

Review Article**Efficacy and safety of Duloxetine compared with placebo for diabetic neuropathy pain: meta-analysis**Hassan MA¹, Cheng XY², Dai Z³, Rahmathullah MN⁴, Shahnawaz⁵, Shamsa H⁶, Fathuma H⁷, Hussein AH⁸¹Dr Mohamed A Hassan,
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ABSTRACT**Background:** Duloxetine is relatively considered as a treatment for diabetic neuropathy pain due it is balanced and potent reuptake inhibitor of both serotonin and nor epinephrine where these neurotransmitters play a great in pain inhibition.**Materials and Methods:** We searched DLX related articles in Pubmed, Cochrane and Embase from 2005 to 2010. 158 articles were found after through search out of which 68 articles were case reports, reviews and meta-analysis, 40 studies were clinical trials but not efficient data was available, 45 studies were RCTs but not related to our topic. Only 5 RCTs included after exclusion. We then performed the meta-analysis of the studies which met our eligibility criteria we performed fixed effect model network meta-analysis to analyze the efficacy of DLX compare to placebo. We chose diabetic neuropathy duration, diabetes mellitus duration, types of diabetes and DLX with regard to MNSI scale.**Results:** 5 published RCTs were included in this meta-analysis no significant difference observed for DLX and DND [(SD mean difference 0.22 (95%CI -0.16 to 0.60); P=0.25)] , on diabetes mellitus duration for HbA1c and fasting blood glucose (FBG) [(SD mean difference -0.00 (95%CI-0.087 to 0.87); P=1.00)] and on types of diabetes[(COR 1.00 (95% CI 0.73 to 1.38; P=0.98)] and [(OR 1.00 (95% CI 0.72 to 1.37); P=0.98)] .DLX shown to have significant efficacious compared to placebo for MNSI (95% CI -0.37 to - 0.03); P=0.02].**Conclusion:** In the fixed effect model analyses of DLX, showed similar efficacy to placebo for efficacy parameters, except on MNSI scale but not clinically relevant.**Keywords:** Duloxetine, serotonin (5-HT), nor-epinephrine, diabetic neuropathy, diabetes mellitus, MNSI, Meta-analysis**Introduction**

Diabetes mellitus is a common disease worldwide which affects millions of people with micro and macro vascular complications, one of the significant micro-vascular complications of diabetic neuropathy which is characterized by painful, tingling and burning sensation in

legs, feet and hands affecting about 30% of chronic diabetes. ^[1,2] The burden of diabetic neuropathy is increasing as the prevalence of diabetes is arising. ^[3] The main Reason of diabetic neuropathy is the damage of the nerves due to prolonged exposure to high level of blood glucose. Even after controlling the blood glucose to prevent or

to slow the neuropathy pain, the situation still requires great effort to treat and it has negative impact on the quality of life in the patients of chronic diabetes. The neurotransmitters which are involved in generating pain signals are serotonin (5-HT) and nor epinephrine (NE) which when stimulate sense inhibitory pain signals.^[4, 5, 6] Duloxetine (DLX) has been shown in preclinical studies to be selective, balanced on potent inhibitor of reuptake of both 5-HT and NE.^[7, 8, 9] In clinical trials the administered doses of DLX ranges from 40 to 120mg daily and has been shown to be safe and effective in the management of major depression^[10, 11, 12, 13, 14] and was also considered the dose 60mg once daily was safe and effective in the treatment of diabetic neuropathy.^[15, 16] The primary objective of this meta-analysis was to compare the efficacy of DLX with placebo in the management of diabetic neuropathy, as to our knowledge no other studies had been published based on our outcomes measures.

Material and methods

A comprehensive data searched on DLX related articles was carried out in Pub med, Cochrane and Embase from 2005 to 2010, a total of 158 articles was published on DLX for the treatment diabetic neuropathic pain, only the published date were sought out. The key words used in the search was DLX, diabetic neuropathic pain (DNP) and RCTs, after exclusion of the clinical trials and reviews, only the 5 RCTs that published on the DLX comparing with placebo for management of diabetic neuropathy was included to perform the meta-analysis.

