Duloxetine for Chronic Pain Conditions
Recommendations for Use

February 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.

The drug Product Information should be consulted for detailed prescribing information.

Patients Who Should NOT Receive Duloxetine.

- ☐ End-stage renal disease (requiring dialysis), severe renal impairment (estimated CrCl < 30 ml/min)
- ☐ Any hepatic impairment, chronic liver disease or cirrhosis
- ☐ Substantial alcohol intake
- ☐ Uncontrolled hypertension
- ☐ 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)
- ☐ Concomitant thioridazine (because of potential risk of cardiac arrhythmia due to drug interaction).
- ☐ Concomitant CYP1A2 inhibitors (e.g., fluvoxamine, cimetidine, ciprofloxacin, enoxacin), thioridazine, linezolid or intravenous methylene blue

Pharmacotherapeutic Considerations in Chronic Pain Conditions

Chronic pain conditions encompass a heterogeneous group of painful disorders, each with its own complex array of pain-generating and inhibiting mechanisms.

There is wide interindividual variation in response to analgesics. The beneficial and harmful responses to treatments cannot be predicted for individuals; therefore, therapeutic trials for various agents are necessary to determine optimal therapy for each patient, and it is reasonable to use a stepped approach to therapy, starting with the agent with the best safety-efficacy-cost value.

Many factors should be considered when selecting drug therapy for chronic pain conditions, including the patient's past responses to medications, drug efficacy profiles for the specific type of pain, specific symptoms being treated; drug safety profiles, patient co-morbidities that may be worsened or simultaneously treated by the drug therapy, and patient convenience and acceptance of therapy.

Overall, the results of various indirect comparative effectiveness studies suggest that duloxetine is comparable to alternative agents in reducing pain for the conditions for which it is FDA-approved (see **Summary of Evidence Review on Comparative Effectiveness of Duloxetine**, page 10). Safety profiles may be generally more important considerations when selecting agents.

Duloxetine and the other serotonin-norepinephrine-reuptake inhibitors (SNRIs), venlafaxine and milnacipran, are generally tried after acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) and before tramadol and other opioids, based on overall safety-efficacy-cost profiles.

The main advantages of duloxetine over other SNRIs are dosing convenience, simpler dosage titration (which may require fewer clinic visits) and larger body of evidence for chronic pain disorders. With more FDA-approved indications, duloxetine may be useful for simultaneously treating the chronic pain disorder and co-occurring disorders (such as depression) with one drug ("dual use").

The usefulness of combination therapy is unclear and evidence is inconsistent and insufficient.[1] There is early evidence suggesting that a combination of analgesics with different mechanisms of action may be more effective than single analgesics but combination therapy may increase the risk of adverse events.[2,3,4,] However, there is also evidence that the efficacy of combination therapy (e.g., duloxetine plus gabapentin) is similar to that of monotherapy (e.g., duloxetine).[5,6,7] Agents with opposite adverse events may also be advantageous; for instance, the insomnia and weight loss effects of duloxetine may be mitigated by the sedative and weight gain effects of the alpha-2-delta (A2D)–binding antiepileptic drugs (AEDs) gabapentin and pregabalin.[5,7]

Stepped Approach: Recommended Indications and Alternative Agents for Duloxetine

Step 1 Formulary Alternatives: Overall best safety–efficacy–cost value
Step 2 Formulary Alternatives: Consider these agents if primary alternatives are inadequate or poorly tolerated
Step 3 Less Preferred Formulary and Nonformulary Alternatives: Lowest safety–efficacy–cost value
In each step, more than one agent as monotherapy or a combination of agents may be tried before proceeding to the next step.

Indication	Step 1 Formulary Alternatives		Step 2 Formulary Alternatives		Step 3 Formulary Alternatives		Step 3 Nonformulary Alternatives	
Painful Diabetic Neuropathy	AED Carbamazepine Gabapentin	SNRI Duloxetine Venlafaxine	AEDs Divalproex Lamotrigine Topiramate Valproate Zonisamide [8]	Counterirritant Capsaicin crm TCAs Amitriptyline Desipramine Nortriptyline	Opioids Hydrocodone / APAP Oxycodone / APAP Morphine Oxycodone Fentanyl TDS[CFU]* Methadone[DRTCP]* * Not for opioid-naive	TCA Imipramine	*AEDs* *Lacosamide* *Pregabalin* *Anesthetic* *Lidocaine patch*	*Antiarrhythmic* *Mexiletine* *NMDARA* *DMQ* *SNRI Opioid* *Tapentadol*
Fibromyalgia	AED Gabapentin SMR Cyclobenzaprine	SNRI Duloxetine Venlafaxine TCA Amitriptyline	SSRIs Citalopram Fluoxetine Paroxetine	SNRI Opioid Tramadol	Opioids See list above		*AED* *Pregabalin* *DA Agonist* *Pramipexole*	*SNRI* *Milnacipran* *SSRI* *Fluvoxamine*
Chronic Musculoskeletal Pain: Low Back Pain	Acetaminophen	Oral NSAIDs Diclofenac Etodolac Ibuprofen Indomethacin Meloxican Naproxen Sulindac	AED Gabapentin SNRI Duloxetine	SNRI Opioid Tramadol	AED Topiramate TCAs Amitriptyline Clomipramine Desipramine Doxepin Imipramine Nortriptyline	TeCA Trazodone SMR / BZD Cyclobenzaprine Diazepam SSRIs Fluoxetine Paroxetine Opioids See list above	*AED* *Pregabalin* *Opioid* *Buprenorphine TDS* *SMR* *Carisoprodol*	*SNRI Opioid* *Tapentadol* *TeCA* *Maprotiline*
Osteoarthritis	Acetaminophen Oral NSAIDs See list above	Counterirritant Capsaicin crm	SNRI Duloxetine	SNRI Opioid Tramadol	Opioids See list above		*Topical NSAID* *Diclofenac*	*SNRI Opioid* *Tapentadol*
Treatment of CIPN in Cancer Survivors	SNRI Duloxetine		TCA Amitriptyline Desipramine Nortriptyline	AED Gabapentin			Combination amitriptyline, ketamine ± baclofen compounded topical gel[‡]	

Formulary status as of 21 January 2015. Refer to the up-to-date National Formulary list available at http://www.pbm.va.gov/PBM/NationalFormulary.asp .

