Abbreviated National PBM Drug Monograph

Duloxetine (Cymbalta) in Painful Diabetic Neuropathy and Fibromyalgia

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VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Also see related monograph of duloxetine in major depressive disorder at www.vapbm.org or vaww.pbm.med.va.gov.

Executive Summary

Painful Diabetic Neuropathy

Efficacy. Two large placebo-controlled trials and one large, long-term routine-care–controlled trial showed that duloxetine (60 mg once daily) relieves pain, increases functionality, and improves quality of life in patients with painful diabetic neuropathy (PDN). Indirect comparisons of NNTs for responder rates suggest that duloxetine is not better than tricyclic antidepressants and antiepileptic drugs in relieving diabetic peripheral neuropathic pain. Duloxetine may not have clear advantages over gabapentin and phenytoin in terms of onset of effect, but relative to alternative formulary agents, it offers the convenience of once-daily dosing and lack of a need for dosage titration. An only moderate analgesic effect may counterbalance these conveniences.

Safety. The long-term safety of duloxetine and its safety in a naturalistic setting are unknown. Duloxetine is associated with an increased risk of hepatotoxicity and hypoglycemic events, although the rates are low overall. Small decreases in diastolic blood pressure were seen in controlled PDN trials, whereas increases in systolic and diastolic blood pressure were seen in MDD trials. Duloxetine is associated with an increased risk of constipation, lethargy, somnolence, and urinary retention.

Cost-effectiveness. No VA-applicable data were available on the comparative cost-effectiveness of duloxetine in PDN. However, this agent may have a greater acquisition cost than some formulary alternatives that have been used for PDN.

Fibromyalgia

In a single good-quality placebo-controlled trial, duloxetine (60 mg twice daily) was shown to be moderately efficacious, safe, and well tolerated in the off-label treatment of patients with fibromyalgia. A subgroup analysis suggested that it was efficacious in women but not men. For this reason, there is a limited role for duloxetine in the treatment of fibromyalgia in the VA patient population.

Recommendations

- Duloxetine should remain nonformulary at the national and VISN levels.
- National criteria for use should be implemented to control utilization.
- Given (1) the lack of direct evidence of the relative treatment benefits of duloxetine in patients with PDN and fibromyalgia, (2) the indirect evidence suggesting that duloxetine is not better than alternative formulary agents, as well as (3) the lack of long-term (> 1 year) safety trials, duloxetine should generally be used as a second-line agent after adequate trials of alternative oral, non-opioid formulary agents.

Introduction

Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor, is the first drug to gain approval by the Food and Drug Administration (FDA) for treatment of diabetic peripheral neuropathic pain (or painful diabetic neuropathy, PDN). While duloxetine is the first drug approved for this indication, a number of other agents have been used off-label for this purpose, such as tricyclic antidepressants and antiepileptic drugs. Duloxetine has also been evaluated in the treatment of fibromyalgia, a chronic musculoskeletal pain disorder that is postulated to involve dysregulation of central serotonin- and norepinephrine-mediated pain inhibitory processes.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating duloxetine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA in the treatment of chronic PDN and fibromyalgia.

FDA–Approved Indication(s) and Off-label Uses

FDA–Approved Indications
Diabetic peripheral neuropathic pain

Off-label Uses
Fibromyalgia syndrome

Current VA National Formulary Alternatives

Listed below by indication are alphabetized lists of selected formulary agents for which there is evidence of efficacy from at least one published double-blind randomized controlled trial of any quality or good-quality systematic review.

Painful Diabetic Neuropathy

Drug Class	Formulary Agents	Restrictions
Antidepressants	*Tricyclics*[1]: amitriptyline, desipramine, imipramine	
	SNRI: Venlafaxine[2]	
Antiepileptics	Carbamazepine[3]	
	Gabapentin[3]	
	Phenytoin,[3]	
	Valproate[4,5]	
Opioids	Tramadol[6]	
	Oxycodone[7,8]	Refer to criteria for use of controlled-release oxycodone
Other	Capsaicin 0.075% cream[9]	

Fibromyalgia

Drug Class	Formulary Agents
Antidepressants	*Tricyclics:* Amitriptyline
	SSRI: Fluoxetine
Muscle relaxant	Cyclobenzaprine
Opioids	Tramadol ± acetaminophen

Source: Goldenberg (2004)[10]

Dosage and Administration

Indication	Dose	Comments
Diabetic peripheral neuropathic pain	60 mg/d Consider starting at lower dose in patients with renal impairment or tolerability concerns.	May be given without regard to meals. A higher dose (120 mg/d) did not provide additional benefit and was less well tolerated. Efficacy beyond 12 wk has not been evaluated.
Fibromyalgia	Dose used in clinical trial (off-label): Start at 20 mg once daily, titrate to 60 mg twice daily over 2 wk, then maintain at 60 mg twice daily.	Efficacy beyond 12 wk has not been evaluated.

Efficacy

Efficacy Measures

PDN

11-point Likert scale. The 11-point Likert scale is a validated numerical rating scale (e.g., ranging from 0 = No pain to 10 = Worst pain possible) that has been one of the most commonly used methods to measure the intensity of neuropathic pain. The primary efficacy measure in the major duloxetine efficacy trials was the change in 24-hour average pain intensity. In addition to assessing average daily pain, the duloxetine clinical trial protocols evaluated worst pain, nighttime pain, and allodynia as secondary outcome measures.

Responder rate for at least 30% improvement in pain. A decrease in pain score from baseline of at least 2 points or at least 30% on an 11-point numeric rating scale has been shown to be clinically relevant in patients with chronic noncancer pain.[11] The use of 30% improvement as the definition of response makes it difficult to compare the results for duloxetine with other agents, since responder rates for at least 50% reduction in pain or at least moderate improvement in pain have usually been reported for other agents in neuropathic (and nociceptive) pain trials.

