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Is duloxetine effective in reducing pain for patients with diabetic neuropathy?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not duloxetine is effective in reducing pain for patients with diabetic neuropathy.

STUDY DESIGN: Systematic review of three English language Randomized Controlled Trials, published between 2010-2015.

DATA SOURCES: Three randomized controlled trials published in peer-reviewed journals comparing the effects of Duloxetine on diabetic neuropathy pain found using the Embase database.

OUTCOME MEASURES: The outcomes were measured by assessing diabetic neuropathy pain reduction, using the Brief Pain Inventory (BPI) average pain item, BPI- severity scale, BPI-interference. Also, individual health outcome was measured by using Patient Global Impression of Improvement (PGI)- Improvement scale, Sheehan Disability Scale (SDS), and Clinical Global Impressions of Severity (CGI-S).

RESULTS: Three studies in the review showed a significant pain reduction for patients with the diabetic neuropathic pain taking a duloxetine vs. a placebo. However, Gao and co-authors showed no statistically different mean change in BPI average pain reduction from baseline to endpoint between the treatment groups in week 8 ($p= 0.125$) and 12 ($p=0.107$). The other two studies showed the statistical significance of primary efficacy results as "p" <0.0001 and "p"$= 0.030$. All three studies showed significant health outcome measured in BPI-interference and NNT.

CONCLUSIONS: There is a significant benefit of using duloxetine for the diabetic neuropathic pain vs. placebo. The most common adverse effect of Duloxetine is nausea, which may discourage the usage and its therapeutic benefit in pain reduction for diabetic neuropathic pain (DNP). Further investigation in the long-term study will reinforce the efficacy and safety of duloxetine as the diabetic neuropathic pain treatment.

KEYWORDS: Diabetic neuropathy, Duloxetine

INTRODUCTION

Diabetic neuropathy is the pain characterized by aching, burning, tingling or stabbing sensation that is often increased at night and affects sleep, but also interferes with daily life, leading to deterioration of the quality of life and a depressive state in severe cases. Diabetes mellitus type I and II both have many severe complications due to dysfunctional glucose metabolism, resulting damage to organs, and vessels. Thus, peripheral nerves with a compromised blood supply also suffer, which may render impaired function of nerves that cause mild to debilitating pain sensations for diabetic patients.[1] However, the pathophysiology of the diabetic neuropathic pain is not entirely understood.[2]

Duloxetine has proven efficacy, relative safety profile, and has been approved for managing the diabetic neuropathic pain. Duloxetine is considered a serotonin and norepinephrine reuptake inhibitor (SNRI). Both serotonin and norepinephrine are neurotransmitters that are an essential part of endogenous pain inhibitory mechanisms in the central nervous system.[2] Thus, by inhibiting the clearance of those neurotransmitters in the CNS, the pain-transmitting pathway is kept at bay longer. For this reason, chronic pain can be managed with duloxetine. Duloxetine is also used to treat major depressive disorder, generalized anxiety disorder, fibromyalgia, and chronic muscle or joint pain. Diabetic neuropathic pain dosage starts at 30 mg daily and may increase to 60 mg daily; maximum dose of 120 mg may not be more efficacious than 60 mg.[2]

A common complication of type 1 and type 2 diabetes is painful neuropathy in the arms and legs. About a quarter of type 2 diabetes patients exhibit nerve damage at the time of diagnosis. Diabetic neuropathy has a lifetime prevalence of approximately 50%.[1] In the US, diabetes health-care cost $245 billion in 2012. Nearly 27% of costs of diabetes is due to diabetes neuropathy.[1] Diabetic neuropathic patients experience a two-fold increase in health-care

expenses at $12,492, and those with severe painful peripheral neuropathy experience a four-fold increase at $30,755.[1]

Currently, we understand the diabetic neuropathy of its epidemiology, etiology, signs, symptoms, diagnostic tests, treatment, and management options. However, the pathophysiology and the interaction between diabetes neuropathy and metabolic risk factors remain unknown. Diabetic neuropathic pain is managed with pain control using antidepressants, such as TCAs and SNRIs. Anticonvulsants, including pregabalin and gabapentin, are also used as treatment option.[2] Diabetic neuropathy is commonly insidious and can lead to foot ulcers, muscle and joint disease due to progressive sensory loss.[2] Duloxetine works against the pain-transmitting pathway to prevent sensory loss and complications, such as foot ulcers. The benefit of duloxetine was established in three 12-week, randomized, blinded, and controlled trials that showed a rapid onset of action and sustained benefit with efficacy in relieving diabetic neuropathic pain at night.[2]

OBJECTIVE

"The objective of this selective EBM review is to determine whether or not Duloxetine is effective in reducing pain with diabetic neuropathy."