AED, Antiepileptic drug; APAP, Acetaminophen; BZD, Benzodiazepine; CFU, Criteria for Use; CIPN, Chemotherapy-induced peripheral neuropathy; Crm, Cream; DA, Dopamine; DMQ, Dextromethorphan / Quinidine combination; DRTCP, Dosing Recommendations for the Treatment of Chronic Pain; IR, Immediate-release; NMDARA, NMDA receptor antagonist; SA, Sustained action (i.e., extended-release, controlled-release); SMR, Skeletal muscle relaxant; SNRI, Serotonin norepinephrine reuptake inhibitor; SSRI, Selective serotonin reuptake inhibitor; TCA, Tricyclic antidepressant; TDS, Transdermal system (patch); TeCA, Tetracyclic antidepressant

[8] Zonisamide is restricted to neurology

[‡] Each 1.31-g dose contained amitriptyline (40 mg), ketamine (20 mg) and baclofen (10 mg) in a pluronic lecithin organogel gel. Compounded by Gateway Compounding Pharmacy in Bismark, ND.[9]

Modification of Stepped Drug Selection: Safety and Dual Use Considerations

Main safety concerns with duloxetine: Serotonergic effects (antiplatelet / bleeding potential; drug interactions leading to serotonin syndrome); blood pressure increases; urinary retention; potential seizures; hyponatremia; and avoidance in severe renal impairment and chronic liver disease or cirrhosis.

Potential dual uses of duloxetine: Chronic pain disorders co-occurring with depression, anxiety, or PTSD.

Co-occurring Condition	Selected Drug Classes Used for Chronic Pain Disorders					
	AEDs	**SNRIs**	**SSRIs**	**TCAs**	**SNRI Opioids**	**Opioids**
Common Conditions in U.S. Veterans						
Coronary Artery Disease (CAD)	Be Aware: Prolongation of PR interval (pregabalin)	Caution, Drug Interaction: Increased bleeding (SNRIs plus antiplatelets or anticoagulants)	Caution: QTc prolongation (citalopram, fluoxetine, paroxetine, sertraline) Caution, Drug Interaction: Increased bleeding (SSRIs plus antiplatelets or anticoagulants) Caution, Modify: Decreased clopidogrel effects (fluoxetine, fluvoxamine, sertraline, CYP2C19 inhibitors)	Contraindication: Use of TCAs except doxepin during acute phase after MI Caution: Orthostatic hypotension Caution / Drug Interaction: QTc prolongation (TCAs with CAD and/or antiarrhythmics)	Caution, Drug Interactions: Tramadol toxicity (quinidine). Digoxin toxicity and alteration of warfarin effects (tramadol).	Contraindication: Methadone if QTc > 500 msec Boxed Warning, Monitor: Prolongation of QTc / TdP (methadone) Drug Interaction: Avoid buprenorphine and antiarrhythmics (QTc prolongation) Caution, Modify: Fentanyl toxicity (amiodarone, diltiazem, verapamil, other CYP3A4 inhibitors). Morphine toxicity (quinidine, other PGP inhibitors)
Cerebrovascular Disease		Caution, Drug Interaction: Increased bleeding (SNRIs plus antiplatelets or anticoagulants)		Caution: Orthostatic hypotension	Caution: Severe hypotension and syncope (tapentadol)	
Diabetes Mellitus, Diabetic Gastroparesis (DGP)	Caution: Unclear effects on gastric emptying. Additive risks of HF (pregabalin plus TZDs) . Metabolic acidosis, a contraindication for metformin (topiramate). Loss of glucose control (pioglitazone or glyburide with topiramate).	Caution: Loss of glucose control Unclear effects of gastroparesis on absorption of duloxetine.	Caution: Hypoglycemia (with fluoxetine) or hyperglycemia (with discontinuation of fluoxetine). Caution, Drug Interaction: QTc prolongation (cisapride or droperidol for gastroparesis with citalopram)	Diagnostic Confusion: Delay in gastric emptying; hold TCAs for 48–72 h before diagnostic gastric emptying tests[10] Contraindication, Drug Interaction: Cisapride for gastroparesis with amitriptyline or protriptyline (QTc prolongation) Drug Interaction: If Possible, Avoid metoclopramide for DGP and TCAs (TCA toxicity, SS, EPS, NMS)	Caution: Unclear effects on gastric emptying (tramadol). Reduced gastric motility (tapentadol)	Diagnostic Confusion; Avoid If Possible: Delay in gastric emptying; hold opioids for 48–72 h before diagnostic gastric emptying tests[10]

Co-occurring Condition	Selected Drug Classes Used for Chronic Pain Disorders					
	AEDs	**SNRIs**	**SSRIs**	**TCAs**	**SNRI Opioids**	**Opioids**
Heart Failure (HF)	Diagnostic Confusion: Peripheral edema (A2D AEDs) Caution: Worsening HF in patients with NYHA Class III or IV HF (pregabalin)		Caution: SIADH, hyponatremia (SSRIs with diuretics)	Caution: Orthostatic hypotension	Avoid: Tapentadol in circulatory shock. Caution: Severe hypotension and syncope (tapentadol).	Caution, Drug Interaction: Prolongation of QTc (methadone or buprenorphine with diuretics) Caution: Orthostatic hypotension
Hypertension		Caution: Increase BP and HR		Caution, Drug Interaction: Orthostatic hypotension (TCAs and antihypertensives)	Caution, Drug Interaction: Severe hypotension and syncope (tapentadol with antihypertensives).	
Obesity / Overweight	Caution: Weight gain (pregabalin)	Coadministration Not Recommended: Venlafaxine and Weight Loss Agents	Caution: Weight loss or gain	Caution: Weight gain		
Prostatitis / Prostatic Hyperplasia		Avoid if possible: Urinary hesitation and retention (SNRIs)		Contraindication: doxepin in urinary retention Caution: Urinary retention (TCAs)		
Seizure Disorder	Dual Use	Caution: Potential risk of seizures	Caution: May cause or worsen seizures	Caution: May cause or worsen seizures	Caution: May cause or worsen seizures Caution, Drug Interaction: Loss of tramadol effects with carbamazepine	Caution: May cause or worsen seizures (high doses) Caution, Drug Interaction: Loss of fentanyl effects or opioid withdrawal symptoms (carbamazepine, phenytoin, other CYP450 inducers)
Conditions that Commonly Occur with Chronic Pain						
Major Depression / Suicidality	Boxed Warning: Suicidal thoughts and behaviors Caution: Amitriptyline toxicity (topiramate)	Dual Use Boxed Warning: Suicidal thoughts and behaviors	Contraindication, Drug Interaction: Use of SSRIs within 14 days of MAOIs Boxed Warning: Suicidal thoughts and behaviors Caution: SS (SSRIs plus serotonergic drugs†). Dual Use	Contraindication / Drug Interaction: Use of MAOIs with TCAs or within the last 14 days (SS) Boxed Warning: Suicidal thoughts and behaviors Dual Use	Contraindication: Acute psychiatric instability / severe depression or uncontrolled suicide risk Contraindication / Drug Interaction: Use of tapentadol within 14 days of MAOIs (cardiac effects) Caution: Risk for suicide or unstable psychiatric disorder. SS and seizures (SNRI opioids used w/ serotonergic drugs).† Tramadol toxicity with fluoxetine,	Contraindication: Acute psychiatric instability / severe depression or uncontrolled suicide risk; or non-nicotine SUD not in remission and not in treatment Drug Interaction: Avoid morphine within 14 days of MAOIs (morphine toxicity) Caution: Risk for suicide or unstable psychiatric disorder