Brief Pain Inventory (BPI)–severity and interference scales. The BPI severity and interference scales measure worst, least, average, and present pain intensity and level of interference with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The pain severity scales range from 0 = "No pain" to 10 = "Pain as bad as you can imagine", and the interference scales range from 0 = "Does not interfere" to 10 = "Completely interferes." One of the main goals of treatment in chronic pain is to improve the patient's functionality. Therefore, the BPI interference scale provides an important measure of the effectiveness of treatment by assessing the impact of pain on the patient's ability to perform various activities, including work.

Global Impression of Change (GIC) Scales. The GIC scale is a validated instrument that consists of seven verbal descriptors ranging from "very much improved" to "very much worse" and is evaluated by the clinician (Clinician's Global Impression of Severity, CGI-S) or reported by the patient (Patient's Global Impression of Improvement, PGI-I). Improvement in pain intensity is only one measure of treatment effect. Since other aspects or adverse effects of treatment may affect a patient's well-being, the GIC attempts to capture the overall effects of treatment on the patient.

5D version of the Euro-QoL Questionnaire (EQ-5D). In the duloxetine study XII extension, this standardized, self-completed health status survey was used in addition to the SF-36 to measure quality of

life. It consists of a simple descriptive profile and a single index value for health status in a 3-level, 5-dimensional format. The scale includes a patient's self-perception of general health (rated from 1 = No problems to 3 = Substantial disability). Examples include general health in terms of mobility, usual activities, and pain level.

Fibromyalgia

Fibromyalgia Impact Questionnaire (FIQ): The FIQ assesses the effects of pain or other symptoms of fibromyalgia on the patient's ability to perform various activities related to work and daily living, as well as the intensity of pain, tiredness, morning tiredness, stiffness, anxiety, and depression. The co-primary outcome measures in the clinical trial were the FIQ pain severity and total score. The scores for pain intensity ranged from 0 to 10, with 10 indicating very severe pain. The FIQ items for fatigue, morning tiredness, and stiffness were secondary outcome measures.

Dolorimetry: In the clinical trial, dolorimetry involved applying a Fischer dolorimeter with a rubber disk of 1 cm^2 to 18 tender point sites (defined by the American College of Rheumatology criteria) at a 90-degree vertical angle and gradually increasing the pressure until the patient indicated verbally that there was discomfort or pain. The tender point pain pressure threshold was averaged for the 18 tender point sites, and the tender point count represented the number of tender points with a threshold of ≤ 4 kg/cm^2. Reliability testing was not done for dolorimetry.

CGI-S, PGI=I, and BPI (short form): As described above, except the CGI-S ranged from 1 = "Normal, not at all ill" to 7 = "Among the most extremely ill patients."

Summary of efficacy findings

PDN

- Evidence of efficacy was limited to unpublished, large, major efficacy and safety trials, including 2 with placebo controls and 1 with routine care as control. Routine care consisted of antidepressants, antiepileptic drugs, and analgesics. Most of the information on these trials was obtained from the product information and Eli Lilly's AMCP-formatted Formulary Submission Document (September 30, 2004). No additional information was available at the FDA's Web site.
- There was no direct evidence that duloxetine is better than other specific agents in the treatment of PDN.
- Duloxetine (60 and 120 mg but not 20 mg per day) was superior to placebo in reducing scores for 24-hour average pain on an 11-point Likert scale. There was no statistically significant difference between the 60- and 120-mg doses. At the recommended dose (60 mg daily), duloxetine reduced average pain by a mean of 2.7 to 2.9 points, indicating a moderate degree of improvement. The changes in pain scores were clinically relevant according to Farrar's criteria (i.e., reduction of ≥ 2 points from baseline).[11] This magnitude of change is comparable to the change of 2.5 seen with gabapentin in a separate PDN trial.[12]
- The responder rates for 50% improvement in pain for duloxetine 60 mg daily versus placebo was 44% versus 21% in Study XII and 39% versus 26% in Study XIII. The NNT (95% CI) in Study XII was 4 (3 to 9) for a 12-week treatment period. This NNT is similar to estimated NNTs standardized to a 12-week treatment duration for some alternative formulary agents (see Data Compilation Tables, page 7). There was no statistically significant difference in the calculated relative benefit in Study XIII; therefore, there was inconsistency in showing the efficacy of duloxetine in terms of responder rates.
- Significant treatment effects are seen with duloxetine at about 1 week. There is also a lack of direct evidence comparing duloxetine with other agents in onset of analgesic effect. Based on

indirect comparisons using different outcome measures, the onset of duloxetine seems to be similar to that seen with gabapentin (1 to 2 weeks)[12] and phenytoin (≤ 2 weeks).[13]

