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Does Oral Dextromethorphan Provide Pain Relief in Patients With Diabetic Neuropathy?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not oral dextromethorphan provides pain relief in patients with diabetic neuropathy.

Study Design: Review of three peer-reviewed, double blind, randomized control trials published between 1995-2012.

Data Sources: Studies were selected through Cochrane Library Collection and PubMed and chosen based on their relevance to the clinical question as well as their inclusion criteria; including adults over the age of 18; and those who were experiencing daily pain of moderate intensity, for at least half of the day, over a span of 3 months.

Outcomes Measured: Each RCT measured the same outcome but in a different way. In the Nelson study, pain relief was measured using a13-word descriptor scale; for the Sani study, pain relief was measured using a category rating scale; and the Shaibani trial measured pain relief using a Pain Relief Rating scale.

Results: It was assessed and recorded in all three RTCs that the efficacy of oral dextromethorphan in pain relief was statistically significant when compared to a placebo.

Conclusions: Oral dextromethorphan has been shown to give pain relief to patients with diabetic neuropathy. With further research using larger sample sizes and assessment of long-term adverse reactions, dextromethorphan may be made a common treatment for diabetic neuropathy.

Key Words: dextromethorphan, diabetic neuropathy, peripheral neuropathy

INTRODUCTION

Diabetic neuropathy (DN) is a common complication of diabetes, where damage to nerves leads to mild/severe disabling pain. It is hypothesized and suggested that diabetic neuropathy is caused by an abnormal hyper excitability induced by excitatory neurotransmitters (NT) such as glutamate and aspartate, which are dependent on activation of NMDA receptors[1]. Therefore, current treatments have been based around drugs that block or inhibit NMDA receptors[1].

In the United States, ~25.8 million people are affected by diabetes (DM). Of that 25.8 million, ~25.6 million are over the age of 20[2]. Between 60-70% of people with DM experience some form of nerve damage, known as diabetic neuropathy. DN and its complications cost the US between $4.6-$13.7 billion annually; most of these costs are attributed to Type 2 diabetics[3]. There is not an exact estimate of how many health care visits result in caring for patients suffering from diabetic neuropathy specifically; however, in 2008, 44,021 DM type 2 patients were identified of getting a minimum of 12 months of continuous follow-up care and 32, 991 DM type 2 patients were found to have ~24 months of continuous health-plan enrollment[4]. The majority of these patients had at least one physician office visit (99.8%), laboratory diagnostic test (96.2%), and other outpatient visits (97.5%)[4]. Although the exact number of health care visits for diabetic neuropathy is unknown, the costs are exponentially high.

Diabetic neuropathy is triggered by multiple factors. The six main factors that can contribute to DN include: metabolic (ex. high blood glucose or long term diabetes); neurovascular (ex. damage to blood vessels that carry oxygen/nutrients); autoimmune (ex. inflammation to nerves); mechanical injury (ex. carpel tunnel); inherited traits (ex. nerve disease); or lifestyle factors (ex. smoking or drinking)[5]. Just like the causes of diabetic

neurothapy are many, the types of diabetic neuropathy are numerous, as well. Diabetic neuropathy can be broken down into four distinct classifications. These classifications include peripheral, autonomic, proximal, and focal[5]. The most common subtype that people experience is peripheral neuropathy. Peripheral neuropathy is characterized by pain or numbness felt in the toes, feet, legs, hands, and/or arms[5]. Autonomic neuropathy causes alterations in organ functions such as digestion, sexual response, perspiration, and bowel and bladder function[5]. Proximal neuropathy, or the opposite of peripheral neuropathy, causes pain in the buttocks, thighs, and/or hips[5]. This pain eventually causes weakness in the legs[5]. Finally, focal neuropathy results in a sudden onset of pain in a specific nerve or nerve group[5]. These weak nerves lead to muscle weakness and/or pain. In focal neuropathy, any nerve/nerve group can be affected[5]. The multiple causes and forms of diabetic neuropathy highlights why this medical condition is interfering with and affecting so many diabetics' lives. Furthermore, this noted information explains why so many healthcare hours and dollars are spent, each year, towards this medical complication.

Currently diabetic neuropathy is managed multiple ways. The first step to take in the control of DN is managing blood sugar levels. Managing and controlling blood sugar levels helps prevent further nerve damage[5]. The next phase in regulating DN is controlling the pain associated with the nerve damage. Presently, a variety of medications are being used to alleviate the patient's discomfort. Common drugs used to treat the pain include tricyclic antidepressants (ex: amitriptyline); antidepressants which include duloxetine, venlafaxine, bupropion, paroxetine, and citalopram; anticonvulsants such as pregabalin or gabapentin; and opioids or opioid-like drugs, including oxycodone or tramadol[5]. An alternative pain reliever for those experiencing diabetic neuropathy is dextromethorphan, an NMDA receptor antagonist. Although multiple medications are available to help reduce nerve damage and pain, these treatments are

not managing everyone. Many people are still struggling and suffering from diabetic neuropathy and its complications.