We have included only those RCTs which are parallel fashion. All the RCTs must report the data of both the efficacy and

safety comparing DLX with placebo. We have excluded those studies which were case reports, clinical trials and studies which were not related to our topic. The quality of included studies was assessed using the JADAD article quality assessment score. All the articles which were published in language other than English were not included in this study. Diagnosis of pain must be at least 3 on MNSI scale was also a part of the eligibility criteria.

Two reviewers independently reviewed the studies for eligibility and the data was abstracted. Data from eligibility studies was extracted on the basis of first author, year of publication, country of origin, type of study, number of patients, age, duration of diabetes mellitus, types of diabetes, duration of diabetic neuropathy and Michigan Neuropathy Screening Instrument (MNSI) scale scores, the disagreements were solved by discussion with the third authors.

Revman software Version 5.3 was used to conduct this Meta analysis. We combine all the results of the studies an estimated the result effect in terms of mean difference (MD) with confident intervals (CI), except for the outcome types of diabetes we expressed the result effect in terms of odds ratio (OR) with 95% confidence interval (CI). All our outcomes showed no heterogeneity ($I^2 < 50\%$) and we used fixed model effect, P value less than 0.05 was considered as a significant result.

Results

Characteristics of the included trials

All together we had searched 58 DLX related published studies, excluded 27 articles (n=27) after carefully reading the abstracts which were review articles, 16 articles (n=16) were excluded as it was

clinical trials and did not match our eligibility criteria. 10 RCTs (n=10) was excluded because those studies were not related to our topic. Finally 5 RCTs (n=5) met our criteria and subsequently the meta-analysis was performed. Jadad scoring system of all the included RCTs was used to estimate the quality of the included studies and is shown in table 1. The baseline characteristics of the included studies in this meta-analysis are provided in table 2. Demographic of the study population are given in table 3.

Analysis of the outcome

By carefully understanding each RCT which are included in this meta-analysis, a set of outcome measures was clearly identified and selected to carry out this study. Our main outcomes were available to access the treatment efficacy of the DLX and its efficacy was tested for the following outcomes; Diabetic Neuropathy Duration (DND), Diabetes Mellitus Duration (DMD) for HbA1c and Fasting Blood Glucose (FBG), types of diabetes, (type 1&2), Michigan neuropathy screening instrument (MNSI). All the outcome analysis showed no heterogeneity as denoted by χ^2 and I^2 . Fixed effect model was used to represent the outcomes. Results of this meta-analysis were presented as intention to estimate the efficacy and to treat.

Effect of DLX on DND

There was no significant difference in DLX compared with placebo for diabetic

neuropathy duration [(SD mean difference 0.22 (95%CI -0.16 to 0.60); P=0.25)]. (Fig.1) The analysis showed that DLX has no relationship with the duration of diabetic neuropathy.

Effect of DLX on DMD (HbA1c and Fasting Blood Glucose)

There was no relationship between DLX and placebo with regard to diabetes duration for HbA1c and Fasting blood glucose and the result showed no statistical difference between the two groups [(SD mean difference -0.00 (95%CI-0.087 to 0.87); P=1.00)]. (Fig.2)

Effect of DLX on type 1 and 2 DM in patients with DND

No significant statistical differences were observed in both type 1 and type 2 diabetes in our meta-analysis shown in figure 3 and 4. DLX showed similar efficacy in both the conditions. The analysis for type 1 and 2 diabetes mellitus for the effect of DLX was [(COR 1.00 (95% CI 0.73 to 1.38; P=0.98)] and [(OR 1.00 (95% CI 0.72 to 1.37); P=0.98)]

Efficacy of DLX with regard to MNSI in DN pain

DLX showed significant statistically [(SD mean difference -0.2 (95% CI -0.37 to -0.03); P=0.02)], with regard to MNSI in patients with DN which resulted in much reduced pain sensation after taking DLX. (Fig.5)

