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Effectiveness of Duloxetine and Pregabalin in Diabetic Peripheral Neuropathic Pain Treatment

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Abstract

This case report addresses diabetic peripheral neuropathic pain (DPNP), a chronic condition associated with diabetes mellitus. There are over 29 million people in the United States who have diabetes (Diabetes latest, 2014). About 25% of diabetics have pain from diabetic peripheral neuropathy (Snyder, Gibbs , & Lindsay, 2016). This is a very challenging and difficult condition to treat as it can negatively affect a person's quality of life. This case report is based on a patient encounter. This is a patient who currently has diabetes, but has not been diagnosed with DPNP. I will examine two different treatment approaches for DPNP, pregabalin and duloxetine, and how effective they are in managing that pain. Pregabalin is classified as an anti-convulsant. Duloxetine is a serotonin norepinephrine reuptake inhibitor. Ten research articles were reviewed that compare the use of pregabalin and/or duloxetine in the treatment of neuropathic pain. They included 4 randomized clinical trials (RCTs), a meta-analysis, a systematic review, a retrospective chart review, a retrospective review of insurance claims, and two prospective studies. In every study, it was found that both duloxetine and pregabalin are effective in treating DPNP. However, there were contradictory findings related to the superiority of one over another. In one study duloxetine, did not have a direct comparison and in another pregabalin was compared to placebo. Three of the studies reported duloxetine superior to pregabalin. In one of these studies, the recommended effective dosage of pregabalin was not always given. One study found pregabalin superior to duloxetine. Another showed suboptimal dose of duloxetine compared to pregabalin. There were also four studies that included gabapentin alone or in combination as a treatment comparison for duloxetine and pregabalin. Side effects are common with both medications and one study showed more minor side effects with duloxetine. Pregabalin was found to have a secondary improvement in sleep. Quality evidence was found supporting the use of pregabalin and duloxetine for effective DPNP treatment.

Background

Millions of people throughout the world are affected by the chronic disease Diabetes Mellitus. It is characterized by a resistance to insulin action, inadequate disseminating endogenous insulin, and an insufficient compensatory insulin secretion reaction (Dunphy, Winland-Brown, Porter, & Thomas, 2015). Diabetes causes long-term damage and many co-morbidities due to chronic hyperglycemia. This can affect a person's eyes, heart, blood vessels, nerves, and kidneys. Macrovascular and microvascular damage is associated with long-term hyperglycemia. "Vascular endothelial dysfunction and inflammation result in fibrosis and intimal thickening, leading to progressive narrowing of the vascular lumen" (Dunphy, Winland-Brown, Porter, & Thomas, 2015, p. 891). This results in ischemia throughout the body due to reduced blood flow through the microvasculature. Common symptoms that are associated with diabetic peripheral neuropathy are pain, burning, allodynia, paresthesia, and hyperalgesia.

The purpose of this report is to address the pain and discomfort associated with peripheral neuropathy by examining two treatment options that are approved by the United States Food and Drug Administration (FDA) for treating diabetic peripheral neuropathic pain. These treatment options are duloxetine and pregabalin. The mechanism of action of pregabalin, an anticonvulsant, includes attaching to the α2-δ subunit of calcium channels in afferent neurons. This action decreases the release of substance P, glutamate and norepinephrine. By doing this, it decreases pain signals that are transmitted to the brain. Duloxetine, an antidepressant, has a mechanism of action that involves obstructing the reuptake of norepinephrine and serotonin in the central nervous system. By doing this it reduces the awareness of pain by lessening pain signals (Tanenberg, et al., 2011). There is an additional medication called tapentadol that is also

approved by the FDA for severe diabetic neuropathic pain that will not be addressed in this case report.

Diabetic peripheral neuropathy and the pain associated with it is a manifestation of the reduced blood flow and inflammation to the microvasculature. This condition is more common in patients with low glycemic control and low serum insulin concentrations. The occurrence increases over time with diabetes. The patient may also experience a loss of sensation and muscle weakness. The pain associated with peripheral neuropathy can lead to mood and sleep disorders (Dunphy, Winland-Brown, Porter, & Thomas, 2015).

The following case provides the background for this case report. This is a 60-year-old woman who has had diabetes type 2 for 10 years. Although she did not present with any peripheral neuropathy, the likelihood of developing this increases with time and having persistent hyperglycemia. The management of blood sugars is crucial with this type of patient and can prevent further disability down the road. By looking at what treatments and dosages are effective for DPNP, we can use this information to successfully treat difficult to manage chronic pain instead of experimenting with different treatments that are ultimately ineffective.