OBJECTIVE

The objective of this systematic review is to determine whether or not oral dextromethorphan provides pain relief in patients with diabetic neuropathy.

METHODS

This review is comprised of three randomized controlled, double blind, clinical trials that meet specific criteria for the comparison of dextromethorphan for pain relief in patients with diabetic neuropathy. The first trial was a RCT double blind study comparing pain relief between dextromethorphan and a placebo. The second RCT double blind study examined the efficacy of dextromethorphan and an active placebo. The third RCT double blind study assessed 3 different study groups. Two groups received a drug combination, while the third group received a placebo. The two combo drugs used were dextromethorphan30/quinidine 30 (DMQ 30/30mg) and DMQ 45/30mg. The only difference between these groups was the strength of dextromethorphan. The populations within all of these trials consisted of adults older than 18 who had daily pain of at least moderate intensity, for at least 50% of the day, for a period of 3 months. The populations excluded from these studies were patients younger than 18 years old and patients who were experiencing any other type of pain not related to their diabetic neuropathy.

Key words used in the research for these studies were dextromethorphan, diabetic neuropathy, and peripheral neuropathy. All articles used in this research were peer-reviewed journals and were investigated via key words on Cochrane Library Collection and PubMed. Selection of the articles researched had to meet several inclusion criteria: material contained in

the article had to be relevant to the proposed clinical question, the article's publishing dates had to be from 1996 to present date, and the articles had to be presented as a patient oriented outcome study. Exclusion criteria included articles published prior to 1996, articles that focused on disease oriented outcomes versus patient oriented outcomes, or articles that included participants suffering from any other type of pain. Statistics used within two of these studies included: control event rate (CER), experimental event rate (EER), number needed to treat (NNT), confidence interval (CI), relative benefit increase (RBI), absolute benefit increase (ABI), and p-value. The other study used p-value, confidence interval, and paired t-test. Below, Table 1 displays the demographics and characteristics of the studies reviewed and used.

Table 1: Demographics and Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Nelson[6] (1997)	Double blind RCT	32	18-85 y/o	-Complete pain diary -Diagnosis of diabetes -Distal, symmetrical DN	-Presence of any other pain condition -Unstable disease process -Liver or kidney disease -Concurrent use of MAOIs	6	Two six-week drug treatment periods (one with the active drug and one with the placebo), separated and completed by a week washout period.
Sang[7] (2002)	Double blind RCT	55	≥18 y/o	-Experiencing moderate pain daily for over a minimum of 3 month span due to DN -Previously failed trial of TCAs for at least 2 weeks or development of side effects -Glucose control -Stable analgesic regimen for 2 weeks	- suffering from any other type of pain -Liver, cardiac or kidney disease -S&Sx of any central neurologic disorder -Concurrent use of MAOI	9	Two randomized placebo controlled, double blind trials took place during this study. The first study was an "efficacy trial" where the effects of dextromethorphan, memantine, and the active placebo (lorazepam) were compared. The second study was a "dose-response" trial of preferred active drug in participants. Their pain and side effects levels were assessed 2x/week.
Shaibani[1] (2012)	Double blind RCT	379	≥18 y/o	-Diagnosed with diabetes type 1 or 2 -Documented glucose control -Experiencing painful diabetic distal sym. sensory/motor polyneuropathy for at least the 3 months prior	-Failing ≥3 pain medications -Require narcotics for pain control -Sensitivity to quinidine or opiates -Prior tx with DMQ	137	All patients were randomly divided into one of three groups Dextormehorphan/quinine (DMQ) 45/30mg, DMQ 30/30mg, and a placebo group. Over a 13 week period pain relief was assessed with 4 different mechanisms.

OUTCOME MEASURED

Although each study had their own method of measurement, the outcome measured was the same. This outcome was pain relief. In the Nelson study, pain relief descriptors were compared with the placebos using a Mann-Whitney U test. The primary outcome variable was the participants' mean pain rating during the last 7 days of the group taking dextromethorphan compared with the last seven days of the trial group taking the placebo. Outcome was calculated using a paired t-test. The second trial, Sani study, used a category rating scale to measure pain relief. Finally, the Shaibani study used a 5-point Pain Intensity Rating Scale, which assessed baseline pain and pain on days 15, 29, 50, 71, and 92 during a clinical visit.

