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Retrospective Chart Review of Duloxetine and Pregabalin in the Treatment of Painful Neuropathy

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Abstract

The primary aims of our study were to compare pregabalin and duloxetine in a neuromuscular clinic for diabetic neuropathic pain (DPN) and to study the effect of these medications in cryptogenic sensory polyneuropathy. We performed a retrospective chart review of 143 patients who were started on pregabalin or duloxetine during a 10-month period in a tertiary neuromuscular outpatient center for neuropathic pain. Duloxetine and pregabalin were started in 103 and 91 patients, respectively. Ninety-two patients tried only one of the two medications while both medications were used at different time periods in 51 patients. Follow-up was available for 87 patients on pregabalin and 89 patients on duloxetine. More patients with neuropathic pain reported an improvement with pregabalin (33%) than duloxetine (21%). Duloxetine (38%) had a higher frequency of side effects compared to pregabalin (30%). However, these differences between pregabalin and duloxetine were not statistically significant. Despite the study's limitations of retrospective design, these findings suggest that both pregabalin and duloxetine are probably effective for neuropathic pain, secondary to diabetes or cryptogenic sensory peripheral neuropathy in a tertiary care academic neuromuscular center. Prospective randomized controlled comparative effectiveness studies are required for both drugs in the treatment of neuropathic pain.

Keywords

Cryptogenic sensory polyneuropathy; diabetic neuropathy; duloxetine; neuropathic pain; peripheral neuropathy; pregabalin

INTRODUCTION

Neuropathic pain is a common neurological symptom in patients being presented to neuromuscular clinics. Traditionally, tricyclic antidepressants such as amitriptyline and antiepileptic medications such as gabapentin were advocated as first-line agents for the treatment of painful peripheral neuropathy. More recently, randomized, double-blind, placebo-controlled trials have led to Food and Drug Administration (FDA) approval of

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pregabalin for neuropathic pain associated with diabetic peripheral neuropathy (DPN) and postherpetic neuralgia (Dworkin et al., 2003; Frampton & Scott, 2004; Lesser, Sharma, LaMoreaux, & Poole, 2004; Rosenstock, Tuchman, LaMoreaux, & Sharma, 2004; Sabatowski et al., 2004), and duloxetine for the treatment of painful diabetic neuropathy (Goldstein, Lu, Detke, Lee, & Iyengar, 2005; Raskin et al., 2005). Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA) that binds the α_2-δ subunit of the presynaptic calcium channel, thereby modulating calcium influx and excitatory neurotransmitter release (Dooley, Donovan, & Pugsley, 2000; Fink et al., 2002; Taylor, 2004). Duloxetine is a serotonin and norepinephrine reuptake inhibitor (Bymaster et al., 2001). Since the FDA approval, there have been no published reports assessing the real life experiences with these medications nor there are any comparisons of duloxetine and pregabalin. We report the efficacy and safety of pregabalin and duloxetine in neuropathic pain patients treated in our academic neuromuscular center over a 10-month period. We performed a retrospective cohort study to compare the effectiveness of these two drugs for neuropathic pain and to compare their side effects.

METHODS

We performed a retrospective chart review of all the patients with neuropathic pain who started on pregabalin between January and October of 2006 and duloxetine between the January and October of 2004 in our tertiary neuromuscular outpatient center. We documented the patient's age, sex, cause of neuropathic pain, type of medication for pain (prebagalin or duloxetine), side effects, response to treatment, and other reasons for drug discontinuation. The typical starting dose for duloxetine was 30 mg/day, which was increased to 60 mg/day in 1 week. Pregabalin was started typically at 50 mg a day and increased every 3–7 days to reach efficacy at a lower dose, a maximum dose of 600 mg daily, or at an intolerable adverse event. Patient-reported response was used to access the efficacy of medications. Response to therapy was classified into no improvement, minimally improved (patients stated that they have some improvement, but they were still symptomatic enough to require either medication discontinuation, change in medication, or increase in dosage), and much improved (no change in medication).