Case Report

Dorothea 60-year-old female
CC: Diabetes recheck

HPI: 60-year-old white female presents to the clinic today for a diabetes check-up. She was diagnosed with diabetes 10 years ago and has been on Metformin since her diagnosis. She states her diabetes is under good control and she checks her blood sugar a couple times a week and it usually runs in the 150-200 range. She saw the diabetes educator last week and was told she needed to eat better and incorporate more fruits and vegetables in her diet. She reports liking

sweets a lot and knows she eats too many. She also drinks three beers two to three times a week. She reports walking a mile a day for exercise. The only concern she has today is that she has been feeling more tired the last few months. She hasn't had any recent changes to her schedule. She works full-time as an information specialist at the University of North Dakota. She states she has been sleeping ok and getting around eight hours of sleep at night. She denies having her thyroid or TSH level checked in the past.

Medications:

Metformin 500 mg po twice daily

Aspirin 81 mg po daily

Lisinopril 20 mg po once daily

Atorvastatin 20 mg po once daily

Multivitamin 1 tablet po once daily

PMH:

Diabetes

Hypertension

Dyslipidemia

Surgeries:

none

Review of Systems:

Constitutional: No weakness, fever or night sweats

Eyes: Patient wears glasses. She reports no blurred vision, eye pain, redness, itching, tearing, diplopia, flashers, floaters or light sensitivity. Last eye exam was 6 months ago.

Ears: Reports no hearing loss, pain, discharge, tinnitus, vertigo, or fullness

Nose: Reports no congestion, epistaxis, postnasal drip, sinus pain or pressure.

Mouth and Throat: Reports no recent dental problems. Last saw dentist in 2016. Denies hoarseness, sore throat, dryness, bleeding gums or lesions.

Head & Neck: Reports no headaches, syncope, swollen glands, pain or neck stiffness

Respiratory: Reports no SOB, wheezing, cough, or hemoptysis

CV: Reports no chest pain or tightness, palpitations, edema, diaphoresis, dizziness, or orthopnea. Denies leg cramps or intermittent claudication.

GI: Reports no abdominal pain, bloating, or cramping. Denies dysphagia, heartburn, dyspepsia, N/V, diarrhea, constipation. No blood in stool or black, tarry stool.

GU: Denies vaginal itch, lesions. Reports no dysuria, urgency, frequency or hematuria.

MS: No joint pain or stiffness. No swelling or motion restriction. No muscle pain.

Neuro: No numbness or tingling to upper or lower extremities.

Objective:

VS: BP-148/98, P-80, RR-20, T-98.6

Labs:

HgbA1C- 8.5%

Lipid panel: Cholesterol-209, LDL- 120, Triglycerides-185, HDL-33

CMP- Normal

TSH- Normal

Diabetic foot exam: Sensation normal. Feet warm and dry. No open lesions or calluses present.

General: Well -developed 60-year-old white female appearing stated age. In no acute distress. Alert and cooperative with exam.

Head: Normocephalic and atraumatic without scalp or facial tenderness.

Eyes: Conjunctivae are pink and sclera are without injection or jaundice.

Ears: TMs shiny and pearly gray with bony landmarks and cone of light visible. No perforations or bulging. Canals without erythema, lesions, or excessive cerumen. Hearing grossly intact.

Mouth: Teeth in good repair. No lesions or exudates in oropharynx or oral mucosa. Uvula rises midline with phonation.

Neck: Trachea midline, thyroid not palpable. No cervical, submandibular, submental, pre-or post-auricular lymph nodes appreciated. Flexion, extension, and rotation without hesitation or limitation.

Chest: Breath sounds clear throughout lung fields without rales, rhonchi, wheezes, or stridor

CV: S1S2 with regular rate and rhythm. No S3, S4, murmurs, clicks or rubs

Abdomen: Non-distended. No tenderness to palpation. Bowel sounds present all 4 quadrants.

MS: Full ROM to all joints without hesitation, pain, clicking, or limitation.

Skin: Warm and dry. No rashes or lesions

Neuro: Speech fluent. Mood euthymic with affect appropriate to situation.