Table 1: Jadad score of the studies

STUDY NAME	JADAD SCORE
Raskin et al 2005	5
Raskin et al 2006	3
Wernicke et al 2006	5
Armstrong et al 2007	5
Tanenbergr RJ et al 2010	3

Table 2: Baseline characteristics of the included studies

STUDY/YEAR	COUNTRY	PRESCRIBED DRUG DOSE(mg)	GROUP ALLOCATION	BLINDING	STUDY TYPE	STUDY SIZE	STUDY DURATION
Raskin et al 2005 (17)	Canada	DLX 60	R	DL	Parallel	348	12weeks
Raskin et al 2006 (18)	Canada	DLX 60	R	U	Parallel	449	28 weeks
Wernicke et al 2006 (19)	U.S.A	DLX 60	R	OL	Parallel	215	13weeks
Armstrong et al 2007 (20)	U.S.A	DLX 60-120	R	DB	Parallel	680	12 weeks
Tanenberg RJ et al 2010 (21)	U.S.A	DLX 60 PGN300	R	OL	Parallel	272	12 weeks

Table 3: Demographics outcomes of the study population

Study ID	Intervention	N	Age	Gender	DMD	DND	MNSI	Type1	Type2
			Mean(Yrs)	M/F	Mean (yrs)	Mean (yrs)	Mean (yrs)		
Raskin et al 2005 [17]	DLX	116	59	55 (F)	13.9	4.5	4.8	17	99
Raskin et al 2006 [18]	Placebo	116	59.2	63 (F)	12.8	4	5.2	14	102
Raskin et al 2006 [18]	DLX	334	60	176/158	12.4	3.1	–	18	316
Raskin et al 2006 [18]	Placebo	115	59.6	58/57	12.4	3.6	–	10	105
Wernicke 2006 [19]	DLX	197	58.1	88/109	13.9	4.6	5	32	165
Wernicke 2006 [19]	Placebo	96	58.5	47/49	13.6	4	5	14	82
Amstrong et al 2007 [20]	DLX	341	60.3	190/151	11.3	4.1	5.2	36	303
Amstrong et al 2007 [20]	Placebo	339	60.1	181/158	11.8	3.9	5.4	37	304
Tanenberg et al 2010 [21]	DLX	138	60.9	83 (M)	12.3	4.8	5.7	–	–
Tanenberg et al 2010 [21]	Placebo	134	61.9	76 (M)	12.5	4.3	5.9	–	–

DLX, Duloxetine; (M), male; (F), Female; DMD, Diabetes Mellitus Duration; DND, Diabetes Neuropathy Duration; MNSI, Michigan Neuropathy Screening Instrument