Co-occurring Condition	Selected Drug Classes Used for Chronic Pain Disorders					
	AEDs	**SNRIs**	**SSRIs**	**TCAs**	**SNRI Opioids**	**Opioids**
					paroxetine and amitriptyline (CYP2D6 inhibitors)..	SS (opioids with SSRIs) Caution, Modify: Decreased codeine effects (fluoxetine, paroxetine, sertraline, CYP2D6 inhibitors). TCA toxicity, SS, QTc prolongation (escitalopram).
Generalized Anxiety Disorder (GAD)	Dual Use (Pregabalin) Caution, Drug Interaction: Amitriptyline toxicity (topiramate)	Dual Use	Caution: SS (SSRIs plus serotonergic drugs†). Dual Use	Dual Use Boxed Warning: Suicidal thoughts and behaviors	Caution: SS (SNRI opioids plus serotonergic drugs†). Tramadol toxicity with fluoxetine, paroxetine and amitriptyline (CYP2D6 inhibitors).	
Posttraumatic Stress Disorder (PTSD)	Caution: Amitriptyline toxicity (topiramate)	Dual Use	Dual Use: Fluoxetine, paroxetine	Dual Use	Contraindication, Drug Interaction: Norepinephrine cardiac effects (use of tapentadol within 14 days of MAOIs) Caution: SS (SNRI opioids plus SSRIs, SNRIs, or TCAs). Tramadol toxicity (with fluoxetine, paroxetine and amitriptyline, CYP2D6 inhibitors).	
Non-nicotine Substance Use Disorder	Caution: Misuse or abuse (A2D AEDs)				Contraindication: SUD not in remission and not in treatment Relative Contraindication, Caution: SUD in treatment or remission	Contraindication SUD not in remission and not in treatment Relative Contraindication, Caution: SUD in treatment or remission
• Alcohol Use Disorder	Dual Use: (Topiramate, potentially gabapentin[11])	Warnings/Precautions: Seizures, hyponatremia	Contraindicated: Sertraline solution (12% alcohol) and disulfiram Caution: May cause or worsen seizures Caution: SIADH, hyponatremia Potential Dual Use: pain and AUD subtypes[11]		Drug Interaction: Avoid alcohol with tapentadol (fatal drug concentrations) Caution / Monitor: May cause or worsen seizures	
• Cocaine Use Disorder	Dual Use: (Topiramate)					

Co-occurring Condition	Selected Drug Classes Used for Chronic Pain Disorders					
	AEDs	**SNRIs**	**SSRIs**	**TCAs**	**SNRI Opioids**	**Opioids**
Specific Patient Populations						
Elderly, Cachectic, and Debilitated	Caution: Use low doses Adjust dose by CrCl: Gabapentin, Pregabalin, Topiramate Age-related Increases in Adverse Effects: Gabapentin, Pregabalin	Caution: Use low doses; risk of hyponatremia.	Caution: SIADH, hyponatremia Not Recommendable in Certain Subgroups: Fluoxetine (anticholinergic)	Caution, Not Routinely Recommendable: Use low doses; anticholinergic, orthostatic and sedative effects	Caution: Use low doses	Caution: Use low doses
Renal Impairment (RI)	Adjust Dose: Gabapentin Pregabalin Topiramate	Avoid: Duloxetine in severe RI (eCrCl < 30 ml/min) No Dosage Adjustment: Duloxetine in mild–moderate RI (eCrCl 30–80 ml/min) Adjust Dose: Venlafaxine Milnacipran in severe RI Caution: Milnacipran in moderate RI	Caution	Caution	Not Recommended: Tapentadol in severe renal impairment Reduce Dose: Tramadol if CrCl < 30	Caution Avoid AVINZA (morphine ER cap) doses > 1600 mg/d: Renal toxicity (fumaric acid)
Hepatic Impairment (HI)	No dosage adjustment: Gabapentin, pregabalin Caution: Topiramate	Avoid: Duloxetine in chronic liver disease or cirrhosis Adjust Dose: Venlafaxine Caution: Milnacipran	Caution	Caution: Increase in LETs (e.g., clomipramine)	Not Recommended: Tapentadol in severe HI (Child-Pugh score 10–15) Reduce Dose: Tapentadol in moderate HI (Child-Pugh 7–9)	Caution
Pregnancy *B –, C –, and D – represent Pregnancy Categories.*	C – A2D AEDs D – Topiramate	C – All 3 SNRIs NDTWS	C – Citalopram, escitalopram, fluoxetine, fluvoxamine, sertraline, vilazodone D – Paroxetine NDTWS – Paroxetine	Use only if B>R C – Amitriptyline, amoxapine, clomipramine, doxepin, protriptyline, trimipramine D – Nortriptyline	C – Use only if B>R NDTWS	B – oxycodone C – other opioids NOWS Avoid during or prior to labor
Breastfeeding	Caution / Use only if B>R: A2D AEDs, Topiramate	Caution / Use only if B>R	Caution: AABM suggests considering paroxetine or sertraline Not Recommended: Citalopram, escitalopram, fluoxetine, vilazodone	Caution / Use only if B>R		Caution / Use only if B>R