RESULTS

In all three RCT double blind studies, the efficacy of dextromethorphan is compared with a placebo or both a placebo and an alternative medication. In the Nelson study, a total of 14 patients entered the study, of which 13 completed both treatments. The patients in this study, first started with a one-week baseline period, followed by two six-week treatment periods, which was separated by a one-week "washout" period[6]. When given the dextromethorphan, the patients first started with 120mg QID and titrated to a maximum of 960mg daily. While one group was randomly given dextromethorphan, the other was receiving the lactose placebo[6]. Every 3 days, a nurse contacted the participants to titrate medication dosage and to assess pain, adverse reactions, and compliance[6]. Every three days the patients increased their medication by 30-60mg/day unless adverse reactions began affecting daily activities, the patient reported complete pain relief, or if the maximum dose was reached[6]. During the last two weeks, week 5 and 6, the highest well-tolerated dose was kept at a constant level[6].

During the last week of the study, dextromethorphan reduced pain by a mean of 24% compared to that of the placebo[6]. Scores were determined by measuring pain relief on a 13-word descriptor scale. The results showed that while on dextromethorphan, pain was relieved: "a lot, 4; moderate, 3; slight, 4; none, 2; and pain worse, 0;" versus the "placebo: a lot, 0; moderate, 0; slight, 6; none, 5; and pain worse, 2[6]. No participant admitted to full pain relief with either treatment period[6]. The means of the global scores were: dextromethorphan: 2.7 and placebo 1.3[6]. Those who reported moderate or better pain relief with dextromethorphan described their lowest pain experience while on the highest dextromethorphan dose tolerated[6]. As shown in Table 2, when measuring pain relief, researchers calculated a p-value of 0.01, indicating that this study was statistically significant.

Table 2: Nelson Study: Dextromethorphan vs. Placebo[6]

Outcome measured	p-value	Confidence Interval (CI)
Pain relief	0.01	95%

In the Sang Study, 23 participants were selected for the study, 19 of who completed the study in its entirety[7]. In this RCT double blind trial, the patients participated in two different trials. The first was an efficacy trial, which consisted of a three period, three treatment balanced Latin square design which assessed the relationship between the maximally tolerated doses (MTD) of dextromethorphan (MTD=960mg), memantine, and an active placebo (lorazepam)[7]. The second study was a dose-response trial, which consisted of a four period, four treatment Latin square design in "responders" comparing the pain relief recorded at different stages of treatment dosing (0, 25, 50, 100%) up to the maximal tolerated dose determined in the first trial, versus the active placebo[7]. During the trials, all medications were dispensed in identical appearing capsules[7]. Each treatment period consisted of a one-week baseline period followed by a seven-week period where the medications were given 4 times throughout the day[7]. A nurse,

also blinded to the study drug, contacted the patient approximately twice weekly to assess the adverse reactions and to titrate the medication. After the 7 weeks, the patients completed a 2-week washout period before beginning the next trial[7]. At the end of the efficacy trial, pain relief was measured using a category rating scale[7]. When comparing the efficacy between dextromethorphan and the active placebo; 13 of 19 patients reported moderate or better pain relief with dextromethorphan compared to the 7 of 19 who reported moderate to better pain relief with the placebo[7]. The findings at the conclusion of the dose-response trial were: zero patients reported moderate or better pain relief with placebo (0% MTD), one patient reported pain relief with 25% MTD, six with 50% MTD, and ten with 100% MTD[7]. Although researchers found that 25% MTD of dextromethorphan was not statistically better than lorazepam, it was concluded that both 50% and 100% MTD of dextromethorphan was statistically better than the placebo[7]. Below, Table 3 compiles a summary of the Sang study's findings. Using the control event rate and the experimental event rate, the relative benefit increase was calculated as 84% and the absolute benefit increase was found to be 31%. Using the ABI, numbers needed to treat was also calculated. Numbers needed to treat for this study was 4. This means that for every 4 people treated with dextromethorphan, one more had pain relief compared to the control group.

