Criteria for Nonformulary Use of Duloxetine in Painful Diabetic Neuropathy

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

These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high-quality, cost-effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.

A summary of the literature review used to support the criteria for non-formulary use of duloxetine is available in the monographs for duloxetine in major depressive disorder and in painful diabetic neuropathy and fibromyalgia available at http://www.pbm.va.gov. Related information may be found in the *Guidance on the Use of Gabapentin* at the same Web site.

Background

Duloxetine, an antidepressant that inhibits reuptake of serotonin and norepinephrine, was approved for the treatment of major depressive disorder (August 2004) and for treatment of pain due to diabetic peripheral neuropathy (September 2004). It is the first drug to be approved specifically for diabetic peripheral neuropathic pain or painful diabetic neuropathy (PDN) in the U.S.; however, the major efficacy trials supporting this indication have not yet been published and are available only as summaries in the manufacturer's dossier of the drug.[1] Duloxetine is also one of the small number of drugs shown to be efficacious in off-label use for fibromyalgia, although subgroup analyses showed benefit only in females.[2] There have been no direct comparisons between duloxetine and other active agents. Indirect comparisons suggest that duloxetine is not better than alternative formulary agents in PDN. Since duloxetine does not appear to be better than the agents available on formulary and its long-term safety is unknown, particularly in regard to risks of hypertension, hepatotoxicity, and hypoglycemia (in patients with PDN) in a naturalistic setting, this guidance recommends duloxetine as a second-line agent.

VA Criteria for Use

All of the following criteria must be met:

1. Patients with painful diabetic neuropathy who have a well documented insufficient response despite an adequate trial (dose and duration) of a **minimum of 2 oral agents,** alone or in combination, using at least one formulary agent from 2 of the 4 drug classes in Table 1 OR patient has documented intolerance, hypersensitivity, or contraindication to listed agents and is therefore precluded from undertaking an adequate trial of at least one agent from 2 of the 4 drug classes. An adequate trial would consist of titrated doses in the dosage ranges shown in Table 1 for at least 6 to 12 weeks.
2. Patients without end-stage renal disease (requiring dialysis), severe renal impairment (estimated CrCl < 30 ml/min), any hepatic impairment, chronic liver disease, substantial alcohol intake, or uncontrolled hypertension.
3. Patients not taking thioridazine (because of potential risk of cardiac arrhythmia due to drug interaction).
4. First prescriptions should be limited to a 30-day supply with no refills to evaluate tolerability. Patients should also be re-evaluated after 12 weeks of therapy. Duloxetine should be tapered and discontinued if it is ineffective.

Table 1 Drug classes for painful diabetic neuropathy

Drug Class	Examples of Formulary Agents with Grade A or B Evidence	Dosage Range (mg/d) (Duration: 6–12 wk)‡
Antidepressants, tricyclic	Amitriptyline[3,4] (Nortriptyline)†	25–150
	Desipramine[3]	12.5–200
	Imipramine[3]	25–225
Antidepressants, SNRI	Venlafaxine[5]	150–225
Antiepileptic drugs	Carbamazepine[3,6]	200–600
	Gabapentin[7]	300–3600
	Phenytoin[3,6]	300
	Valproate[8,9]	500–1200
Opioid	Tramadol[10]	50–400

Table shows formulary agents with recommendation ratings of Grade A (strongly recommend; always acceptable) or Grade B (recommend, may be effective). Evidence rating scheme based on the methods used by the third U.S. Preventive Services Task Force,[11] modified to include only randomized placebo-controlled trials. Good-quality systematic reviews are referenced as sources of primary trials.

Abbreviations: SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor

† Nortriptyline, a metabolite of amitriptyline, has also been used in clinical practice, although a literature search found no placebo-controlled clinical trials evaluating this agent as monotherapy (Grade I, Insufficient Evidence). Usual dose is similar to that of amitriptyline.

‡ Based on fixed or titrated dosage regimens used among different clinical trials. Titrate doses based on patient response; maximal doses are not necessarily required for an adequate trial.

An adequate trial of each alternative agent is considered to be 6 to 12 weeks, based on the usual duration of treatment in placebo-controlled studies. A treatment duration of 6 to 8 weeks is suggested to assess response to gabapentin (see *Guidance on the Use of Gabapentin* at http://www.pbm.va.gov).

These criteria do not preclude prior use of agents / classes not listed in Table 1; however, patients should be given adequate trials of a minimum of two listed (recommendable) agents prior to considering duloxetine. The criteria suggest tramadol, a nonscheduled opioid, as a prior treatment alternative to duloxetine. The combination of tramadol and either tricyclic antidepressants or serotonin reuptake inhibitors should be avoided if possible due to increased risks of seizures and serotonin syndrome. The criteria do not recommend a prior trial of schedule II to IV opioids before considering duloxetine. In general, schedule II to IV opioids should be considered after adequate trials of non-opioid agents. However, patients already prescribed schedule II to IV opioids may be considered for duloxetine therapy as a therapeutic alternative as long as at least one agent from another listed class has also been given an adequate trial (i.e., the minimum of 2 agents is met).