METHODS

The keywords used on Embase for this systematic review research include "diabetic neuropathy" and "duloxetine". Three double-blinded, randomized controlled trial studies were found on Embase that target the patient population with diabetic neuropathy, using duloxetine therapy as intervention vs. placebo therapy to examine the efficacy of duloxetine in reducing

neuropathic pain. In addition, these three randomized controlled trial studies measured the quality of life as in a relationship with others, sleeping, walking ability, mood, and enjoyment of life. Therefore, they are Patient-Oriented Evidence that Matters (POEM) based studies with the intention to treat. These three studies, Gao 2010, Yasuda 2011, and Guo 2015, were published in peer-reviewed journals in the English language, between 2010 and present.

Inclusion criteria used for this review were RCTs published since 2000, the subject's age between 20 and 80, diabetic peripheral neuropathic daily pain, and type I, II diabetes. Exclusion criteria used for this review were the use combination therapy, unstable glycemic control, and the presence of severe comorbid conditions.

This systematic review presents various measurements used in three RCT studies to demonstrate the clinical significance of the duloxetine intervention vs. placebo, including LS mean changes, "p"-values, number needed to treat (NNT), number needed to harm (NNH), relative benefit increase (RBI), absolute benefit increase (ABI), and confidence interval (CI).

Table 1. the demographics and characteristics of the included studies

Study	Type	# of pts	Age	Inclusion criteria	Exclusion criteria	W/D	Interventions
Gao, 2010 (1)	RCT	215	≥ 18 yrs	- Patients with diabetic peripheral neuropathy had a rating of ≥4 on the Brief Pain Inventory 24-hour average pain item - Men and women - daily pain for ≥6 months before entry into the study	- unstable glycemic control (Hgb A1c >12%) -any medical or other condition mania, bipolar disorder, psychosis -at risk for suicide as judged by the investigator - taking any monoamine oxidase inhibitors within 14 days before visit 2 - history of hepatic dysfunction or other severe medical conditions	36	60 or 120 mg of duloxetine vs. matching placebo.

Yasuda, 2011 (2)	RCT	339	20 - <80 yrs	- men and women -have sustained pain for ≥ 6 months as a result of distal symmetric polyneuropathy caused by type 1 or type 2 diabetes mellitus - glycated hemoglobin (HbA1c) ≤ 9.4% at screening, fluctuation of HbA1c ≤ 1.0% at 42–70 days before screening -the 24-h average pain score rated by the 11-point Rating Scale ≥ 4	- patients with psychiatric diseases, i.e., mania, bipolar disorder, depression, anxiety disorders, eating disorders, or patients with a history of any pharmacotherapy during the past year. - Complication that might affect the assessment of DNP, i.e., neurological disorders unrelated to diabetic neuropathy, a skin condition in the area could alter sensation and other painful conditions.	1	duloxetine 40 or 60 mg/day once daily vs. placebo against DNP.
Guo & Gao, 2015 (3)	RCT	405	≥ 18 yrs	- DPNP had a rating of ≥ 4 on the Brief Pain Inventory-Modified Short Form-Severity weekly average pain item. -Presented with bilateral DPNP began in the feet with relatively symmetrical onset. -The daily pain had to be present for at least 6 months.	-unstable glycemic control (hemoglobin A1c > 12%) -mental illnesses, the risk for suicide -serious or unstable cardiovascular, hepatic, renal, respiratory, or hematological illness -symptomatic peripheral vascular disease -Presence of other serious medical conditions.	56	Duloxetine 60 mg/day vs. placebo against DNP.

OUTCOME MEASURES

Three studies in this systematic review measured the outcome of pain reduction as a result of duloxetine intervention vs. placebo with various scales. The first study by Gao 2010 measured the Brief Pain Inventory (BPI) average pain item as the primary efficacy, measuring 24-h average pain score on an 11-point Likert scale, 0 being “no pain” and 10 being “worst possible” by patients. The secondary efficacy outcome measures the BPI-severity and BPI-interference that assess the pain severity and interference with function, 0 being “no interference” to 10 being “complete interference.” Another secondary efficacy measure was the BPI average pain of 30% and 50% reduction from baseline to endpoint. In addition, the Clinical

Global Impressions of Severity (CGI-S), the Patient Global Impression of Improvement (PGI-I), and the Athens Insomnia Scale (AIS) were also measured.[2]

The second study by Yasuda 2011 measured the weekly mean 24-h average pain severity score on the 11-point scale as a primary efficacy. A secondary efficacy was measured by the pain severity for 24-h worst pain and night pain on an 11-point scale. Also, Patient's Global Impression of Improvement (PGI-I) Scale, which is a 7-point scale, 1 being "very much improved" and 7 being "very much worse" was recorded at 2, 4, 8, and 12 weeks. In addition, the severity and interference portions of Brief Pain Inventory (BPI) recorded at randomization and weeks 2, 4, 8 and 12.[3]