Neuropathic pain etiologies were grouped into the eight categories of diabetes, hereditary, infection/toxic, autoimmune, cryptogenic sensory polyneuropathy (CSPN), nerve entrapment, nutritional, and miscellaneous (Table 1). Duloxetine- and pregabalin-related efficacy, and the side effects were compared between various groups.

STATISTICAL METHODS

For descriptive purposes, we presented categorical data as frequencies and compared differences (efficacy and side effects) between various neuropathic pain groups using chi-square and Fisher exact test. For continuous variables, we reported mean ± standard deviation.

RESULTS

We reviewed the medical records of 143 patients with painful peripheral or cranial neuropathy. The male-to-female ratio was 1:1.1. The mean presenting age was 56 ± 12 years (range: 27–84 years). Follow-up data were available for 128 (90%) patients. The causes of neuropathic pain were diabetes, 40 (28%); CSPN, 34 (24%); nerve entrapment, 26 (18%); autoimmune, 13 (9%); hereditary, 11 (8%); miscellaneous, 9 (6%); infection/toxic, 8 (6%); and nutritional, 2 (1%).

Duloxetine and pregabalin were started in 103 (72%) and 91 (64%) patients, respectively. Both medications were administered at different time periods in 51 patients. The mean doses of pregabalin and duloxetine were 217 ± 128 mg/day (range: 50–600 mg/day) and 59± 14 mg/day (range: 30–120 mg/day), respectively. Efficacy, side effect, and the reasons for discontinuing medication are shown in Table 2. Overall, an improvement in neuropathic pain (minimally or much improved) was seen in 48% patients who were on pregabalin and 41% for those on duloxetine ($p = .44$). Pregabalin resulted in much improvement in 12 diabetic neuropathic pain patients. Of these 12 patients, five were taking 150 mg and four were taking 300 mg per day. Pregabalin doses were not available for two patients. Six patients could not tolerate duloxetine, five had diabetic neuropathic pain, and one had peripheral neuropathy with monoclonal gammapathy of unknown significance. Of the 40 diabetic patients affected with neuropathic pain, 31 had tried duloxetine and the follow-up data were available for 23 patients. Of these 23 patients, seven reported minimal or much improvement and nine showed no response. Most of the patients were taking duloxetine worth 60 mg daily, except that one patient with no improvement or much improvement was taking duloxetine worth 30 mg daily each, and one patient with much improvement was taking duloxetine worth 90 mg daily. One patient did not take duloxetine due to concerns about increased suicidal risk as mentioned in the package insert. A comparison in efficacy and side effects between the two medications was noted across various neuropathic pain groups and the results are displayed in Table 3. The largest groups, diabetes and CSPN, had better outcomes (much improved) with pregabalin (38% and 30%, respectively) than with duloxetine (30% and 14%, respectively), but this was not significant ($p = .16$). Specific side effects from both the medications are shown in Table 4. Pregabalin was associated with weight gain in seven patients, and of these, three were on a 150 mg daily dose, two were on a 300 mg daily, and no dose was available for two patients.

Overall, pregabalin (33%) was associated with higher cases reporting their pain to be “much improved” than duloxetine (21%) ($p > .05$). Duloxetine and pregabalin showed no statistically significant difference in either efficacy or side effects between the various groups of neuropathic pain patients.

DISCUSSION

Duloxetine and pregabalin are both FDA approved for the treatment of painful DPN based on randomized, double-blinded, placebo-controlled trials. Randomized controlled trials (RCTs) report neuropathic pain control data in the form of a responder rate (>50% pain reduction in 11-point Likert scale, over 24-hr time period) as compared to placebo. Multiple