A2D AEDs, Antiepileptics that bind to the alpha-2-delta subunit of voltage-activated calcium channels; AABM, American Academy of Breastfeeding Medicine; B>R, Benefits outweigh risks; DGP, Diabetic Gastroparesis; HI, Hepatic impairment; LET, Liver enzyme tests; NDTWS, Neonatal drug toxicity or withdrawal symptoms; NOWS, Neonatal Opioid Withdrawal Syndrome; NMS, Neuroleptic malignant syndrome; OAT, Opioid agonist therapy (methadone, transmucosal buprenorphine); PGP, P-glycoprotein; RI, Renal impairment; SS, Serotonin syndrome; TdP, Torsade de Pointes; TZD, Thiazolidinedione (antidiabetics; e.g., pioglitazone, rosiglitazone)

† Serotonergic drugs include SSRIs, SNRIs, TCAs, triptans, drugs that affect the serotonergic system (mirtazapine, trazodone, tramadol), MAOIs and other drugs that impair serotonin metabolism.

Clinical Properties of SNRIs

Property	Duloxetine	Milnacipran	Venlafaxine
CONTRAINDICATIONS	Serotonin Syndrome: avoid MAOIs 5 /14 days†; also avoid linezolid and i.v. methylene blue	Serotonin Syndrome; avoid MAOIs 5 / 14 days; also avoid linezolid and i.v. methylene blue	Serotonin Syndrome; avoid MAOIs 7 / 14 days† Hypersensitivity
BOXED WARNINGS	Suicidal thoughts and behaviors	Suicidality and antidepressant drugs	Suicidal thoughts and behaviors
WARNINGS AND PRECAUTIONS	Hepatotoxicity Orthostatic hypotension, falls, syncope Serotonin syndrome Abnormal bleeding Severe skin reactions Discontinuation symptoms Activation of mania / hypomania Angle-closure glaucoma Seizures Blood pressure increase Avoid CYP1A2 inhibitors, thioridazine Hyponatremia Diabetes, loss of control Slow gastric emptying Urinary hesitation and retention	Suicidality Serotonin syndrome Blood pressure and heart rate increases Seizures Hepatotoxicity Discontinuation symptoms Abnormal bleeding Dysuria / Lower urinary tract obstructive disorders Avoid with substantial alcohol use and in chronic liver disease (increased transaminases) Angle-closure glaucoma	Clinical worsening / Suicide risk Serotonin syndrome Blood pressure increase Abnormal bleeding Angle-closure glaucoma Activation of mania / hypomania
Most Common Adverse Reactions	Incidence ≥5% and at least twice that of placebo: Nausea Dry mouth Somnolence Constipation Decreased appetite Hyperhidrosis	Incidence ≥5% and greater than placebo: Nausea Headache Constipation Dizziness Insomnia Hot flush Hyperhidrosis Vomiting Palpitations Heart rate increased Dry mouth Hypertension	Incidence ≥5% and at least twice that of placebo: Nausea Somnolence Dry mouth Sweating Abnormal ejaculation Anorexia Constipation Erectile dysfunction Libido decreased
Drug Interactions	Avoid MAOIs Avoid CYP1A2 inhibitors; e.g., fluvoxamine, cimetidine, ciprofloxacin, enoxacin (increase duloxetine concentrations) Avoid thioridazine (arrhythmias) CYP2D6 inhibitors (increase duloxetine concentrations) Drugs metabolized by CYP2D6 with narrow therapeutic index (use caution; e.g., TCAs, phenothiazines, Type 1C antiarrhythmics) Alcohol (liver injury); avoid in patients with substantial alcohol use CNS Acting Drugs (use caution) Antiplatelets and Anticoagulants; e.g., NSAIDs, Aspirin, Warfarin (may increase risk of bleeding)	Avoid MAOIs Avoid digoxin (postural hypotension, tachycardia) Serotonergic Drugs Triptans (serotonin syndrome; use caution) Catecholamines (potential paroxysmal hypertension and arrhythmia) CNS-active drugs, Clomipramine (use caution) Clonidine (duloxetine may inhibit antihypertensive effect)	Avoid MAOIs Avoid alcohol (increase venlafaxine concentrations) CNS-active drugs (use caution) Serotonergic Drugs (e.g., MAOIs, triptans, SSRIs, other SNRIs, linezolid, lithium, tramadol, or St. John's wort) Antiplatelets and Anticoagulants; e.g., NSAIDs, Aspirin, Warfarin (may increase risk of bleeding) Weight loss agents (not recommended) Cimetidine (use caution in hypertension, elderly, or hepatic dysfunction) Ketoconazole (use caution in CYP2D6 extensive metabolizers) Metoprolol (use caution; monitor BP)
Geriatric Patients	No overall age-related differences in safety or effectiveness Increased risk for falls No dosage adjustment necessary but consider potential for increased sensitivity to drug	Consider predominant renal excretion of drug May be at greater risk of hyponatremia	No overall age-related differences in safety or effectiveness May be at greater risk of hyponatremia No dosage adjustment necessary but consider potential for increased sensitivity to drug
Use in Hepatic Impairment	Avoid in chronic liver disease or cirrhosis	No dosage adjustment	Mild (Child-Pugh 5–6) and Moderate (Child-Pugh 7–9): Reduce total daily dose by 50% Severe (Child-Pugh 10–15) or Hepatic Cirrhosis: reduce dose by 50% or more; individualize
Use in Renal Impairment	Avoid in severe renal impairment (eCrCl <30 ml/min) Mild–Moderate (eCrCl 30–80 ml/min): No dosage adjustment	Mild: No dosage adjustment Moderate: Use caution Severe (eCrCl 5–29 ml/min): reduce daily dose by 50% to 25 mg twice daily; may increase to 50 mg twice	Mild (CrCl 60–89 ml/min) or Moderate (CrCl 30–59 ml/min): reduce total daily dose by 25% to 50% Hemodialysis or Severe Renal Impairment (CrCl <30 ml/min): reduce

