 5-15.

21. Russel J, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder.: results from a 6-month, randomized, double-blind, placebo-controlled, fixed-dose trial. Pain 2008; 136: 432-444.

22. Murakami M, Osada K, Mizuno H, et al. A randomized, double-blind, placebo-controlled phase III trial of duloxetine in Japanese fibromyalgia patients. Arthritis Research & Therapy (2015) 17:224. DOI 10.1186/s13075-015-0718-y.

23. Sultan A, Gaskell H, Derry S, et al. Duloxetine for painful diabetic neuropathy and fibromyalgia pain: systematic review of randomized trials. BMC Neurology 2008; 8: 29.

24. Vlainch R, Issy AM, Gerola LR, SakataRK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasmaserotonin, norepinephrine and dopamine concentrations in fibromyalgia. Clin J Pain 2011; 27: 285-288.

25. Kastrup J, Peteren P, Dejgard A, Angelo HR, Hilsted J. Intravenous lidocaine infusion- a new treatment of chronic painful diabetic neuropathy. Pain 1987; 28: 69-75.

26. Raphael JH, Southall JL, Kitas GD. Adverse effects of intravenous lidocaine therapy in fibromyalgia syndrome. Rheumatology 2003; 42(1): 185-186.

27. Vlainch R, Issy AM, Gerola LR, Sakata RK. Effect of intravenous lidocaine on manifestations of fibromyalgia. Pain Pract 2010; 10(4): 301-305.

28. Raphael JH, Southall JL, Treharne GJ, Kitas GD. Efficacy and adverse effects of intravenous lidocaine therapy infibromyalgia syndrome. BMC Musculoskeletal Disorders 2002; 3: 21.

29. AlbertoniGiraldes AL, Salomao R, Leal PDC, et al. Effect of intravenous lidocaine combined with amitriptyline on pain intensity, clinical manifestations and concentrations of IL-1, IL-2 and IL-8 in patients with fibromyalgia: A randomised double-blind study. Int Journal of Rheumatic Diseases (2016) 19; 10: 946-953.

30. Hung-lun J, Yang HK, Horazeck C, Huh BK. The Analgesic Effect of Lidocaine Infusion in a Fibromyalgia Patient Population is Significantly Better in Non-Smokers. American Society of Anesthesiologists conference proceedings 2013: http//www.asaabsracts.com. Accessed on 26.04.2014.

Conflict of Interest: None
Source of Support: Nil