RCTs studying the role of pregabalin and duloxetine in treating DPN have found a high responder rate anywhere from 40% to 52% and from 49% to 68%, respectively, depending on their dose and fixed or flexible schedule as well as the type of analysis (baseline or last observation carried forward; Arezzo, Rosenstock, Lamoreaux, & Pauer, 2008; Freynhagen, Strojek, Griesing, Whalen, & Balkenohl, 2005; Goldstein et al., 2005; Lesser et al., 2004; Raskin et al., 2005; Rosenstock et al., 2004; Tolle, Freynhagen, Versavel, Trostmann, & Young, 2008; Wernicke et al., 2006). We did not use the Likert scale. We asked our patients whether they were improved or not on medication, and if improved whether they were "minimally improved" or "much improved." This corresponds to several categories in the Patient's Global Impression of Change (PGIC) scale (1—very much improved; 2—much improved; 3—minimally improved; 4—no change) (Guy, 1976). RCTs in DPN patients have reported a combined PGIC "very much" or "much improved" rate of 43%–67% with pregabalin and 51%–57% with duloxetine, which is higher than 38% and 30% seen in our diabetic group with pregabalin and duloxetine, respectively. Lower efficacy with pregabalin in our study may be explained by the use of a lower mean dose. Follow-up efficacy data were not available in our study for 20% of the patients taking pregabalin and 26% taking duloxetine. Our study population was different from the RCTs due to the lack of rigid inclusion and exclusion criteria and lack of rigid titration schedules. (Lesser et al., 2004; Rosenstock et al., 2004) (Goldstein et al., 2005; Raskin et al., 2005; Wernicke et al., 2006)

A large number of patients discontinued pregabalin in our diabetic neuropathic pain patients (59%) as compared to only 11%–21% of the DPN patients reported in the literature (Arezzo et al., 2008; Freynhagen et al., 2005; Lesser et al., 2004; Rosenstock et al., 2004; Tolle et al., 2008). The mean dose of our patients (250 mg) was lower than that used in the literature (300 mg; Lesser et al., 2004; Rosenstock et al., 2004). The various reasons for discontinuation were the intolerable side effects, lack of compliance, and lack of efficacy, which in our study were 18%, 6%, and 41%, respectively, compared to 11%, 3%, and 1%, respectively, in the study by Rosenstock et al. (2004). A higher rate of discontinuation, secondary to lack of efficacy, in our study could be explained by a lower dose and absence of adherence to a rigid protocol that would be done in a RCT. Most of the common side effects reported with the intake of 300 mg/day pregabalin are dizziness (27%–36%), somnolence (20%–24%), infection (10%–15%), peripheral edema (7%–11%), nausea (8%), headache (7%–9%), blurred vision (5%), and euphoria (5%–6%; Lesser et al., 2004; Rosenstock et al., 2004). We noted that weight gain (10%), sedation (4%), and increased appetite (4%) were the most frequent side effects in our study. Weight gain was not dose dependent and was seen with both 150 and 300 mg/day.

A larger number of patients discontinued duloxetine in our diabetic group (66%) compared to the RCTs (13%–25%) done for DPN patients with a 60 mg/day dose of duloxetine (Goldstein et al., 2005; Raskin et al., 2005; Wernicke et al., 2006). The mean dose of our patients (58 mg) was equivalent to that used in the literature (60 mg; Goldstein et al., 2005; Raskin et al., 2005; Wernicke et al., 2006).) Various reasons for the discontinuation of duloxetine were intolerable side effects, lack of efficacy, and miscellaneous (inability to afford medication) in 35%, 28%, and 7%, respectively, compared to the reported rates of 33%–59%, 3%–4%, and 38%–43%, respectively (Goldstein et al., 2005; Raskin et al., 2005; Wernicke et al., 2006). Lower efficacy in our study could be explained by a less rigid

methodology for determining response and a very heterogeneous patient population compared to a RCT. Also, in routine clinical care, we might discontinue a drug more readily in the presence of mild side effects compared to the management of adverse events in the formal trial design of a RCT. The most common side effects reported with the intake of a 60 mg/day dose of duloxetine are dizziness (10%–16%), somnolence (8%–20%), constipation (7%–15%), dry mouth (7%), nausea (17%–28%), headache (11%), fatigue (12%), diarrhea (11%), hyperhidrosis (9%), nasopharyngitis (8%), and insomnia (5%; Goldstein et al., 2005; Raskin et al., 2005; Wernicke et al., 2006). Nausea (11%), sedation (7%), and sexual dysfunction (5%) were the most frequent side effects in our study.