Assessment:

Diabetes Mellitus type 2

Dyslipidemia

HTN

Plan:

1. Increase Metformin 1000 mg po twice daily.
2. Discussed with patient that the goal is to get her HgbA1C down to < 6.0%. We will recheck her HgbA1C in 3 months. Patient is encouraged to reduce her intake of sweets and eat more fruits and vegetables and follow the recommendations from the diabetic educator. She is encouraged to keep exercising daily. Patient is agreeable to this.
3. Lisinopril/Hydrochlorothiazide (HCTZ) 20 mg/12.5 mg po once daily.
4. Discussed with patient that I would like her to purchase a blood pressure monitor and check her BP a couple of times a week and record. Then follow-up with me in 1 month to reassess if we can continue with the current blood pressure medication or if we need to add on a second medication. Patient is agreeable to this.
5. Increase Atorvastatin 40 mg po once daily. Discussed with patient that her Triglycerides are still elevated and her HDL is lower than what I would like it to be. Hopefully with her diet changes and increased medication this will improve. We will recheck her Lipids at her 3-month follow-up.
6. Patient is to return to the clinic or follow-up sooner than 1 month with any other questions or concerns.

Literature Review

The following is a review of the current literature related to the efficacy of treatment for DPNP with the medications pregabalin and duloxetine in adult patients. Pregabalin and duloxetine are currently two of three medications approved for treatment of DPNP by the FDA. The third medication is tapentadol extended release for severe DPNP. Pregabalin is classified as an anti-convulsant and is indicated for neuropathic pain, fibromyalgia, and post-herpetic neuralgia. Duloxetine is classified as a serotonin-norepinephrine reuptake inhibitor and is indicated for depression, generalized anxiety disorder, fibromyalgia, musculoskeletal pain, and neuropathic pain. There have been numerous clinical trials examining the effectiveness of pregabalin and duloxetine for treating DPNP. Some of these studies included additional medications as comparisons. Gabapentin is one of those medications along with amitriptyline.

Lunn, Hughes, and Wiffen conducted a systematic review that looked specifically at duloxetine for treating neuropathic pain, in addition to fibromyalgia and chronic pain. Eighteen trials with a total of 6407 participants were identified. They reviewed eight published studies with 2728 adult patients with diabetic neuropathic pain (2014). They found that there was moderate quality of evidence that the use of duloxetine in daily dosages of 60 mg and 120 mg were effective for treating painful diabetic peripheral neuropathy (PDPN). However, lower dosages were not effective. The review also concluded that minor side effects were common with the duloxetine dosages of 60 mg and more specifically with the 120-mg dosage. These minor side effects included headache, dry mouth, feeling sick, too sleepy or too awake, dizziness, and constipation. One out of 6 people discontinued duloxetine due to side effects. (Lunn, Hughes, & Wiffen, 2014).

Three randomized, double-blind and comparable 13-16 week trials were conducted to determine pregabalin efficacy in treating diabetic peripheral neuropathy (DPN), post-herpetic neuralgia, and spinal cord injury. The randomized control trials (RCTs) included a 52-week expansion trial. Participants in the DPN RCT received dosages of either 300 mg or 600 mg a day or a placebo. This was administered over twelve weeks after a week of titration. The patients selected had moderate to severe pain with a chronic, unrelenting neuropathic pain (Ogawa, Arakawa, Hayakawa, & Yoshiyama, 2016). They found considerable pain improvement after one week. This improvement lasted the extent of the trial. It was concluded that in treating central and neuropathic pain, pregabalin was repeatedly effective. Additionally, it was found that pregabalin improved sleep disorder scores compared to the placebo after one week. They also found that in the peripheral pain trials, patients that withdrew from the trial due to side effects related to treatment was somewhat higher than in the comparable studies. This was attributed to the two different dosage regimens.