Property	Duloxetine	Milnacipran	Venlafaxine
		daily depending in response End-stage Renal Disease: Not recommended	total daily dose by 50% or more; individualize
Pregnancy	Use only if potential benefits justify risks C – Possible evidence of fetal risk Unknown placental transfer Late third trimester use of SNRIs have been linked to serious neonatal complications	Use only if potential benefits justify risks C – Possible evidence of fetal risk Unknown placental transfer Late third trimester use of SNRIs have been linked to serious neonatal complications	Use only if potential benefits justify risks C – Possible evidence of fetal risk Known placental transfer Late third trimester use of SNRIs have been linked to serious neonatal complications
Lactation	Consider risks / benefits; use caution. Excreted in human milk	Consider risks / benefits; use caution. Excreted in human milk	Not recommended; discontinue drug or nursing; consider risks / benefits Excreted in human milk

Sources: Product Information for individual agents as of 3 Feb 2015

† # / # days: Avoid use of MAOI within [first number of days] after stopping the SNRI / Avoid use of SNRI within [second number of days] of stopping MAOI; e.g., "avoid MAOIs 5 / 14 days" = avoid MAOIs within 5 days after stopping the SNRI / avoid SNRI within 14 days of stopping MAOI.

Dosage and Administration of Duloxetine

Refer to prescribing information for complete information on dosage and administration.

Pain Indication	Initial Dose	Target Dose	Maximum Dose†	Comments
	Dose (mg/day) given once daily			
Diabetic Peripheral Neuropathic Pain	60	60	60	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.
Fibromyalgia	30	60	60	Start at 30 mg once daily for 1 week before increasing to 60 mg once daily. Some patients may respond to the initial dose.
Chronic Musculoskeletal Pain	30	60	60	Start at 30 mg once daily for 1 week before increasing to 60 mg once daily. Some patients may respond to the initial dose.
Treatment of Chemotherapy-induced Neuropathy (off-label)	30	60	60	Based on results of a single, unverified 5-week phase III trial.[12] Duloxetine dosage: 30 mg once daily x 1 week then 60 mg daily x 4 weeks.

† There is no evidence that doses higher than 60 mg confer additional benefit. Higher doses increase the risk of adverse events.

Issues for Consideration

FDA-approved Indications

- Major Depressive Disorder
- Generalized Anxiety Disorder
- Diabetic Peripheral Neuropathic Pain
- Fibromyalgia
- Chronic Musculoskeletal Pain (established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis)

Therapeutic Response. Since 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. 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

Discontinuing Duloxetine

Patients who lack a documented therapeutic response to an adequate therapeutic trial of duloxetine should be gradually tapered off the drug and reassessed. 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.

Table 1 Adequate Trial Durations for Duloxetine

Indication	Duration of an Adequate Trial	Comments
Painful Diabetic Neuropathy	12 weeks	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.
Fibromyalgia	8–12 weeks	Based on duration of clinical trials and lack of additional benefit from subsequent dosage increase in week-8 nonresponders.
Chronic Musculoskeletal Pain	7–13 weeks	Based on duration of clinical trials and study protocol allowing dosage increase in week-7 nonresponders.
Treatment of Chemotherapy-induced Neuropathic Pain in Cancer Survivors (off-label)	5 weeks	Based on duration of a single clinical trial.

Renewal of Prescriptions

- First prescriptions should be limited to a 30-day supply with no refills to evaluate tolerability. Patients should also be re-evaluated after an adequate trial duration for the condition being treated (Table 1). Duloxetine should be tapered and discontinued if there has been no response and continued if there has been at least partial response.

Summary of Evidence Review on Comparative Effectiveness of Duloxetine

Indication	Alternative Oral and Topical Agents	Comparative Effectiveness (">" means 'better than')
Painful Peripheral Diabetic Neuropathy	<u>Evidence of Efficacy</u> Carbamazepine[13,14,15] Duloxetine Duloxetine / Gabapentin Combination (DGC)[16] Gabapentin[16,17] Mexiletine[18,19] Pregabalin[16] Tapentadol[16,20] Venlafaxine[14,16] <u>Inconsistent Evidence of Benefit</u> Amitriptyline[14,16,19,21] Capsaicin, topical[16,22] Lacosamide[19] Lamotrigine[19] Topiramate[23,19] <u>Insufficient Evidence</u> Antipsychotics[24] Desipramine[25,26] Dextromethorphan / Quinidine (DMQ)[27] Imipramine[28] Lidocaine, 5% topical[29] Nortriptyline[30] Oxycodone[31] Valproate[19] Zonisamide[19] <u>Evidence of Inefficacy</u> Fluoxetine[32] Lacosamide 200 mg[27] Levetiracetam[33] Oxcarbazepine 1200 mg[27] Pregabalin 150 mg[27] Topiramate 100, 200 and 400 mg[27] Zonisamide 540 mg[27]	Overall: • Duloxetine ~ Gabapentin, Pregabalin[34] For Pain Reduction Benefit–Risk: • Unclear[14] • Gabapentin > Venlafaxine > Pregabalin > DGC > Duloxetine > Placebo > Amitriptyline[16] For Pain Reduction: • Amitriptyline ~ Topical Capsaicin, Desipramine, Lamotrigine, Pregabalin[21] • Unclear for desipramine,[26] imipramine[28] and nortriptyline[30] • Few and variable differences overall among 29 interventions[19]; indirect comparisons from those with 2 or more RCTs: ○ NRS Pain Reduction: [Oxycodone ~ Gabapentin ~ Tramadol ~ Pregabalin 300 mg or more ~ Duloxetine 40 mg or more] > [Lamotrigine ~ Lacosamide ~ Pregabalin 150 mg or less ~ Duloxetine 20 mg or less][19] ○ VAS Pain Reduction: [Capsaicin 0.075% topical ~ Venlafaxine]; [Venlafaxine ~ Lacosamide ~ Oxcarbazepine] > [Topiramate]; Capsaicin 0.075% topical > Lacosamide, Oxcarbazepine, Topiramate[19] ○ 30% and 50% Pain Reduction, >2 RCTs: Pregabalin 300 mg or more ~ Duloxetine 40 mg or more ~ Venlafaxine ER[19] • Pregabalin > [Carbamazepine ~ Venlafaxine][35] • Few differences found from 45 indirect drug-drug comparisons involving 7 drugs and 17 drug-dose combinations from 17 RCTs[27]: ○ Duloxetine 60 mg > DMQ 60/60 mg, Lacosamide 600 mg, Topiramate 400 mg[27] ○ Pregabalin 600 mg > DMQ 60/60 mg, Lacosamide 600 mg, Topiramate 400 mg[27] ○ 36 drug-drug comparisons showed similar effects, including: Duloxetine 60 mg ~ Pregabalin 300/600 mg ~ Oxcarbazepine 1800 mg ~ Lacosamide 400 mg ~ DMQ 90 / 60 mg[27] For NRS-50 Responder Rate (NNT): • ≥2 Active Arms: Pregabalin 600 ~ Duloxetine 60 mg[27] For Improvement in Sleep: • Pregabalin 150–600 mg ~ Lacosamide 600 mg ~ Duloxetine 60 mg[27] For Global Improvement: • ≥2 Active Arms: Duloxetine 60 mg ~ Lacosamide 400/600 mg ~ Oxcarbazepine 1800 mg ~ Pregabalin 600 mg[27] For Risk of Adverse Events: • ≥2 RCTs: Gabapentin ~ Desipramine ~ Pregabalin 300 mg or more ~ Lamotrigine ~ Duloxetine 40 mg or more ~ Amitriptyline ~ Lacosamide[19] For Risk of Discontinuation: • Similar to Placebo, ≥2 RCTs: Sodium valproate ~ Tramadol ~ Oxycodone ~ Pregabalin 150 mg or less ~ Gabapentin ~ Duloxetine 20 mg or less ~ Pregabalin 300 mg or more ~ Lamotrigine ~ Duloxetine 40 mg or more ~ Amitriptyline[19] • Worse than Placebo, ≥2 RCTs: Topiramate ~ Lacosamide ~Capsaicin 0.075% topical ~ Oxcarbazepine[19] • Indirect Comparisons, ≥2 Active Arms: ○ [Lacosamide 200 mg ~ Pregabalin 150 mg ~ Duloxetine 60 mg] > Topiramate 200/400/600 mg, Oxcarbazepine