The third study by Guo 2015 collected data of the weekly mean of daily pain ratings including average, worst, and night pain on an 11-point Likert scale as a primary efficacy measure. The BPI-S and the PGI-I were secondary efficacy measures. Additionally, the BPI-I, which ranges from 0 being "does not interfere" with 10 being "completely interferes" and the Sheehan Disability Scale, SDS, which range from 0 being "not at all" to 10 being "extremely" were assessed for the health outcome.[4]

RESULTS

The Gao 2010 study showed statistically insignificant differences in the LS mean changes of BPI 24-h average pain as –2.31±0.18 in the placebo group and –2.69±0.19 in duloxetine treatment groups, "p" =0.124. However, there was a significant difference in placebo and duloxetine group in secondary efficacy measures, including BPI-S and BPI-I item. During the 12-week period, the BPI-S item "pain right now" was significantly decreased at "p" =0.012 and the BPI-I item "walking ability" showed improvement at "p" =0.016. In addition, the other secondary efficacy measures, CGI-S at P=0.036 and PGI-I at "p" =0.028, were signaled

remarkable improvement in duloxetine group. Table 2 and 2-1 shown below explains the above results.[2]

In regards to safety, the rate of adverse events was not statistically significant between the two groups. However, treatment-emergent adverse events (TEAEs) revealed following results: nausea at "p" = 0.0001, somnolence at "p" = 0.015, anorexia at "p" =0.010, and dysuria at "p" = 0.009. Duloxetine-treated patients had 16.7% of discontinuation rate as opposed to placebo group in 3.7% due to adverse effects.[2]

Table 2. Brief Pain Inventory 24-hour average pain as assessed by LOCF

Group\ measures	Baseline to endpoint LS mean changes	Statistical significance ("p" value)
Placebo	–2.31±0.18	"p"=0.124
Duloxetine treatment	–2.69±0.19	"p"=0.124

Table 2-1. Secondary efficacy measures as assessed by LOCF

Group\ measures	BPI-severity : pain right now	BPI-interference : walking ability	PGI-I Patient Global Impression of Improvement	CGI-S Clinical Global Impressions of Severity
Placebo	-1.99±0.25	-1.82±0.23	2.64±0.10	-0.99±0.11
Duloxetine	-2.72±0.26	-2.45±0.24	2.32±0.11	-1.24±0.11
"p" value	0.012	0.016	0.028	0.036

The 24-h average pain score demonstrated a significant improvement in the duloxetine 40 and 60 mg groups vs. placebo group in the Yasuda 2011 study with a "p" value <0.0001. The 24-h average pain score compared from baseline to endpoint has following mean changes: the

combined duloxetine at -2.47 ± 0.18, duloxetine 40 mg at -2.41 ± 0.21, duloxetine 60 mg at -2.53 ± 0.21, and placebo groups at -1.61 ± 0.18. As secondary efficacy measures, significant improvement in the health outcome was noted in BPI-I score in walking ability at "p"= 0.0228, relationship with other people at "p" = 0.0076, sleep at "p"= 0.0378, and enjoyment of life at "p"= 0.0089. Table 3 and 3-1 shown below explains the above results.[3]

About 8.8% of study subjects left the study due to adverse effects, including somnolence at "p" =0.0007, nausea at "p" <0.0001, and dizziness at "p"= 0.0354. Higher incidence rate of adverse effects in duloxetine-treated group vs. placebo group was statistically significant at "p"= 0.0153.[3]

Table 3. Mean changes of the 24-h average pain over 12 week

Group\ measures	Baseline to endpoint LS mean changes	Statistical significance (p value)
Combined duloxetine	-2.47 ± 0.18	Week 1,2,3 & 6 = "p" <0.005 Week 4,5,7,8,9,10 &11 = "p" <0.0001
40 mg duloxetine	-2.41 ± 0.21	
60 mg duloxetine	-2.53 ± 0.21	
Placebo	-1.61 ± 0.18	

Table 3-1. Mean changes of BPI-Interference over 12 week

	Walking ability	Relationship with other	Sleep	Enjoyment of life
Combined duloxetine	-2.31±0.23	-1.32±0.23	-2.15±0.24	-2.15±0.23
Placebo	-1.82±0.23	-0.77±0.23	-1.69±0.24	-1.59±0.23
"p" value	0.0228	0.0076	0.0378	0.0089