Our data derived from a clinical practice setting are valuable in guiding clinicians as it more likely mirror the situation in day-to-day practice. DPN patients seen in neurology clinics have various comorbidities and other medications (psychiatric and pain including opioids). The RCTs have excluded these patients from the DPN and pregabalin or duloxetine trials, and the data available are valid only for a selected group of patients with well-controlled Diabetes Mellitus (DM), no systemic illnesses, no other pain medications, and no opioids. Despite being a retrospective chart review study, it is our first attempt at comparing the efficacy and side effects between duloxetine and pregabalin for neuropathic pain treatment. Ideally, this needs to be studied in a prospective randomized trial, but it is unlikely that such a trial will be performed by the pharmaceutical industry. Rather, a prospective comparative efficacy study of these drugs will require an investigator-initiated trial. Such a trial is in a planning phase. This retrospective review provides the preliminary data to form the basis for a prospective comparative trial.

Although there are various RCTs to study the role of pain medications in DPN, there is a lack of therapeutic trials to study CSPN, the second most common Peripheral Neuropathy (PN) in academic neurology clinics (Barohn, 1998). CSPN is the most common category of neuropathy in tertiary care clinic (Wolfe & Barohn, 1998). The previous published studies using duloxetine and pregabalin were only performed in patients with diabetic neuropathy (Arezzo et al., 2008; Dworkin et al., 2003; Frampton & Scott, 2004; Freynhagen et al., 2005; Goldstein et al., 2005; Lesser et al., 2004; Raskin et al., 2005; Rosenstock et al., 2004; Sabatowski et al., 2004; Tolle et al., 2008; Wernicke et al., 2007). Cryptogenic sensory polyneuropathy is an understudied group of painful neuropathy (Barohn, 1998). We show that pregabalin may be a useful therapeutic agent in CSPN patients with side effects and efficacy comparable to DPN patients. On the basis of our retrospective study, duloxetine was less effective than pregabalin for CSPN-related neuropathic pain, although this difference was not statistically significant.

The main drawbacks of this study are its retrospective design and the fact that the number of patients started on these medications did not have a follow-up data available. This, however, does mimic, to a large extent, the patterns encountered in clinical practice. Another weakness of this study is the concomitant use of other pain medications. We cannot exclude an additive effect. Most patients were on stable medication doses at the time of the initiation of either pregabalin or duloxetine. Moreover, the duration of the follow-up varied in these patients. Therefore, we could not estimate the time for the onset of pain reduction.

Despite the limitations of the design of our study, it shows that at least some patients with neuropathic pain from conditions other than DPN and postherpetic neuralgia may benefit from pregabalin and duloxetine. There was no statistically significant difference in efficacy based on the patients' responses in this retrospective review. Large, prospective, randomized studies comparing the effectiveness of pregabalin and duloxetine are needed for CSPN, DPN, and other conditions with neuropathic pain.

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TABLE 1

Various causes of neuropathic pain in patients being presented to an academic neuromuscular clinic

Major categories	Subcategories
Autoimmune	Acute inflammatory demyelinating polyneuropathy (AIDP)
	Celiac disease (Hadjivassiliou et al., 2006); Graft versus host disease in transplant patients (Amato, Barohn, Sahenk, Tutschka, & Mendell, 1993)
	Chronic inflammatory demyelinating polyneuropathy (CIDP)
	Distal acquired demyelinating symmetric neuropathy (DADS; Katz, Saperstein, Gronseth, Amato, & Barohn, 2000; Saperstein, Katz, Amato, & Barohn, 2001)
	Multiple myeloma and monoclonal gammapathy of unknown significance (MGUS; Kelly, 1985; Kelly, Kyle, Miles, O'Brien, & Dyck, 1981)
	Sjogren's syndrome (Mellgren, Conn, Stevens, & Dyck, 1989)
	Systemic lupus erythematosus (SLE; Feinglass, Arnett, Dorsch, Zizic, & Stevens, 1976)
Cryptogenic	Cryptogenic sensory polyneuropathy (CSPN; Wolfe et al., 1999)
Diabetes related	Distal sensory polyneuropathy
	Radiculopathy
	Radiculoplexopathy
Hereditary	Charcot Marie Tooth disease
	Hereditary neuropathy with pressure palsy
	Peripheral neuropathy with multiple lipomas
Infection/toxin related	Hepatitis C
	Human immunodeficiency virus (HIV)
	Postherpetic neuralgia
	Cancer with chemotherapy
Miscellaneous neuropathic pain group	Critical care illness (Bolton, Gilbert, Hahn, & Sibbald, 1984)
	Idiopathic brachial or lumbosacral plexitis
	Mitochondrial disorder (Schroder, 1993)
	Primary systemic amyloidosis (Kelly, Kyle, O'Brien, & Dyck, 1979)
	Reflex sympathetic dystrophy
	Unknown etiology
Nerve entrapment	Carpal tunnel syndrome
	Meralgia paresthetica
	Occipital neuralgia
	Radiculopathy not associated with diabetes
	Thoracic neuralgia associated with neurofibromatosis type 1 or arachnoid cyst
	Trigeminal neuralgia
Nutritional	Post gastric bypass peripheral neuropathy
	Vitamin B12 deficiency