Indication	Alternative Oral and Topical Agents	Comparative Effectiveness (“>” means ‘better than’)
		1800 mg[27] ○ Pregabalin 300 mg > Topiramate 400 mg, Lacosamide 600 mg, Oxcarbazepine 1800 mg[27]
Fibromyalgia	Evidence of Efficacy Amitriptyline[21,38] Cyclobenzaprine[36,37] Duloxetine[38,39] Milnacipran[38,39,43] Pregabalin[43] Tramadol[53] Inconsistent Evidence of Benefit SSRIs (citalopram, fluoxetine, fluvoxamine, paroxetine)[37,38] Single-trial Evidence Antipsychotics[24] Gabapentin[17] Oxycodone[31] Pramipexole[40] Venlafaxine[41] Evidence of Inefficacy Nortriptyline[42]	Overall: • Duloxetine ~ Pregabalin, Milnacipran[43] For Pain Reduction: • [Duloxetine ~ Pregabalin][43] > Milnacipran[44] • SNRIs, Pregabalin > TCAs, SSRIs[38] • Amitriptyline >Duloxetine, Milnacipran[44] For FIQ Improvement: • Duloxetine ~ Milnacipran ~ Pregabalin[43] For Improvement in Sleep: • Duloxetine ~ Pregabalin[43 44] • Duloxetine > Milnacipran[44] • Pregabalin > Milnacipran[43] • TCAs[38] • Amitriptyline > Duloxetine, Milnacipran[44] • Inconsistent: Duloxetine[39,43 44] • Ineffective: Milnacipran[39,44] For Quality of Life Improvement: • SNRIs ~ Pregabalin[38] • Duloxetine ~ Milnacipran[39] or > Milnacipran[44] • Ineffective: Amitriptyline[44] For Fatigue Improvement: • SNRIs[38] • Pregabalin[44] • Amitriptyline > Duloxetine, Milnacipran[44] • Milnacipran > Duloxetine[44] • Inconsistent: Duloxetine,[38,39,44] Milnacipran[39] For Depressed Mood: • Duloxetine > Milnacipran[44] Incidence of Adverse Events (least / best to highest incidence): • Overall: Duloxetine ~ Milnacipran ~ Pregabalin[43] • Headache: Gabapentin > Pregabalin, Duloxetine, Milnacipran, Venlafaxine[45] • Nausea: Pregabalin > Duloxetine, Milnacipran, Venlafaxine[45] • Diarrhea: Milnacipran, Pregabalin, Gabapentin > Venlafaxine > Duloxetine[45] • Weight Gain: Venlafaxine > Milnacipran > Duloxetine, Gabapentin > Pregabalin[45] For Tolerability (WDAEs): • SNRIs ~ Pregabalin ~ TCAs[38] For Differential Efficacy / Safety in Subgroups[46] • Duloxetine: no differential effects for fibromyalgia with vs. without depression [46] • Other medications have insufficient evidence
Chronic Musculoskeletal Pain Chronic Low Back Pain	Evidence of Efficacy or CPG Recommendation Acetaminophen[56] Buprenorphine TDS[47] Duloxetine[47,48] NSAIDs[47,48,49,50,56] Tramadol[47,48,49] Tapentadol[53] Inconsistent Evidence of Efficacy Antidepressants[56]:	For Pain Reduction: • NSAIDs > Buprenorphine TDS, Strong Opioids > Duloxetine[47] • Duloxetine ~ COX-2Is, Strong Opioids, Tramadol[48] • Strong Opioids ~ NSAIDs, Antidepressants[53] • Morphine ~ Naproxen[49] • Tramadol > Celecoxib[53] • Antidepressants[51] For Global Improvement:

Indication	Alternative Oral and Topical Agents	Comparative Effectiveness (“>” means ‘better than’)
	• Amitriptyline, Desipramine, Doxepin, Imipramine, Maprotiline, Nortriptyline, Paroxetine, Trazodone[51] • Amitriptyline/Imipramine, Bupropion, Clomipramine, Desipramine, Fluoxetine, Maprotiline, Nortriptyline, Paroxetine[52] Strong Opioids[47,48,53,54] <u>Insufficient Evidence of Efficacy</u> Skeletal muscle relaxants (cyclobenzaprine, carisoprodol)†[55] Benzodiazepines (diazepam)†[55] Antiepileptics[56]: • Gabapentin, pregabalin, topiramate (for chronic radiculopathy) • Topiramate, gabapentin (for nonradicular low back pain) • Gabapentin (for spinal stenosis)	• Tramadol[47] For Disability Reduction: • Strong Opioids[47] • Strong Opioids ~ NSAIDs, Antidepressants[53] • Morphine ~ Naproxen[49] • Tramadol[49,53] • Evidence of Inefficacy: Antidepressants[51], Buprenorphine TDS[53] For Incidence of Adverse Events: • Morphine ~ Naproxen[49] For Pain Relief, Tolerability: • Tapentadol ER > Oxycodone ER Refer to the VA/DoD Clinical Practice Guideline on Diagnosis and Treatment of Low Back Pain
Osteoarthritis	Hip, Knee or Hand: • Acetaminophen[57,58,59,60] • Duloxetine[61] • NSAIDs, oral[57,58,59,60,61,62,63] • Tapentadol ER[20] • Tramadol[58,59,60,61,63,64] • Strong Opioids[58,59] Topicals for Knee or Hand (Not effective for hip osteoarthritis): • Capsaicin, topical low-strength[58,59,60] • NSAIDs, topical[58,60]	Pain, Function, Stiffness: • Duloxetine ~ NSAIDs, Tramadol, Strong Opioids[61] • NSAIDs >/~ Acetaminophen[57,62,63,65] Pain Relief, Tolerability: • Tapentadol ER > Oxycodone ER[20] Refer to the VA/DoD Clinical Practice Guideline on Nonsurgical Management of Hip and Knee Osteoarthritis[58]
Nonspecific	<u>Insufficient Evidence</u>: • Salicylate-containing Topical Rubefacients[66]	
Treatment of Chemotherapy-induced Peripheral Neuropathies in Adult Cancer Survivors	<u>Single Phase III Trial Evidence</u> • Duloxetine (for pain reduction; may be better for oxaliplatin than paclitaxel neuropathy)[9,67] <u>Inconclusive Evidence</u> • Nortriptyline[9,68] • Amitriptyline[9,68] • Combination amitriptyline, ketamine ± baclofen compounded topical gel[9‡] • Venlafaxine[67,68] • Oxcarbazepine[68] <u>Single Negative Trial But Other Data and Experience Supportive of Benefit</u> • Gabapentin[9] <u>Evidence of Inefficacy</u> • Lamotrigine[9]	No direct or indirect comparative studies. More data supporting duloxetine than venlafaxine.[67]
Gastropathic / Gastroparetic Pain	<u>Mentioned in Practice Guideline</u>[10] Gabapentin Nortriptyline (avoid amitriptyline because of greater anticholinergic effects) Pregabalin Tapentadol	Lack of randomized placebo- and active-controlled trials NB: Gastroparesis may reduce duloxetine absorption because the tablet is enteric coated. Other agents without this potential problem are probably preferred.

Indication	Alternative Oral and Topical Agents	Comparative Effectiveness (“>” means ‘better than’)
	Tramadol Expert Opinion[69,70] Acetaminophen NSAIDs TCAs SSRIs SNRIs Ineffective for Idiopathic Type of Gastroparesis Nortriptyline[71]	

A2D AEDs, Antiepileptics that bind to the alpha-2-delta subunit of voltage-activated calcium channels; FIQ, Fibromyalgia Impact Questionnaire (assesses physical function and symptoms); NSAIDs, Nonsteroidal anti-inflammatory drugs including COX-2 selective inhibitors, oral or topical unless otherwise specified; SNRIs, Serotonin norepinephrine reuptake inhibitors (specifically, duloxetine and milnacipran in reference 38); TDS, Transdermal system (buprenorphine 5–40 mcg/h)

† Short-term use of these agents as adjunctive therapies to analgesics may be considered for acute exacerbations of chronic low back pain

‡ In a phase III trial, each 1.31-g dose contained amitriptyline (40 mg), ketamine (20 mg) and baclofen (10 mg) in a pluronic lecithin organogel gel; compounded by Gateway Compounding Pharmacy in Bismark, ND.

Prepared: February 2015. Contact: Francine Goodman, PharmD, National PBM Clinical Pharmacy Program Manager – Formulary, VA Pharmacy Benefits Management Services (10P4P)

REFERENCES

1 Chaparro LE, Wiffen PJ, Moore RA, Gilron I. Combination pharmacotherapy for the treatment of neuropathic pain in adults. Cochrane Database Syst Rev. 2012 Jul 11;7:CD008943

2 Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, Reader S. A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community-derived people with knee pain. Ann Rheum Dis. 2011 Sep;70(9):1534-41

3 Pareek A, Chandurkar N, Ambade R, Chandanwale A, Bartakke G. Efficacy and safety of etodolac-paracetamol fixed dose combination in patients with knee osteoarthritis flare-up: a randomized, double-blind comparative evaluation. Clin J Pain. 2010 Sep;26(7):561-6

4 Frakes EP, Risser RC, Ball TD, Hochberg MC, Wohlreich MM. Duloxetine added to oral nonsteroidal anti-inflammatory drugs for treatment of knee pain due to osteoarthritis: results of a randomized, double-blind, placebo-controlled trial. Curr Med Res Opin. 2011 Dec;27(12):2361-72. Epub 2011 Nov 9. Erratum in: Curr Med Res Opin. 2012 May;28(5):822

5 Irving G, Tanenberg RJ, Raskin J, Risser RC, Malcolm S. Comparative safety and tolerability of duloxetine vs. pregabalin vs. duloxetine plus gabapentin in patients with diabetic peripheral neuropathic pain. Int J Clin Pract. 2014 Sep;68(9):1130-40

6 Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, Cruccu G, Skljarevski V, Freynhagen R. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"--a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. Pain. 2013 Dec;154(12):2616-25

7 Tanenberg RJ, Irving GA, Risser RC, Ahl J, Robinson MJ, Skljarevski V, Malcolm SK. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. Mayo Clin Proc. 2011 Jul;86(7):615-26

8 Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract. 2014 Feb;14(2):167-84. [Funded by Pfizer.]