Table 3: Sang Study: Dextromethorphan vs. Active placebo (lorazepam)[7]

CER Placebo Lorazepam	EER Oral Dextromethorphan	RBI	ABI	NNT	p-value
0.37	0.68	0.84	0.31	4	0.12

In the Shaibani Study, 131 participants were randomized into the Dextromethorphan 45/quinidine 30mg (DMQ 45/30) group and 123 were randomized into the placebo group[1]. In the DMQ 45/30mg group, 131 participants started, but only 79 completed the study[1]. Of the 123 who were in the placebo group, only 89 completed the trial[1]. Throughout the study, all of the

participants completed a 13-week, phase 3 RCT where four pain rating scales were applied daily using diaries and five-clinic visits[1]. On days 1, 15, 29, 50, 71, and 92, a 6-point categorical Pain Relief Rating Scale was used to record and classify the relief of their leg pain, compared with baseline[1]. The primary analysis assessed the profile of daily Pain Rating Scale scores of the experimental group compared to those of the control group using a mixed-effects regression model[1]. Researchers found that in both the overall profile and on days 30, 60, 90, the DMQ 45/30mg was statistically significant in pain relief when compared to the placebo[1]. Researchers also saw a 30% Pain Rating Scale score reduction for 83% of the patients on DMQ 45/30mg compared to a reduction in only 61% of the patients on the placebo[1]. Finally, 66% of participants taking DMQ 45/30mg compared to 39% of the placebo group achieved a 50% reduction on the pain scoring scale[1]. Table 4, summarizes the results calculated and recorded for the Shaibani study. Once again, using the control event rate and the experimental event rate, the RBI and ABI were calculated. In this study the relative benefit was calculated as 39% and the absolute benefit increase was recorded as 66%. Numbers needed to treat for this study was also 4.

Table 4: Shaibani Study: DMQ 45/30mg vs. Placebo[1]

CER Placebo	EER DMQ 45/30mg	RBI	ABI	NNT	p-value
0.39	0.66	0.69	0.27	4	0.001

DISCUSSION

This systematic review assessed the use of dextromethorphan for pain relief in patients with diabetic neuropathy. Although dextromethorphan is FDA approved as a cough suppressant, due to its mechanism of action, it has been found to help relieve neuropathy as well. Dextromethorphan is an attractive medication because it is a low affinity, non-competitive,

channel blocking NMDA receptor antagonist[6]. It is hypothesized that by blocking these receptors, it would inhibit the abnormal CNS excitation seen in diabetics and potentially alleviate their experienced pain[6]. Even though each study reviewed was structured differently, the final results were similar. As hypothesized, dextromethorphan proved to relieve pain better than its competing placebo. Therefore, these studies give physicians and patients another treatment option for diabetic neuropathy.

Even with the successful results of these findings, the studies researched had several limitations. Between all three trials, the population of participants who actually completed the entire study was low. The sample sizes 13, 19, and 254 respectively do not represent the generalized population. Another hindering aspect of the studies was that each study was conducted and measured differently. While the Nelson study only looked at dextromethorphan and a placebo, the Sani study also used memantine and the active placebo, lorazepam, which may or may not have been the placebo used in the other two. Finally, the third study, done by Shaibani, not only used a combo drug of dextromethorphan and quinidine, but also compared the results of different strengths of the dextromethorphan given. A final limitation of all three studies was the lack of investigating the long-term effects of the drug on each patient. As a cough suppressant, some adverse reactions seen with dextromethorphan include dizziness, fatigue, abdominal pain, nausea, and potential abuse. However, as a long term high-dose medication, other adverse reactions may be seen. Changing a drug's dosage and length of treatment warrants careful evaluation of the drug before prescribing it. None of the studies followed the patients long enough to record and track the effects of the drug long term. The result of the studies is inclusive as an overview for the U.S. population due to several factors: the trials' use of unlike controls (different drugs, drug combinations, and strength of drugs), the lack

of participants who completed all three studies, and the lack of investigation of long-term effects. Despite the limitations of these studies, hope for a new treatment for diabetic neuropathy still persists.

CONCLUSION

Diabetic neuropathy is a common medical problem seen in diabetics. Although numerous treatments are currently on the market for pain relief, many patients are still not seeing benefits from these medications. Dextromethorphan has recently been tried as an alternative medication and has been proven to be a safe and effective for pain relief in patients with DN. In the three randomly controlled, double blind clinical trials that were reviewed, it was found that dextromethorphan decreased the amount of pain experienced from the neuropathy more than that of the placebo. Although these trials show positive results statistically in the use of dextromethorphan as a pain reliever, further studies must be done to warrant the appeal for the use in treating diabetics. Two main issues that should be addressed in future studies are the size of the study groups and long-term effects of the drug being investigated. A larger research population will enable the results to give a better representation of the US population as well as a stronger validity to the results. Examination of the long-term effects of this particular drug is important, as this drug was not originally manufactured for pain relief. Detecting, knowing, and understanding all possible adverse reactions for any medication is very important, especially when it is being used to treat a chronic condition. Even with the limitations presented, these three studies give hope for future treatments for the debilitating diabetic neuropathy.

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