A retrospective analysis done by Yang, Qian, and Liu studied health insurance claims from 2006-2011 in the United States to further examine DPNP treatment models. Out of the 12,074 patients, 21.6% were given pregabalin, 45% were given gabapentin and 5.2% started duloxetine. There were also 20 patients that were prescribed a combination of duloxetine and pregabalin. The recommended doses per the FDA are up to 300 mg a day for pregabalin and 60 mg a day for duloxetine. “More than 60% of duloxetine-treated patients were receiving the recommended dose, although 31.0% were receiving just 30 mg/day. Patients treated with pregabalin (91.3%) received less than 300 mg/day” (Yang, Qian, & Liu, 2015, p. 2079). Often, patients received less than the recommended dosage. Of the patients that received pregabalin, 55% received 150 mg/day and sometimes even lower dosages. This despite clinical evidence

showing that dosages this low are comparable to receiving a placebo and do nothing for symptom control. Anticonvulsants are the most frequently prescribed medications for DPNP for those patients that are newly diagnosed, however these medications were often discontinued early. It was also found that within three months of medication initiation, 50% of patients discontinued their prescription. The one-year discontinuation rates for duloxetine-64.4%, and pregabalin-76.7% (Yang, Qian, & Liu, 2015).

A prospective observational 6-month study that included 2575 patients examined the effectiveness of pregabalin, duloxetine and gabapentin on DPNP (Happich, et al., 2014). They found that younger patients switched to or started duloxetine. These patients also worked for pay more often and had higher alcohol intake. They were more often receiving treatment from a general practitioner and not a neurologist. They more frequently had depression and type 2 diabetes. They had previous treatment with other antidepressants, non-opioid analgesics and opioids. They also had more disease-related problems, more severe pain, and poor mental health. They found that patients treated with pregabalin and gabapentin were not treated with appropriate dosages. This could explain the outcomes of the study, that patients treated with duloxetine showed substantially superior improvements in efficacy measures than those treated with gabapentin or pregabalin. The duloxetine patients often received recommended dosages with an average daily dosage of 53.9 mg. The average daily dosage of pregabalin was 173.5 mg (Happich, et al., 2014). This contrasted with the previous study from Yang et. al. that showed suboptimal dosages of duloxetine were used for treating DPNP (2015).

A prospective 6-month study done by Roy et al., not only compared the efficacy of duloxetine and pregabalin, but also examined the cost effectiveness of both medications for treating DPNP. The study was conducted in a diabetic clinic in South India. The patients were

not previously treated with either drug. Fifty patients were treated with pregabalin and 50 patients were treated with duloxetine. The Neuropathic Pain Scale and the Neuro-Qol questionnaires were used to assess patient's pain. In treating neuropathic pain, duloxetine was found to be more effective than pregabalin, but was more expensive. However, both medications were shown to significantly reduce DPNP. Fourteen patients dropped out that were taking duloxetine and 2 that were taking pregabalin. The discontinuation was due to a combination of adverse events, cost, alternative therapy, and termination of treatment (Roy, Kuriakose, Varma, & Jacob, 2017).

A double-blind RCT done by Boyle et al. (2012), examined the pain-relieving efficacy of duloxetine, pregabalin, and amitriptyline along with their secondary effect on sleep, quality of life and daytime functioning in patients with DPNP. This secondary effect on mood and sleep may play a part in the successful treatment of patients with DPNP. Between February 2007 and March 2009, 83 subjects with diabetes type 1 and 2 participated in the study. Twenty-seven were given pregabalin, 28 amitriptyline, and 28 duloxetine. When compared with placebo, pregabalin, duloxetine and amitriptyline all reduced pain with not one medication better than another. There was a 50% improvement in subjective pain which is comparable to similar studies. As far as sleep continuity, there was a pronounced reduction in REM sleep and sleep was very disjointed with duloxetine, but duloxetine did improve performance on sensory motor tasks and improved central nervous system stimulation (Boyle, et al., 2012). Whereas, pregabalin stimulated sleep. As far as medication effects on daytime activity function, it was comparatively ineffective. A higher number of side effects also were found in the subjects treated with pregabalin.

One RCT examined patients that were originally treated with gabapentin >= 900 mg/day for DPNP and had an unsatisfactory response with a pain score >=4 using a 0-10 pain scale.

These patients were then randomized to be treated with either pregabalin (n=134), duloxetine (n=138), or a combination of gabapentin and duloxetine (n=135). The purpose of this study was to determine if treatment with duloxetine was substandard in comparison to treatment with pregabalin. The duloxetine dosage was titrated up to 60 mg/day after one week. The pregabalin dosage was titrated up to 300 mg/day after one week. The third group treated with a combination of gabapentin/duloxetine remained on the initial dosage of gabapentin >=900 mg/day in addition to titrating the dosage of duloxetine up to 60 mg/day. Researchers reported that considerably more patients discontinued the duloxetine (n=27) due to side effects than with the pregabalin or the gabapentin/duloxetine combination. These side effects included, nausea, decreased appetite, excessive perspiration, and insomnia. However, peripheral edema was greater with the use of pregabalin. Researchers concluded that treatment with duloxetine was non-inferior to pregabalin and gabapentin/duloxetine for DPNP. They also found that adding duloxetine to the gabapentin was effective in treating DPNP similar to using pregabalin or duloxetine alone. (Tanenberg, et al., 2011).