- Duloxetine may be dosed once daily for treatment of PDN. Formulary agents that may be dosed in a single daily dose for PDN include venlafaxine extended-release and phenytoin.
- There was no significant treatment effect in measures of dynamic allodynia (not defined) in both placebo-controlled trials, so duloxetine did not improve the only specific neuropathic pain quality that was evaluated. Other characteristics of neuropathic pain were not assessed, such as paresthesias, dysesthesias, and hyperalgesia.
- Most domains of functionality measured on the BPI showed statistically significant changes in favor of duloxetine at the 60 and 120 mg dosage levels but no significant treatment difference was seen with 20 mg per day as compared with placebo. There were no significant differences between duloxetine and placebo in terms of interferences with relationships with other people and with sleep, except with the 120- mg daily dose in 1 of 2 trials.
- In terms of SF-36 quality of life measures, duloxetine 60 mg daily showed inconsistent results between the 2 placebo-controlled trials. The only consistent treatment benefits were seen with the 120-mg daily dose for bodily pain, general health perceptions, and mental health. Duloxetine was superior to placebo on the EQ-5D in both major efficacy trials. When compared with routine care in a 52-week open-label extension trial (Study XII-extension), duloxetine showed significant improvements in the bodily pain domain of the SF-36 ($p = 0.021$). Duloxetine was also better than routine care on the EQ-5D ($p = 0.001$); however, this result should be interpreted with caution as the therapy-by-investigator interaction was significant. No significant treatment effect was observed with the 20-mg dose of duloxetine.
- A direct effect on reducing 24-hour average pain scores, independent of effect on mood scores, accounted for 89% to 100% of the total treatment effect.
- Data on the efficacy of duloxetine from a 52-week extension trial was not available. The long-term efficacy of duloxetine beyond 52 weeks has not been evaluated.

Fibromyalgia

- Evidence of the efficacy of duloxetine in fibromyalgia is limited to one good-quality randomized controlled trial, in which duloxetine (60 mg twice daily for 12 weeks) was associated with moderate reductions in the total score on the Fibromyalgia Impact Questionnaire and improvements in quality of life and disability scores; however, significant improvement with duloxetine occurred in the overall population and females only, whereas a treatment benefit was not shown in men.
- The study population consisted primarily of women; therefore, the overall results may not be generalizable to all men with fibromyalgia or to a veteran population.
- Patients who had intolerance to or lack of response to antidepressants were excluded from the trial; therefore, the results may not be generalizable to patients who have had inadequate responses to antidepressants.
- The efficacy of duloxetine in fibromyalgia beyond 12 weeks has not been evaluated and its therapeutic benefit in fibromyalgia remains to be validated by other trials.

For further details on the efficacy results of the clinical trials, refer to *Appendix: Clinical Trials* (page 11).

Adverse Events (Safety Data)

Deaths and Other Serious Adverse Events

In pooled analyses of placebo-controlled trials in PDN, there were no statistically significant differences in the frequencies of serious adverse events between duloxetine and placebo and between duloxetine 60 mg and 120 mg daily.

Common Adverse Events

In the major efficacy trials for PDN, the most common adverse events observed on duloxetine (frequency of 5% or greater and at least twice the rate in placebo-treated patients) were similar to those observed in MDD, except dizziness (17%, 14%, and 6% on duloxetine 120, 60, and 20 mg, respectively, versus 6% on placebo) and asthenia (8%, 4%, and 2% versus 1%) were reported as most common adverse events in PDN and not MDD patients.

Other Adverse Events

PDN

Vital sign changes. Small increases in heart rate (1.6 bpm) and decreases in diastolic blood pressure (-1.7) were observed during duloxetine therapy as compared with placebo (–0.2 bpm and 0.3 mm Hg, respectively; $p \leq 0.05$). The pattern of blood pressure changes in patients with PDN was dissimilar to the systolic and diastolic pressure increases seen in patients with MDD. There were no significant treatment differences in potentially clinically relevant changes in vital signs.

Weight. A small but significant change in weight was observed during duloxetine therapy as compared with placebo (–1.1 vs. 0.2 kg; $p \leq 0.05$). There were no significant treatment differences in potentially clinically relevant changes in body weight.

QTc interval changes. A statistically significant *decrease* in Fridericia's corrected QTc interval (QTcF) occurred on duloxetine 120 mg daily versus placebo (–2.86 versus 0.57 msec; $p = 0.033$). There was no significant treatment difference in this measure when results were pooled for all duloxetine doses. One (0.2%) of 528 duloxetine-treated patients and no placebo patients experienced a QTcF of 500 msec or greater at anytime in the placebo-controlled trials.

Glucose control. In controlled trials, approximately 10% of patients experienced hypoglycemic events, and significant hypoglycemic episodes (undefined) occurred more frequently on duloxetine than placebo (0.06 versus 0.05 episodes per week, or 1 episode every 17 versus 20 weeks, respectively; p-value not reported). Small increases in fasting glucose occurred in both duloxetine and placebo groups (0.98 versus 0.35 mmol/l, or 18 versus 6.3 mg/dl; $p = 0.022$). HgA1c showed no significant treatment differences (–0.03 and –0.05 for duloxetine and placebo, respectively).

Hepatotoxicity. In PDN trials, increases in alanine transaminase to > 3 times the upper limit of normal occurred in 1.68% (8/477) of patients treated with duloxetine as compared with 0% (0/187) of patients on placebo.

Selected adverse events that may be relevant to drug selection in elderly patients (age ≥ 65 years).[14] Specific safety data were not reported for the 357 patients aged ≥ 65 years who received duloxetine in PDN trials. No overall differences in safety or effectiveness have been observed between elderly and younger patients. *Constipation, lethargy, and somnolence* were treatment-emergent adverse events that occurred at a significantly higher frequency on duloxetine than placebo in PDN trials. There was no significant treatment difference in the rate of *falls*. The rate of *urinary retention* with duloxetine was not significantly different from that of placebo in patients with PDN (1.4% versus 0.0%; $p = 0.077$). In a separate analysis of *obstructive voiding* symptoms as adverse events in men and women treated with duloxetine for MDD, stress urinary incontinence, or benign prostatic hyperplasia (BPH) in clinical trials, the overall rate of obstructive voiding symptoms, including urinary retention, was low but occurred more

frequently on duloxetine (1.0%, 20/2097) than on placebo (0.4%, 6/1732; p < 0.05).[15] In the unpublished trial in men with benign prostatic hyperplasia, 2.8% (2/69) of the duloxetine-treated patients and none (0/44) of the placebo-treated patients experienced obstructive voiding symptoms (p = 0.5), and one patient discontinued after the second episode. Symptoms of obstructive uropathy and bladder irritation were not improved by duloxetine treatment. Therefore, the limited information from these clinical trials, when considered altogether, suggest that duloxetine may be associated with an increased risk of obstructive voiding symptoms.