TABLE 2

Comparison of efficacy and side effects in neuropathic pain patients using pregabalin and duloxetine

	Pregabalin		Duloxetine		
	Number[a]	**Percentage**	**Number**[a]	**Percentage**	***p***
Number of patients	91	63.6	103	72	
Dose (in mg)	217 ± 128	(range: 50–600)	59 ± 14	(range: 30–120)	
Follow-up available	87	97	89	86	.03
Efficacy					
No improvement	36/69	52.2	46/78	59.0	.47
Minimally improved	10/69	14.5	16/78	20.5	.35
Much improved	**23/69**	**33.3**	**16/78**	**20.5**	**.09**
Side effects	22/74	30.0	32/85	37.6	.29
Medication continued	25/76	32.9	24/89	27.0	.61
Medication stopped due to lack of efficacy	25/51	49.0	32/65	49.2	.58
Medication stopped due to side effects	12/51	23.5	16/65	24.6	.81
Medication stopped due to a combination of lack of efficacy and side effects	8/51	15.7	12/65	18.5	.51
Medication stopped due to financial reasons	6/51	11.8	3/65	4.6	.22

[a]Due to the unavailability of retrospective study design follow-up data for all the patients, the denominator represents the number of patients in that group to whom the follow-up data were available.

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TABLE 3

Comparison of side effects and efficacy of pregabalin and duloxetine in various neuropathic pain conditions