Other Pain Syndromes

Nondiabetic neuropathic pain. The evidence to date supports the use of duloxetine only for neuropathic pain related to diabetes mellitus. Further studies are needed to assess the benefits and risks of duloxetine in other types of neuropathic pain.

Fibromyalgia. A good-quality placebo-controlled trial showed that duloxetine (60 mg twice daily) was moderately efficacious, safe, and well tolerated in the off-label treatment of patients with fibromyalgia, although a subgroup analysis suggested that it was efficacious in women but not men. The study involved 12 weeks of treatment in a mostly female population; therefore, the results may not be generalizable to a veteran population or to long-term therapy. In addition, the results may not be generalizable to patients with certain lifetime psychopathology, patients with unstable medical or psychiatric illness, and patients who are resistant to antidepressants, since patients with these characteristics were excluded from the trial. Other randomized controlled trials are needed to verify the results and to further define duloxetine's place in therapy.

Contraindications

Hypersensitivity; monoamine oxidase inhibitor (MAOI) co-therapy (or within 14 days of discontinuing an MAOI); uncontrolled narrow-angle glaucoma (because of increased risk of mydriasis with duloxetine)

Dosage and Administration

Indication	Oral Dose	Comments
Diabetic peripheral neuropathic pain	60 mg once daily Consider starting at lower dose in patients with mild to moderate renal impairment or tolerability concerns. Based on anecdotal experience, some experts would recommend starting at 30 mg once daily for 5 or more days to minimize nausea.	Avoid in patients with severe renal impairment (estimated creatinine clearance < 30 ml/min). May be given without regard to meals. In patients with PDN, a higher dose (120 mg/d) did not provide additional benefit and was less well tolerated. Efficacy beyond 12 wk has not been evaluated. The effect of slowed gastric emptying (e.g., due to diabetes) on the stability of duloxetine's enteric coating has not been evaluated. In extremely acidic conditions, duloxetine is hydrolyzed to form naphthol; therefore, caution is advised in patients with delayed gastric emptying.

Dosing in Special Patient Populations

Renal impairment. Duloxetine is not recommended for patients with end-stage renal disease (requiring dialysis) or in severe renal impairment (estimated creatinine clearance < 30 ml/min).

Hepatic impairment. Duloxetine metabolism and elimination are markedly decreased in patients with clinically evident hepatic insufficiency. Duloxetine is not recommended in patients with any hepatic insufficiency.

Elderly patients. Although no age-based dosage adjustment is recommended for elderly patients (≥ 65 years old), use caution when titrating the dose of duloxetine because elderly patients may exhibit increased sensitivity.

Pregnancy / Labor and Delivery. The use of duloxetine in pregnant females and its effects during labor and delivery have not been adequately studied. Selective serotonin reuptake inhibitors as well as serotonin and norepinephrine reuptake inhibitors have been associated with complications requiring prolonged hospitalization, respiratory support,

and tube feeding in neonates exposed to these agents late in the third trimester of pregnancy. Symptoms included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. They may be consistent with a direct toxic effect of the drugs, or possibly, a drug discontinuation syndrome. Some cases were consistent with serotonin syndrome. Weigh potential risks and benefits of duloxetine when considering its use in pregnant women and during labor and delivery, and consider tapering duloxetine during the third trimester.

Nursing. Breastfeeding during duloxetine therapy is not recommended.

Monitoring

Therapeutic response. Since the efficacy of duloxetine has not been evaluated beyond 12 weeks and individuals may experience disease progression over time, treatment goals, including pain relief and functional capacity, should be individualized and the effectiveness of duloxetine in meeting those goals should be systematically reassessed throughout therapy.

The patient's level of pain control, functional ability, and satisfaction with therapy should be evaluated when assessing response to therapy.[12,13] A 0–10 numeric rating scale (0 = No Pain and 10 = Worst Pain Imaginable) is suggested for measuring pain intensity, and a similar numeric rating scale or other validated instrument may be used for evaluating functional ability. At each visit, patients should be asked to rate their pain intensity for current pain, least pain in the previous week, and usual or average pain in the previous week, as well as the intensity of pain and duration of pain relief after taking the current therapy. On a regular basis (e.g., every 6 months), patients should be asked about their functional ability, including employment, enjoyment of life, emotional distress (depression and anxiety), housework, hobbies, sleep, mobility, self-care, and sexual function. A multidimensional assessment of pain is encouraged. Additional information and pain resources can be obtained at http://www.vachronicpain.org/pages/pain_resources.htm

Clinical worsening and suicide risk. Patients with co-existing depression should be carefully observed for clinical worsening of depression and suicidality, particularly at the onset of therapy and after any dosage changes. For patients who develop persistent worsening of depressive symptoms or severe, new, or abrupt-onset suicidality, a different therapeutic regimen should be considered. Use similar precautions in patients with other psychiatric and nonpsychiatric disorders because of the possibility of co-morbidity with major depressive disorder. Patients should also be monitored for possible activation of mania/hypomania, particularly if the patient has a history of bipolar disorder.