Tolerability

The frequency of withdrawals due to adverse events in patients with PDN was similar to that seen in patients with MDD. Withdrawals due to adverse events in the PDN trials occurred in 14% of 568 duloxetine-treated patients as compared with 7% of 223 placebo-treated patients (p = 0.008). Common adverse events that led to withdrawal of treatment and were considered to be treatment-related (i.e., occurred in at least 1% of duloxetine-treated patients and at a rate of at least twice that of placebo) were nausea, dizziness, somnolence, and fatigue. In pooled analyses of placebo-controlled trials, only nausea led to a significantly higher rate of withdrawals from duloxetine (3.5%) as compared with placebo (0.4%; p = 0.013). The 120-mg dose of duloxetine is less well tolerated than the 60-mg dose (data not reported).

Long-term safety

Duloxetine was as safe and well tolerated as routine care in a 52-week extension study in patients with PDN. Fasting glucose increased by 1.03 mmol/l (18.5 mg/dl) in patients treated with duloxetine and decreased by 0.56 mmol/l (10.1 mg/dl) in patients on routine care; the difference was statistically significant (p = 0.026). Long-term glucose control, as reflected in HgA1c, showed no treatment differences (mean increase of 0.51% in duloxetine patients versus 0.26% in routine care patients). The safety of duloxetine beyond 52 weeks has not been evaluated.

For further details on the safety results of the clinical trials, refer to *Appendix: Clinical Trials* (page 11).

Data Compilation Tables

PDN

Differences in responder rates and calculated number-needed-to-treat are shown in Table 1 for the two placebo-controlled trials.

Table 1 Responder rate for ≥ 50% improvement in pain

Study	XII	XIII
Responder rate–Duloxetine 60 mg/d, %	44	39
Responder rate–Placebo, %	21	26
Treatment duration, wk	12	12
Relative Benefit Increase (95% CI), %	29.1 (14.4 to 41.2)	17.1 (0.4 to 31.0)
Absolute Benefit Increase (95% CI), %	23.0 (11.2 to 34.7)	12.7 (0.5 to 24.8)
NNT (95% CI)	4 (3–9)	NSD

NSD, No statistically significant difference between treatments in responder rate

In indirect comparisons, the calculated NNT of 4 (95% CI: 3 to 9) for at least 50% improvement in pain after 12 weeks of treatment with duloxetine 60 mg (Study XII) does not appear to be better than estimated NNTs (95% CI), standardized to a 12-week treatment period, for tricyclic antidepressants (1.2, 0.88 to 2.0),[a] the antiepileptic drugs, carbamazepine (0.4, 0.3 to 0.6), gabapentin (2.5, 1.6 to 5.8), and phenytoin

[a] Based on NNT (95% CI) of 2.9 (2.1–4.7) for 4 to 6 weeks (an average of 5-weeks was assumed).[1]

(0.4, 0.2 to 0.6),[b] and extended-release venlafaxine 150–225 mg daily (2.2, 1.5 to 7).[c] Interpretation of these NNTs should be made cautiously because the original NNTs (i.e., the NNTs before standardizing to a 12-week timeframe) may have been calculated using different meta-analytic methods[1,3] and different definitions of response were used in the original trials. Adjustments of the NNTs to the same follow-up time assumed that the relative treatment benefits were constant over time. There was inconsistency between the two trials in showing a treatment benefit in terms of responder rates, with Study XIII showing no treatment difference (calculated p = 0.061).

Fibromyalgia

Responder rates in the fibromyalgia trial showed a statistically significant treatment difference among female patients only, and therefore, an NNT could be calculated for only this subgroup (which represented 89% of the 207 study patients) (Table 2).

Table 2 Responder rate for ≥ 50% improvement in FIQ pain score

Population	All Patients	Females Only
Responder rate–Duloxetine 120 mg/d, %	27.7	30.3
Responder rate–Placebo, %	16.7	16.5
Treatment duration, wk	12	12
Relative Benefit Increase (95% CI), %	13.6 (–0.1 to 25.4)	16.9 (2.2 to 29.3)
Absolute Benefit Increase (95% CI), %	11.4 (0.2 to 22.6)	14.1 (2.1 to 26.2)
NNT (95% CI)	NSD	7 (4–48)

FIQ, Fibromyalgia Impact Questionnaire
NSD, No statistically significant difference between treatments in responder rate

NNTs are available for other agents shown to be efficacious in fibromyalgia; however, they are difficult to compare with the NNT for duloxetine in females because they refer to *all* study patients, are based on different response measures, and are calculated using any, as opposed to at least 50%, improvement. In meta-analyses, the NNT for symptom improvement with antidepressants (tricyclics, selective serotonin reuptake inhibitors, and S-adenosylmethionine) was 4 (95% CI, 2.9 to 6.3) for a mean treatment duration of 8 weeks (range, 3 to 24 weeks) based on trials involving patient populations consisting of 83% to 100% women.[16] The NNT for global improvement with therapy on cyclobenzaprine was 4.8 (95% CI: 3.0 to 11) over a mean treatment period of 6 weeks (range, 2 to 24 weeks) in a predominantly (95%) female population.[17]

Acquisition Costs

Drug costs for PDN and fibromyalgia are shown in Table 3. Using the cost per ABI (or cost times NNT), the cost of duloxetine associated with treating the number of individuals that need to be treated for one additional patient to obtain 50% pain reduction in a 12-week period is about $702 in PDN and $2458 in fibromyalgia. Extrapolated to 52 weeks, the estimated annual costs of treatment for one patient to experience 50% pain relief would be $3042 and $10,651. These annualized costs represent a “best case” scenario because they assume that the relative response to duloxetine remained the same and therefore, the NNT was still 4, at 52 weeks.