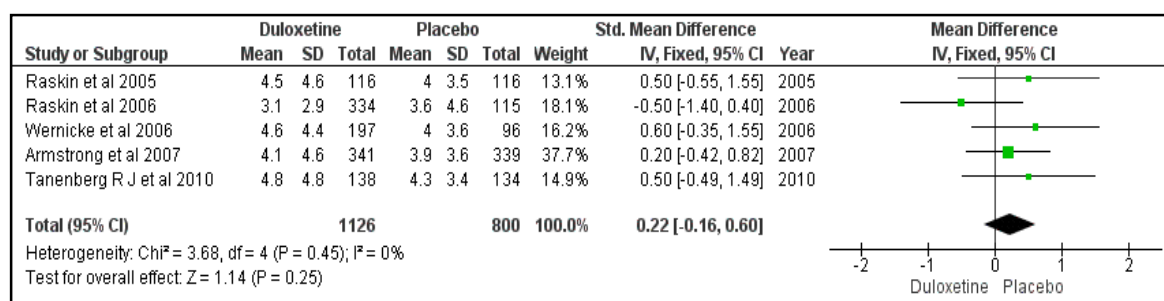


Fig.1 DLX relationship with the duration of Diabetic Neuropathy

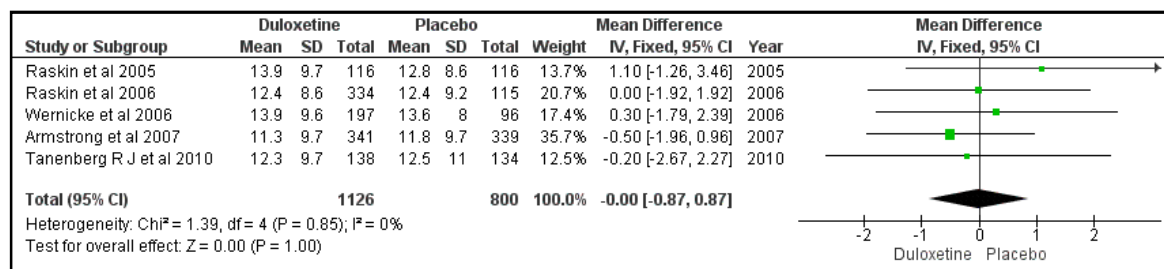


Fig.2 DLX relationship with Diabetes Mellitus Duration

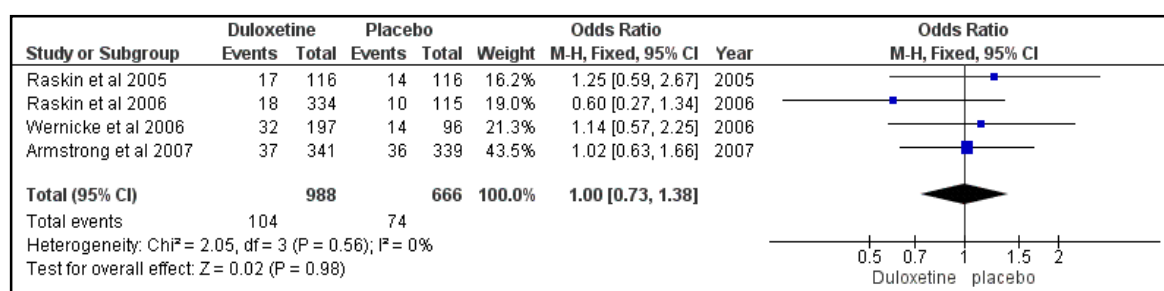


Fig.3 DLX effect on type 1 DM

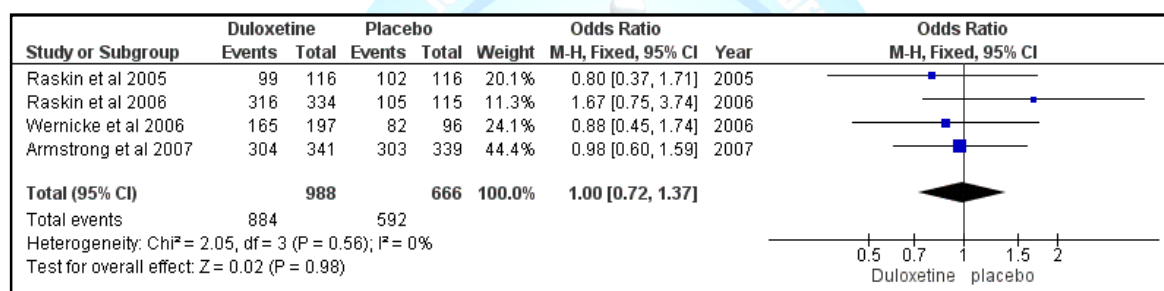


Fig.4 DLX effect on type 2 DM

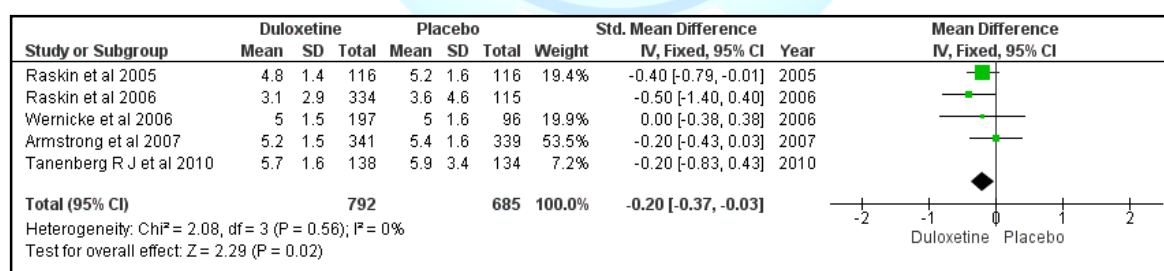


Fig.5 DLX efficacy for MNSI

Discussion

We conducted this meta-analysis to set out the comparison of efficacy and safety of DLX compare with placebo which is approved in the management of Diabetic Neuropathy (DN), however the only approved licensed drugs prescribed for DN

are Duloxetine, Pregabline and Gabapentine. Two small trials studied on the drug control released Oxycodone which has been used in the management of painful DN. [22, 23] The treatment period of the studies included in our meta-analysis range from 12 to 28 weeks, our outcomes for DLX efficacy

versus placebo in this study was as follows: Diabetic Neuropathy Duration (DND), Diabetes Mellitus Duration, types of diabetes and with regard to MNSI scale. To our knowledge, no meta-analysis have been reported according to our outcome parameters, the results of our study was shown to have no heterogeneity ($I^2 < 50$) and low risk of bias according to the funnel plot. There was no statistically significant difference ($P=0.25$) in patients treated with DLX compare to placebo who have diabetic neuropathy duration of mean years between 4 to 13. According to Raskin et al, [17] DLX 60 mg taken once daily in one group and twice daily in another group for DN have shown same efficacy which was found to be consistent with our study results, which means DLX taken once daily or twice daily can significantly reduced pain but have greater efficacy than placebo regardless the duration of the DN. DLX did not show any adverse outcome on glycemic control or lipid profiles but showed slight changes in chemistry and HbA1c but was considered clinically not significant. The use of DLX for treating Diabetic Neuropathy especially in older patients may be limited due to risk of adverse cardiovascular effects, even though DLX as the first line treatment for