A randomized, double-blind COMBO-DN study examined the Neuropathic Pain Symptom Inventory (NPSI) of patients initially to determine a baseline, then after either pregabalin or duloxetine therapy for eight weeks, and then again after an eight-week increased dose/combination therapy. The study also showed that diabetic patients present with differing sensory profiles in their response to pain. The initial therapy was 300 mg pregabalin or 60 mg duloxetine. If patients had <30% improvement, then the patients receiving duloxetine, increased to 120 mg and patients receiving pregabalin increased to 600 mg or a combination of 300 mg pregabalin and 60 mg duloxetine. In the primary therapy duloxetine worked better for pain. “The present exploratory analyses of data collected in the COMBO-DN study suggest that duloxetine

and pregabalin have different effects on distinct neuropathic pain components in diabetic peripheral neuropathy" (Bouhassira, et al., 2014, p. 2174). In patients not responding to the initial monotherapy of duloxetine, the combination of duloxetine and pregabalin was favorable in patients with persistent and induced pain. In patients where dysesthesia/paresthesia is pronounced, increasing the duloxetine to 120 mg/day was more advantageous (Bouhassira, et al., 2014).

A meta-analysis was used to examine the tolerability and effectiveness of duloxetine to pregabalin and gabapentin compared with a placebo in treating DPNP. A total of eleven RCTs were reviewed, with 3 studies on duloxetine, 6 on pregabalin, and 2 on gabapentin. A 24-hour average pain severity was used to assess treatment effectiveness. Duloxetine, pregabalin and gabapentin were found to be exceptional compared to the placebo. Duloxetine was associated with more incidences of nausea, headache, dizziness, and sleepiness. It also had greater occurrences of discontinuation compared to placebo. This was a similar case with pregabalin. Pregabalin was associated with somnolescence and dizziness along with greater discontinuation compared to placebo. In the direct comparison of pregabalin and duloxetine, three effectiveness outcomes were considered; seven tolerability outcomes, 24-hour pain severity, and Patient Global Impression of Improvement/Change (PGI-I/C). There was found to be no difference in 24-hour PS between pregabalin and duloxetine. It was found that the PGI-I/C was preferential to pregabalin, and duloxetine was preferred in the tolerability outcomes (Quilici, et al., 2009).

A retrospective chart review done in a neuromuscular outpatient clinic examined the use of duloxetine and pregabalin for diabetic neuropathic pain (DNP) over a 10-month period. In addition, the chart review examined the effect of these two medications on cryptogenic sensory polyneuropathy. This is a common type of neuropathy seen in patients over 50 years of age. One

hundred and three patients were started on duloxetine and 91 patients were started on pregabalin. Those patients taking pregabalin (33%) conveyed a greater improvement in neuropathic pain compared to the patients taking duloxetine (21%). Compared to pregabalin (30%), duloxetine (38%) had more reported side effects. There were no significant differences between duloxetine and gabapentin. This retrospective review suggests that duloxetine and pregabalin would both be effective in treating DPN secondary to either cryptogenic sensory polyneuropathy or diabetes mellitus. (Mittal, et al., 2011).

Learning Points

When using the recommended doses of pregabalin and duloxetine, both are very effective medications to use for DPNP. However, when providers prescribe ineffective dosages of these medications, they do not work and lead patients to discontinue these medications preemptively.

Duloxetine and pregabalin have minor side effects that many patients are unable to tolerate. They may discontinue these medications early due to these side effects. Having patients use the lowest recommended dosage for both medications may lessen the chance of developing adverse drug reactions as the side effects increase with an increase in dosage.

Pregabalin was found to improve patient's sleep in addition to DPNP in one study. This secondary component might improve the patient's overall well-being, quality of life, and level of functioning. Further studies would be warranted.

One study found that both medications have different effects on neuropathic pain components. The examination of a patient's unique sensory profiles in response to pain could provide more accurate information for future treatment options. This finding would also benefit from replication.

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