[b] Based on NNT (95% CI) of 2.3 (1.6–3.8) for carbamazepine over 2 weeks; 3.8 (2.4–8.7) for gabapentin over 8 weeks; and 2.1 (1.5–3.6) for phenytoin over 2 weeks.[3]

[c] Based on NNT (calculated 95% CI) of 4.5 (3–14) for venlafaxine extended-release 150–225 mg daily over 6 weeks.[2]

Table 3 Acquisition costs for duloxetine

Indication	Dose (mg/d)	Cost/Day/Patient	Cost/Year/Patient	Cost/ABI/12 wk[†]
Painful diabetic neuropathy	60	$2.09	$763	$702
Fibromyalgia (off-label)	120	$4.18	$1526	$2458

Lowest VA costs as of 3 December 2004

[†] Cost per ABI (Absolute Benefit Increase) is the cost associated with treating the number of individuals that need to be treated for one additional patient to gain at least 50% pain relief during a 12-week period; see Table 1 and Table 2.

Pharmacoeconomic Analysis

A cost-effectiveness analysis was performed from a societal perspective on a subpopulation of 233 patients with PDN from the 52-week extended phase of Study XII, which compared duloxetine (60 mg twice daily) with routine care (antidepressants, antiepileptic drugs, and analgesics). The results were available only from an abstract of a poster presentation.[18] Total costs (direct medical and indirect productivity loss cost) were adjusted to 2002 dollars using the Consumer Price Index. Incremental cost-effectiveness ratios (ICERs) were calculated relative to the bodily pain (BP) subscore on the Medical Outcomes Study Short Form 36 (SF-36), and the bootstrap method was applied to make statistical inferences on the ICER. Duloxetine was considered to significantly improve the SF-36 BP score as compared with routine care; however, the p-value was not significant ($p = 0.05$). Duloxetine was stated to be the more cost-effective (ICER = –$429 / 1 BP; $p = 0.04$) and dominant ($p = 0.06$) therapy.

Based on data from a retrospective analysis of claims databases of managed health care plan members in the U.S. (information from AMCP dossier), the high end of the range determined for drug utilization for diabetic neuropathy could be assumed to be a 200 annual days' supply. Using an average wholesale price of $3.56 for a 60-mg dose of duloxetine, the total cost of duloxetine per treated member per month (PTMPM) is $59.33. By comparison, the cost PTMPM was $13.63 for tricyclic antidepressants, $79.07 for gabapentin, $85.75 for SNRIs, and $96.54 for controlled-release oxycodone. The total cost PTMPM among patients taking a single pain medication (39.3% of all patients studied) was $22.36, whereas it was $103.60 for patients taking multiple drugs (60.7% of all patients).

The findings of these pharmacoeconomic analyses will have limited applicability to the VA.

Conclusions

In patients with painful diabetic neuropathy, duloxetine is moderately efficacious and generally safe and well tolerated. Its relative treatment benefits in comparison with alternative agents have not been determined in head-to-head trials. In terms of efficacy, indirect comparisons suggest that duloxetine is not better than a number of alternative agents currently on the VA national formulary. In patients with fibromyalgia, a single good-quality trial showed an analgesic benefit in women only. Long-term studies are needed to determine the efficacy and safety of prolonged use of duloxetine.

Recommendations

- Duloxetine should remain nonformulary at the national and VISN levels.
- National criteria for use should be implemented to control utilization.
- Given (1) the lack of direct evidence of the relative treatment benefits of duloxetine in patients with PDN and fibromyalgia, (2) the indirect evidence suggesting that duloxetine is not better than alternative formulary agents, as well as (3) the lack of long-term (> 1 year) safety trials, duloxetine should generally be used as a second-line agent after adequate trials of alternative oral, non-opioid formulary agents.

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Prepared January 2005. Contact person: F. Goodman, PharmD, BCPS

Appendix: Clinical Trials

A literature search was performed on PubMed/Medline (1966 to September 2004) using the search terms *duloxetine* and *Cymbalta*. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.

Placebo-controlled double-blind randomized controlled trials in patients with diabetic peripheral neuropathic pain