Blood pressure and heart rate. Duloxetine has been associated with increases in systolic and diastolic blood pressure in patients with major depressive disorder and decreases in diastolic blood pressure in patients with PDN. Increases in heart rate were observed in both patient populations.

Drug interactions. Duloxetine is a moderate inhiitor of CYP2D6. Use caution in patients concurrently treated with CYP2D6 substrates such as tricyclic antidepressants (e.g., amitriptyline, desipramine, imipramine, nortriptyline), phenothiazines, and type 1C antiarrhythmics (e.g., propafenone, flecainide). Plasma concentrations of tricyclic antidepressants may need to be monitored and the dosage decreased to reduce the risk of serious ventricular arrhythmias. Concomitant use of duloxetine and thioridazine is not recommended because of the potential risk of serious ventricular arrhythmias and sudden death due to increased plasma thioridazine concentrations.

Discontinuation symptoms. Monitor for discontinuation symptoms when stopping and tapering the dose of duloxetine. (See Discontinuing Duloxetine below.)

Discontinuing Duloxetine

Patients who lack a documented therapeutic response to an adequate (12-week) trial of duloxetine should be gradually tapered off the drug and reassessed. Although duloxetine showed a statistically significant treatment effect on a 0 to 10 numeric pain rating scale 1 week after initiation of therapy in clinical trials,[14] the duration of treatment that constitutes an adequate trial was not assessed. A 12-week treatment period is suggested to assess response to duloxetine, based on the time point of primary outcome measures in clinical trials and to allow clinicians a reasonable amount of time to re-assess patient response.

Discontinuation symptoms (e.g., dizziness, headache, irritability, nausea, nightmare paresthesia, and vomiting) have been reported when duloxetine was abruptly stopped in patients with major depressive disorder. When duloxetine is to be discontinued, the dose should be gradually tapered. Abrupt cessation of duloxetine should be avoided whenever possible.

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The checklist below is suggested as a template to follow when processing prescriptions for duloxetine.

Criteria	Yes	No
The answers to items A and B must be YES in order to meet criteria.		
A. Patient has painful diabetic neuropathy.	☐	☐
B. Patient has well documented insufficient response despite an adequate trial (dose and duration) of at least one oral agent, used alone or in combination, from 2 of the following 4 drug classes (minimum of 2 oral agents, total) OR patient has documented intolerance, hypersensitivity, or contraindication to the following agents and is therefore precluded from undertaking an adequate trial of at least one oral agent from 2 of the 4 drug classes.	☐	☐

Check all drug classes in which there is documentation that at least one oral agent has been tried for at least 6 to 12 weeks at the doses shown.

Painful Diabetic Neuropathy

☐ 1) Antidepressants, tricyclic: e.g., amitriptyline (nortriptyline) 25–150 mg/d; desipramine 12.5–200 mg/d; imipramine 25–225 mg/d
☐ 2) Antidepressants, SNRI: e.g., venlafaxine 150–225 mg/d
☐ 3) Antiepileptic drugs: e.g., carbamazepine 200–600 mg/d, gabapentin 300–3600 mg/d, phenytoin 300 mg/d, valproate 500–1200 mg/d
☐ 4) Opioid: e.g., tramadol 50–400 mg/d
The criteria suggest tramadol, a nonscheduled opioid, as a prior treatment alternative to duloxetine. The criteria do not recommend a prior trial of schedule II to IV opioids before considering duloxetine. However, patients already prescribed schedule II to IV opioids may be considered for duloxetine therapy as long as the minimum of 2 prior agents is met.

If applicable, briefly describe intolerance, hypersensitivity, or contraindication that precludes adequate trial of a minimum of 2 oral agents from different drug classes. _____

Exclusions	Yes	No
If the answer to ANY item below is YES, then the patient should NOT receive duloxetine.		
Patient has end-stage renal disease (requiring dialysis)	☐	☐
Patient has severe renal impairment (estimated CrCl < 30 ml/min)	☐	☐
Patient has hepatic impairment or chronic liver disease	☐	☐
Patient has substantial alcohol intake	☐	☐
Patient has uncontrolled narrow-angle glaucoma or uncontrolled hypertension	☐	☐
Patient is taking thioridazine or monoamine oxidase inhibitors	☐	☐