neuropathic pain. [26, 27, 28, 29, 30] Therefore in older patients the anti-convulsant Gabapentine can be effective to treat diabetic neuropathy. [31] Our study did not explain the effect of DLX for age group, therefore, additional research must be performed in older patients in order to determine the efficacy, tolerability and safety of DLX used for DN.

According to Wernicke et al, [19] DLX is a safe and showed better efficacy than routine care for management of DN. There was no statistical significant difference in

relationship between DLX & placebo with respect to DMD and with regard to type 1&2 diabetes. According to Tanenberg et al, [21] patients who were treated with DLX had no significant change in HbA1c levels and also no significant difference were found in fasting blood glucose levels in patients with DLX compare to placebo ($P=0.02$). Therefore DLX has no significant effect on DMD in HbA1c level which was in consistent with our results ($P=1.00$) where as in a study, Wernicke et al [19] showed significant mean difference in HbA1c with slight increase in patients treated with DLX ($P<0.001$) which indicates further studies may be required for HbA1c levels in patients treated with DLX. There was significant difference observed for patients treated with DLX compare to placebo on the MNSI score ($P=0.02$) who had at least value of 3 on MNSI scale which showed that patient complain of less pain episodes taking DLX.

In conclusion, based on the analysis of our outcomes, which was analyzed in our Randomized Controlled Trials that included in our meta-analysis, we hereby conclude that DLX compared with placebo showed similar efficacy in treatment of the Diabetic neuropathic pain. DLX showed no significant result for HbA1c and Fasting blood glucose with patients who have long term Diabetes duration and also with type 1 and type 2. There was statistical significant, but not clinically relevant, difference between DLX and placebo groups on MNSI scale. This meta-analysis showed that DLX have similar efficacy compared to placebo in most outcomes. Further studies are warranted to support our study before application in the routine care.

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