<table>
<tr><th>Reference
Country
(Jadad score)
Source</th><th>Study Design
Analysis Method
Study Treatment (N)
Permitted co-medications</th><th>Eligibility Criteria
Age, Gender
Other Patient Characteristics</th><th>Efficacy Results (DUL vs. PBO)</th></tr>
<tr><td>HMAW, Study XII—Acute therapy
U.S., Puerto Rico, Canada, Argentina (24 centers)
(Not calculable)
Product Information, dossier</td><td>Phase II MC DB PG PC RCT Fixed dose
Modified ITT
Duloxetine 60 b.i.d. (113) (40 b.i.d. x 3 d then 60 b.i.d.)
Duloxetine 60 q.d. (114)
Duloxetine 20 q.d. (115)
Placebo (115)
x 12 wk
Co-meds not reported</td><td>Pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes mellitus (DM); symmetrical onset in feet; daily pain ≥ 6 mo; dx confirmed by score of at least 3 on the Michigan Neuropathy Screening Instrument; HgA1c ≤ 12%; mean pain score ≥ 4 on 24-h average pain score on patient diary; age ≥ 18 y
Age (mean) 60.1 y; 77.2% Caucasian; 61.5% male
88.4% had type 2 DM; mean duration of DM 11.25 y; mean duration of painful diabetic neuropathy (PDN) 3.74 y; mean 24-h average pain severity 5.9</td><td>Withdrawals due to insufficient efficacy: not reported
Primary Efficacy Measure: Weekly mean of 24-h average pain severity scores, 11-point Likert scale; change from baseline to study endpoint
<table>
<tr><th>Treatment</th><th>BL (All pts)</th><th>Δ Ave Pain</th></tr>
<tr><td>DUL120</td><td>5.90</td><td>–3.24**†</td></tr>
<tr><td>DUL 60</td><td>5.90</td><td>–2.89**</td></tr>
<tr><td>DUL20</td><td>5.90</td><td>–2.36</td></tr>
<tr><td>PBO</td><td>5.90</td><td>–1.91</td></tr>
</table>
**, p ≤ 0.001 vs. PBO
†, p ≤ 0.05 vs. DUL20
Significant treatment differences in favor of DUL120 (–1.4) and DUL60 (–1.3) over DUL20 (–0.7; p < 0.05 for both doses) and placebo (–0.4; p ≤ 0.001 for both doses) in reducing the 24-h average pain score were shown as early as wk 1.
Most secondary efficacy measures showed significant differences in favor of DUL60 and DUL120. All primary and secondary efficacy measures, except for worst pain and CGI-S, showed no significant treatment differences with DUL20. No significant treatment differences were shown for dynamic allodynia at any dose of DUL.
Likert-30 Responder Rate
<table>
<tr><th>Treatment</th><th>Likert-30</th><th>ARR</th><th>NNT</th><th>95% CI</th></tr>
<tr><td>DUL120</td><td>65%*†</td><td>18%</td><td>5</td><td>3–18</td></tr>
<tr><td>DUL60</td><td>64%*</td><td>17%</td><td>6</td><td>3–23</td></tr>
<tr><td>DUL20</td><td>51%</td><td>4%</td><td>NSD</td><td>NSD</td></tr>
<tr><td>PBO</td><td>47%</td><td>—</td><td>—</td><td>—</td></tr>
</table>
Table shows proportion of patients who responded, defined as at least 30% reduction in Likert pain score, and corresponding Absolute Risk Reduction (ARR) and calculated number-needed-to-treat (NNT).
*, p ≤ 0.05 vs. PBO</td></tr>
</table>

<table>
<tr><th>Reference
Country
(Jadad score)
Source</th><th>Study Design
Analysis Method
Study Treatment (N)
Permitted co-medications</th><th>Eligibility Criteria
Age, Gender
Other Patient Characteristics</th><th>Efficacy Results (DUL vs. PBO)</th></tr>
<tr><td></td><td></td><td></td><td>†, p ≤ 0.05 vs. DUL20</td></tr>
<tr><td>HMAVa, Study XIII
U.S., Puerto Rico (28 centers)
(Not calculable)
Product information, dossier</td><td>Phase III, MC DB PG PC RCT Acute therapy phase
MITT, MMRM, LOCF
DUL 60 b.i.d. (112)
DUL 60 q.d. (114)
PBO (108)
X 12 wk
Co-meds not reported</td><td>Pain due to bilateral peripheral neuropathy caused by type 1 or 2 diabetes mellitus (DM); symmetrical onset in feet; daily pain ≥ 6 mo; score ≥ 3 on Michigan Neuropathy Screening Instrument; stable glycemic control with HbA1c ≤ 12%; mean pain score ≥ 4 on 24-h average pain score; age ≥ 18 y
60.7 y; 78.1% Caucasian, 61.1% male
91.0% had type 2 DM; duration 10.22 y; duration PDN 3.83 y; mean 24-h average pain severity 6.05</td><td>Primary efficacy measure: Change from baseline in weekly mean of 24-h average pain scores, 11-point Likert scale
<table><tr><th>Treatment</th><th>Change in Ave. Pain</th></tr><tr><td>DUL60</td><td>–2.69**</td></tr><tr><td>DUL120</td><td>–3.13**</td></tr><tr><td>PBO</td><td>–1.59</td></tr></table>**, p ≤ 0.001 vs. PBO
Significant treatment differences in favor of DUL120 (–1.1) and DUL60 (–1.3) over placebo (–0.4; p ≤ 0.001 for both doses) in reducing the 24-h average pain score were shown as early as wk 1.
Most secondary efficacy measures showed significant treatment differences. Outcome measures for which no significant difference was shown for DUL60 but a significant difference was found with DUL120 were Brief Pain Inventory Interference–General Activity, –Normal Work, –Relationship with Other People; –Sleep, and –Enjoyment of Life, and Hamilton Depression Rating Scale (17-item) Total Score. No significant difference was shown for either DUL dose for dynamic allodynia.
Likert-30 Responder Rate
<table><tr><th>Treatment</th><th>Likert-30</th><th>ARR</th><th>NNT</th><th>95% CI</th></tr><tr><td>DUL120</td><td>60%</td><td>17%</td><td>6</td><td>3–24</td></tr><tr><td>DUL60</td><td>59%</td><td>20%</td><td>5</td><td>3–14</td></tr><tr><td>PBO</td><td>42%</td><td>—</td><td>—</td><td>—</td></tr></table>See description of corresponding table for Study XII.
Discrepancy between text and figure 2 in Product Information in % with ≥ 30% pain reduction from baseline. Text states DUL120, 69%; DUL60, 63%; PBO, 39%. NNTs: 5 for each DUL dose.</td></tr>
</table>