	Pregabalin							Duloxetine						
	Diabetes *N* (%)	**CSPN *N* (%)**	**Nerve entrapment *N* (%)**	**Inflammatory *N* (%)**	**Hereditary *N* (%)**	**Infection/toxic *N* (%)**	**Others*** *N* (%)**	**Diabetes *N* (%)**	**CSPN *N* (%)**	**Nerve entrapment *N* (%)**	**Inflammatory *N* (%)**	**Hereditary *N* (%)**	**Infection/toxic *N* (%)**	**Others *N* (%)**
Total number of patients	40	34	26	13	11	8	11	40	34	26	13	11	8	11
Number of patients taking medication	20 (50)	17 (50)	20 (77)	11 (85)	8 (73)	6 (75)	9 (82)	31 (78)	28 (82)	14 (54)	8 (62)	8 (73)	6 (75)	8 (73)
Mean dose (mg/day)	250 ± 137	200 ± 112	206 ± 122	260 ± 196	196 ± 119	138 ± 31	236 ± 80	58 ± 11	54 ± 13	63 ± 20	69 ± 23	60 ± 0	60 ± 0	60 ± 0
Dose range (mg/day)	150–600	50–1,600	150–600	50–600	50–300	75–1,000	150–300	30–90	30–60	30–120	60–120	60	60	60
Follow-up available for efficacy*	16	10	14	10	8	4	7	23	22	10	6	7	3	7
Efficacy														
No improvement	8 (50)	6 (60)	7 (50)	4 (40)	4 (50)	3 (75)	4 (57)	9 (39)	14 (64)	7 (70)	4 (67)	5 (71)	2 (67)	5 (70)
Minimally improved	2 (13)	1 (10)	2 (14)	3 (30)	2 (25)	0	0	7 (30)	5 (23)	1 (10)	1 (17)	1 (14)	1 (33)	0 (10)
Much improved	6 (38)	3 (30)	5 (36)	3 (30)	2 (25)	1 (25)	3 (43)	7 (30)	3 (14)	2 (20)	1 (17)	1 (14)	0	2 (20)
P value for efficacy comparison between 2 medications in various neuropathic pain conditions**	0.20	0.31	0.80	0.63	0.62	0.50	0.75	0.20	0.31	0.80	0.63	0.62	0.50	0.75
Follow-up data available for side effects	18	12	14	10	8	4	8	28	21	11	7	7	4	7
Side effects	4 (22)	4 (33)	2 (14)	4 (40)	3 (38)	2 (50)	3 (38)	10 (36)	12 (57)	2 (18)	1 (14)	2 (29)	2 (50)	3 (43)
P value for side effects comparison between 2 medications in various neuropathic pain conditions**	0.62	0.40	0.92	0.51	0.55	1.00	0.97	0.62	0.40	0.92	0.51	0.55	1.00	0.97
Follow-up data available for medication continuation status	17	14	15	10	8	4	8	29	22	11	7	8	4	8
Medication continued	7 (41)	2 (14)	7 (47)	4 (40)	3 (38)	0	2 (25)	10 (35)	3 (14)	3 (27)	2 (29)	2 (25)	2 (50)	2 (25)
Reason for stopping medication****														
Lack of efficacy	7 (41)	6 (43)	7 (47)	3 (30)	4 (50)	3 (75)	3 (38)	8 (28)	14 (64)	7 (64)	4 (57)	5 (63)	2 (50)	4 (50)
Side effects	3 (18)	4 (29)	3 (20)	4 (40)	1 (13)	2 (50)	3 (38)	10 (35)	11 (50)	2 (18)	1 (14)	1 (13)	0	3 (38)
Financial/compliance	1 (6)	3 (21)	1 (7)	0	0	0	0	2 (7)	1 (5)	0	0	0	0	0

*Due to the unavailability of retrospective study design follow-up data for all the patients, the number of patients to whom the follow-up data were available was used as the denominator to calculate the percentages.

**p value was >.05 for efficacy and the side effects comparison between pregabalin and duloxetine in all the subgroups of the neuropathic pain patients.

***Others included nutritional and miscellaneous groups due to small sample size.

****Some patients discontinued medication after a combination of side effects and no improvement with medication.

TABLE 4

Side effects experienced by neuropathic pain patients who were treated with either duloxetine or pregabalin

System involved, duloxetine (%) vs. pregabalin (%)	Side effect	Duloxetine (*N* = 85)	Pregabalin (*N* = 74)
Neurological, 17 (20%) vs. 10 (14%)	Sedation	6	3
	Dizziness	2	2
	Blurred vision	2	2
	Nightmares	1	1
	Insomnia	1	1
	Increased paresthesias	1	1
	Myoclonic jerks	1	0
	Headaches	1	0
	Diplopia	1	0
	Speech problems	1	0
Gastrointestinal, 13 (15%) vs. 3 (4%)	Nausea/vomiting/gastrointestinal upset	9	2
	Lower GI bleed	1	0
	Loss of appetite	1	0
	Constipation	0	1
	Sore throat	1	0
	Dry mouth	1	0
Endocrine, 3 (4%) vs. 12 (16%)	Weight gain	0	7
	Increased appetite	0	3
	Fatigue	2	1
	Hair loss	1	0
Psychiatric, 4 (5%) vs. 1 (1%)	Mood swings/irritability	3	0
	Depression	1	0
	More talkative	0	1
Autonomic, 3 (4%) vs. 2 (3%)	Leg edema	0	1
	Hand swelling	0	1
	Swollen head sensation	1	0
	Pruritis	1	0
	Night sweats	1	0
Musculoskeletal, 1 (1%) vs. 3 (4%)	Stiffness	0	1
	Jaw tenderness	0	1
	Chest tightness	1	1
Genitourinary, 5 (6%) vs. 0 (0%)	Sexual dysfunction	4	0
	Urinary retention	1	0
Cardiovascular, 1 (1%) vs. 0 (0%)	Hypertension	1	0