Duloxetine-treated patients experienced significantly higher pain relief compared to that of placebo-treated patients in Guo 2015 study. As primary efficacy measure, 12th week LS mean change of 24-h average pain in duloxetine was measured at -2.40±0.14 and placebo at -1.97±0.14. Its LS mean change difference with 95% CI was -0.43 with "p" = 0.030. The pain reduction of 50% in BPI-Severity average pain was collected as 46.0% in the duloxetine-treated group and 29.4% in the placebo group with "p" = 0.001 and NNT = 6.0. Table 4 and 4-1 shown below explains the above results.[4]

Discontinue rate of the duloxetine-treated group was higher at 8.4 % than that of the placebo group at 4.0%. Statistical significance between the two groups in adverse events as following: nausea at "p" =0.010, somnolence at "p" <0.001, and asthenia at "p" =0.002.[4] Table 4-2 shown below explains the above results.[4]

Table 4. LS mean changes of 24-h average pain

Group\ measures	Baseline to endpoint LS mean changes	Statistical significance ("p" value)
Placebo	–1.97±0.14	"p"=0.030
Duloxetine treatment	–2.40±0.14	"p"=0.030

Table 4-1. BPI-severity average pain 50% reduction "p" = 0.001

CER Placebo-treated	EER Duloxetine-treated	Relative benefit increase (RBI) EER- CER / CER	Absolute benefit increase (ABI) EER - CER	Number needed to treat (NNT) 1/ABI
0.294	0.46	0.56	0.166	6.02

Table 4-2. Treatment-emergent adverse events

	Nausea	Somnolence	Asthenia
"p" value	0.010	<0.001	0.002
NNH	14.5	12.7	20.0

DISCUSSION

Duloxetine is one of the SNRI drugs that has been widely used for treating major depressive disorder and generalized anxiety disorder. It is also used for chronic pain symptoms, such as fibromyalgia, diabetic neuropathy, and chronic low back pain. This drug is used as 'off-label' for osteoarthritis of the knee and stress urinary incontinence in women. The FDA has approved Cymbalta in 2004, which is the brand name for duloxetine. The generic version of Cymbalta in the delayed-release capsule was approved by the FDA in 2013. Duloxetine is covered by many commercial insurance plans and Medicare, which makes the drug more accessible. Coupons can also be found online, which decreases the price of duloxetine at local pharmacies even further.[5]

Duloxetine has the FDA black box warning of increased risk for suicidal thoughts and behavior, which is common in the antidepressant drug class. Duloxetine should not be used concurrently or within 2 weeks of discontinuation of monoamine oxidase inhibitors (MAOIs) for treating psychiatric disorders. Similarly, patients on linezolid or IV methylene blue should refrain from using duloxetine. More common adverse reactions to duloxetine include headaches, drowsiness, fatigue, nausea, abdominal pain, weight loss, and weakness. Less common adverse reactions to duloxetine include flushing, increased blood pressure, palpitations, insomnia, dizziness, agitation, diaphoresis, decreased libido, constipation, diarrhea, erectile dysfunction, and tremor.[5]

During the search for Randomized Controlled Trial studies for this review on PubMed and Embase, it was challenging to find studies on duloxetine monotherapy regime. Also, during the search, the RCT studies on treating diabetic neuropathy pain frequently presented different treatment modalities, including TCAs, anticonvulsants, and opioids.

Each study in this systematic review—Gao 2010, Yasuda 2011, and Guo 2015—presented the various limitations of their studies. In the study by Gao 2010, the outcome may be affected by the higher placebo response in Asian studies compared with western studies. The major depressive disorder patients included in this study may have yielded a high placebo response. Despite the fact that the other two studies were also conducted in Asia, less bias in their studies was suspected as they excluded the major depressive disorder patients from their studies. All three studies were conducted over 12 weeks, which lacks the long-term effect of the drug on study subjects.

CONCLUSION

Three randomized controlled trial studies in this systematic review investigated the efficacy of duloxetine therapy for treating diabetic neuropathy. The outcome measured in those studies showed a statistical significance in pain reduction as well as the improvement of the quality of life in diabetic neuropathy patients. Despite the potential adverse reactions of duloxetine therapy, diabetic neuropathy patients can be benefited in symptom reduction, preventing worsening pain, and its complications.

In regards to the methodology of randomized controlled trials, one can dispute the validity of brief pain inventory score as it is based on patient's subjective pain rating. To achieve reliable and reproducible outcomes of RCT studies, study subjects must be able to rate their pain

objectively without being biased by variable personal pain tolerance level. For that reason, future RCT studies may incorporate ways to ensure a universal pain rating method. Moreover, future RCT studies using duloxetine as monotherapy for treating diabetic neuropathy for different ethnic backgrounds and over an extended period will strengthen the conclusion of this systematic review. Lastly, future RCT studies showing the duloxetine efficacy in comparison of two groups with early and late onset symptomatic neuropathy patients would guide clinicians when to initiate duloxetine therapy for maximum benefit.

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