Active-controlled trials in patients with diabetic peripheral neuropathic pain

Reference Country Trial Name (Jadad score) Article Source	**Study Design Analysis Method Study Treatment (N) Permitted co-medications**	**Eligibility Criteria Age, Gender Other Patient Characteristics**	**Efficacy Results (DUL vs. Comparator)**	**Safety Results (DUL vs. Comparator)**	**Conclusions *Comments***
HMAW, Study XII-Extension U.S., Puerto Rico, Canada, Argentina (24 centers) — (Not calculable) Product Information, dossier, conference abstract[19]	Phase II MC, long-term, OL RCT; patients re-randomized to treatment MITT DUL 60 b.i.d. (222) Routine care (115) x 52 wk Routine care consisted of antidepressants, antiepileptic drugs, and analgesics	Same as Study XII-Acute therapy above. 59.8 y; 77.2% Caucasian; 60.8% male 88.4% had type 2 DM; duration of DM 11.6 y; duration of PDN 3.67 y; mean 24-h average pain 5.91	SF-36 bodily pain subscale and EQ-5D Index: DUL was stated to be significantly better than routine care (data not reported); however, p = 0.05	*Withdrawals due to adverse events* 14.4% vs. 9.6% (p = 0.232); most frequently MI and HTN *Serious Adverse Events* 14.4% vs. 19.1% (p = 0.276) *Treatment-emergent adverse events* Significantly higher on DUL: None Significantly higher on Routine Care: vomiting, pain in foot, nail fungal infection, hyperglycemia, cataract extraction, conjunctivitis, diabetic retinopathy, sinus congestion *Specific AEs* HR: small, significant increases on DUL vs. RC Treatment-emergent increased vital signs: NSD Treatment-emergent potentially clinically relevant vital signs: NSD Fasting glucose: 1.03 vs. –0.56 mmol/l (18.5 vs. –10.1 mg/dl; p = 0.026) Hypoglycemic events and HgA1c: NSD	DUL (120 mg/d) was safe and well-tolerated in the long-term treatment of diabetic neuropathic pain. DUL was superior to routine care on several measures of quality of life. DUL was associated with a small but statistically significant increase in fasting glucose; overall diabetes control did not seem to be affected during observation period of up to 52 wk. *A cost-effectiveness study was performed on a subpopulation of 233 patients. See text under Pharmacoeconomic Analysis.*

Observational studies in patients with diabetic peripheral neuropathic pain

Reference **Country** **Trial Name** **(Jadad score)** **Source**	**Study Design** **Analysis** **Method** **Study** **Treatment (N)** **Permitted co-medications**	**Eligibility Criteria** **Age, Gender** **Other Patient Characteristics**	**Efficacy Results**	**Safety Results**
HMBT, Study XIV (Safety) Argentina, Australia, Brazil, Canada, Chile, Taiwan (Not calculable) Product information, dossier	Phase III MC PG OL MITT DUL 120 q.d. (115) DUL 60 b.i.d. (334) x 28 wk Co-meds not reported	Eligibility same as for HMAVa, Study XIII above, except mean pain score of at least 4 on the 24-h average pain severity score was not an inclusion criterion. Age (mean) 59.9 y; 58.1% Caucasian; 52.1% male 93.8% type 2 DM; duration 12.4 y; duration PDN 3.2 y	*Primary measure:* Change from baseline to study end point in 24-h average pain severity: Data not reported *Secondary measures:* worst pain, night pain, CGI-S, PGI-I, Brief Pain inventory (severity and interference scales); Beck Depression Inventory-II, Beck Anxiety Inventory; Short-Form McGill Pain Questionnaire, allodynia—Data not reported	*Serious Adverse Events* 68/671, 10.1% *Withdrawals due to adverse events* 135/671, 20.1%; most frequently nausea, dizziness, vomiting, fatigue, somnolence *Specific AEs* Mean change in sitting HR 3.6 bpm; SBP, –0.7; DBP, 0.3; weight, –0.5 kg Patients with potentially clinically relevant values for vital signs or weight: generally ≤ 2%

Pooled analyses in patients with diabetic peripheral neuropathic pain

Reference Source	**Study Design Study Treatment (N)**	**Eligibility Criteria Age, Gender Other Patient Characteristics**	**Safety Results**	**Conclusions *Comments***
Pooled study (XII, XII-Extension, XIII, XIV) Dossier	Pooled study from 4 other studies DUL exposure (N): 568 in 2 Placebo-controlled trials 222 in routine care–controlled study 449 in open-label safety study	Not reported	*Withdrawals due to adverse events* Placebo-controlled trials: 79/568, 13.9% vs. 16/223, 7.2% (p = 0.008); only nausea was significantly higher (3.5% vs. 0.4%; p = 0.013) *Serious Adverse Events* Placebo-controlled trials (XII and XIII): 19 (3.3%) vs. 10 (4.5%) (NSD); also NSD between DUL60 and DUL120. 10 deaths (most common cause was MI); no evidence of systemic drug toxicity *Total Adverse Event Rates* Placebo-controlled trials, Treatment-emergent adverse events significantly higher on any DUL: nausea, somnolence, dizziness, constipation, dry mouth, decreased appetite, asthenia, anorexia, hyperhidrosis, ED, tremor, lethargy, hypersomnia, urinary retention *Specific AEs* Arrhythmias: Not reported Constipation: 11.3% vs. 3.1% (p < 0.001) Fall: 1.1% vs. 0.0% (NSD) Lethargy: 1.8% vs. 0.0% (p = 0.033) Somnolence: 15.5% vs. 4.5% (p < 0.001) Urinary retention: 1.4% vs. 0.0% (p = 0.077) Weight change: –1.1 vs. 0.2 kg (p ≤ 0.05) Sitting HR: 1.6 vs. –0.2 bpm (p ≤ 0.05) Sitting DBP: –1.7 vs. 0.3 mm Hg (p ≤ 0.05) Potentially clinically relevant changes in vital signs or weight: NSD Sustained increases in BP: NSD QTc: DUL120 –2.86 vs. PBO 0.57 msec (p = 0.033); NSD for all DUL doses vs. PBO; NSD in QTc prolongations Hypoglycemia: 0.06 vs. 0.05 episodes/wk (p ≤ 0.05); frequency very low; 90% of patients in both groups had no hypoglycemic events Change in Fasting Glucose: 0.98 vs. 0.35 mmol/l (18 vs. 6.3 mg/dl; p = 0.022) Δ HgA1c: NSD	*Results may be biased since only company-sponsored studies were included in the pooled analysis.*

Placebo-controlled double-blind randomized controlled trials in patients with fibromyalgia

Reference Country Trial Name (Jadad score)	**Study Design Analysis Method Study Treatment (N) Permitted co-medications**	**Eligibility Criteria Age, Gender Other Patient Characteristics**	**Efficacy Results (DUL vs. PBO)**	**Safety Results (DUL vs. PBO)**	**Conclusions *Comments***
Arnold (2004)[20] U.S. (18 outpatient centers) Duloxetine Fibromyalgia Trial (Jadad = 5, Good)	MC DB PC PG RCT ITT, Mixed-effects Model for Repeated Measures, Last Observation Carried Forward, subgroup analyses Duloxetine (DUL) 20 q.d. to 60 b.i.d., forced titration in first 2 wk, then 60 b.i.d. (104) Placebo (PBO) (103) x 12 wk Co-meds: Acetaminophen up to 2 g/d; Aspirin up to 325 mg/d	≥ 18 yo; primary fibromyalgia (FM) (American College of Rheumatology criteria); ≥ 4 on Fibromyalgia Impact Questionnaire (FIQ)-pain; reliable; intelligible. Excluded pts with associated rheumatic or other medical disorders that contributed to fibromyalgia symptoms; substance abuse in last yr; dysthymia; primary psychiatric disorder other than major depressive disorder (MDD); intolerance to > 3 psychoactive drugs or > 1 SSRI; failure to respond to ≥ 2 adequate regimens of 2 difference classes of antidepressants for depression or fibromyalgia. DUL vs. PBO: Age, mean, y: 49.9 vs. 48.3 Female, %: 88.5 vs. 89.3 (23/207, 11% were male) White, %: 88.5 vs. 85.4 Current MDD episode, %: 35.6 vs. 40.8 Previous antidepressant use, %: 33.7 vs. 49.5 (p = 0.024)	*Primary efficacy measures* FIQ-pain subscore (range, 0–10), mean change: –1.98 vs. –1.35; difference (95% CI): –0.63 (–1.45 to 0.19) (p = 0.130) FIQ total score (range, 0–80), mean change: –13.46 vs. –7.93; difference (95% CI): –5.53 (–10.43 to –0.63) (p = 0.027) *Secondary efficacy measures* Significant (p < 0.05) differences in favor of DUL were seen in most secondary efficacy measures, including SF-36 (6/10 domains), QoL in Depression Scale total score, and Sheehan Disability Scale. Responder Rate (≥ 50% reduction in FIQ-pain subscore at end point): 27.7% vs. 16.7% (p = 0.06). No treatment interaction with MDD for primary efficacy measures. Women had significantly greater improvement and male patients on DUL did not respond significantly on primary or secondary efficacy measures. Path analysis showed that the direct treatment effect on pain (as opposed to depression) accounted for a major portion (61.1%–83.3%, depending on the outcome measure) of the total effect. *Withdrawals due to insufficient efficacy*: 9/104 (8.6%) vs. 13/103 (12.6%)	*Withdrawals due to adverse events*: 18/104 (17.3%) vs. 11/103 (10.7%) (NSD) *Serious Adverse Events*: not reported *Total AEs*, no. of pts experiencing ≥ 1 AE: 94/104 (90.4%) vs. 77/103 (74.8%) (p = 0.003) *Treatment-emergent adverse events* reported significantly more frequently on DUL: insomnia, dry mouth, constipation; mostly mild–moderate in intensity. HR, mean change from baseline to end point: 3.53 vs. not reported (p = 0.005) SBP / DBP, mean change: 1.26 / 0.58 vs. not reported (NSD) Sustained hypertension, n: 2 vs. 1 (NSD) Weight: data not reported (NSD) QTc elevation: None	Duloxetine (60 mg b.i.d. for 12 wk) was found to be efficacious on most outcome measures in subjects with primary fibromyalgia with or without major depressive disorder, particularly in women, and was safe and well tolerated. Results may not be generalizable to longer treatment periods, all men with fibromyalgia, patients with certain lifetime psychopathology, patients with unstable medical or psychiatric illness, and patients who are resistant to antidepressants. *The study population consisted of mostly women and therefore is not representative of a typical VA population. Of note, no treatment benefit of DUL was shown in men.* *Sample size calculations were based on a 1.4-point difference in FIQ-pain score; no treatment difference was shown for this outcome measure.* *Although all randomized patients were included in analyses, 40% of patients did not complete the study, mostly due to adverse events, personal conflict, and lack of efficacy.* *Research was supported by Eli Lilly and Company.*