9 Hershman DL, Lacchetti C, Dworkin RH, Lavoie Smith EM, Bleeker J, Cavaletti G, Chauhan C, Gavin P, Lavino A, Lustberg MB, Paice J, Schneider B, Smith ML, Smith T, Terstriep S, Wagner-Johnston N, Bak K, Loprinzi CL; American Society of Clinical Oncology. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jun 20;32(18):1941-67

10 Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. Am J Gastroenterol. 2013 Jan;108(1):18-37

11 Johnson BA. Pharmacotherapy for alcohol use disorder. In: UpToDate, Saitz R, Hermann R (Eds), UpToDate, Waltham, MA. (Accessed on 27 January 2015.)

12 Smith EM, Pang H, Cirrincione C, Fleishman S, Paskett ED, Ahles T, Bressler LR, Fadul CE, Knox C, Le-Lindqwister N, Gilman PB, Shapiro CL; Alliance for Clinical Trials in Oncology. Effect of duloxetine on pain, function, and quality of life among patients with chemotherapy-induced painful peripheral neuropathy: a randomized clinical trial. JAMA. 2013 Apr 3;309(13):1359-67 [National Cancer Institute (NCI)–funded cooperative research networks trial]

13 Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014 Apr 10;4:CD005451

14 Griebeler ML, Morey-Vargas OL, Brito JP, Tsapas A, Wang Z, Carranza Leon BG, Phung OJ, Montori VM, Murad MH. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. Ann Intern Med. 2014 Nov 4;161(9):639-49

15 Saeed T, Nasrullah M, Ghafoor A, Shahid R, Islam N, Khattak MU, Maheshwary N, Siddiqi A, Khan MA. Efficacy and tolerability of carbamazepine for the treatment of painful diabetic neuropathy in adults: a 12-week, open-label, multicenter study. Int J Gen Med. 2014 Jul 2;7:339-43

16 Rudroju N, Bansal D, Talakokkula ST, Gudala K, Hota D, Bhansali A, Ghai B. Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: a network meta-analysis. Pain Physician. 2013 Nov-Dec;16(6):E705-14. Erratum in: Pain Physician. 2014 Mar-Apr;17(2):203

17 Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014 Apr 27;4:CD007938. doi: 10.1002/14651858.CD007938.pub3

18 Oskarsson P, Ljunggren JG, Lins PE. Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. Diabetes Care. 1997 Oct;20(10):1594-7

19 Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract. 2014 Feb;14(2):167-84. [Funded by Pfizer.]

20 Merchant S, Provenzano D, Mody S, Ho KF, Etropolski M. Composite measure to assess efficacy/gastrointestinal tolerability of tapentadol ER versus oxycodone CR for chronic pain: pooled analysis of randomized studies. J Opioid Manag. 2013 Jan-Feb;9(1):51-61. [Authored by Janssen Global Services, manufacturer of tapentadol.]

21 Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2012 Dec 12;12:CD008242

22 Derry S, Moore RA. Topical capsaicin (low concentration) for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2012 Sep 12;9:CD010111.

23 Wiffen PJ, Derry S, Lunn MP, Moore RA. Topiramate for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2013 Aug 30;8:CD008314

24 Seidel S, Aigner M, Ossege M, Pernicka E, Wildner B, Sycha T. Antipsychotics for acute and chronic pain in adults. Cochrane Database Syst Rev. 2013 Aug 29;8:CD004844

25 Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992 May 7;326(19):1250-6

[26] Hearn L, Moore RA, Derry S, Wiffen PJ, Phillips T. Desipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014 Sep 23;9:CD011003

[27] Ney JP, Devine EB, Watanabe JH, Sullivan SD. Comparative efficacy of oral pharmaceuticals for the treatment of chronic peripheral neuropathic pain: meta-analysis and indirect treatment comparisons. Pain Med. 2013 May;14(5):706-19

[28] Hearn L, Derry S, Phillips T, Moore RA, Wiffen PJ. Imipramine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014 May 19;5:CD010769

[29] Derry S, Wiffen PJ, Moore RA, Quinlan J. Topical lidocaine for neuropathic pain in adults. Cochrane Database Syst Rev. 2014 Jul 24;7:CD010958

[30] Derry S, Wiffen PJ, Aldington D, Moore RA. Nortriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Jan 8;1:CD011209

[31] Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014 Jun 23;6:CD010692

[32] Max MB, Lynch SA, Muir J, Shoaf SE, Smoller B, Dubner R. Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. N Engl J Med. 1992 May 7;326(19):1250-6

[33] Wiffen PJ, Derry S, Moore RA, Lunn MP. Levetiracetam for neuropathic pain in adults. Cochrane Database Syst Rev. 2014 Jul 7;7:CD010943

[34] Quilici S, Chancellor J, Löthgren M, Simon D, Said G, Le TK, Garcia-Cebrian A, Monz B. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. BMC Neurol. 2009 Feb 10;9:6.

[35] Razazian N, Baziyar M, Moradian N, Afshari D, Bostani A, Mahmoodi M. Evaluation of the efficacy and safety of pregabalin, venlafaxine, and carbamazepine in patients with painful diabetic peripheral neuropathy. A randomized, double-blind trial. Neurosciences (Riyadh). 2014 Jul;19(3):192-8

[36] Tofferi JK, Jackson JL, O'Malley PG. Treatment of fibromyalgia with cyclobenzaprine: A meta-analysis. Arthritis Rheum. 2004 Feb 15;51(1):9-13

[37] Goldenberg DL. Initial treatment of fibromyalgia in adults. In: UpToDate, Atlas SJ, Park L (Eds), UpToDate, Waltham, MA. (Accessed on 15 January 2015.)

[38] Nüesch E, Häuser W, Bernardy K, Barth J, Jüni P. Comparative efficacy of pharmacological and non-pharmacological interventions in fibromyalgia syndrome: network meta-analysis. Ann Rheum Dis. 2013 Jun;72(6):955-62

[39] Häuser W, Urrútia G, Tort S, Uçeyler N, Walitt B. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia syndrome. Cochrane Database Syst Rev. 2013 Jan 31;1:CD010292

[40] Holman AJ, Myers RR. A randomized, double-blind, placebo-controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum. 2005 Aug;52(8):2495-505

[41] Sayar K, Aksu G, Ak I, Tosun M. Venlafaxine treatment of fibromyalgia. Ann Pharmacother. 2003 Nov;37(11):1561-5

[42] Heymann RE, Helfenstein M, Feldman D. A double-blind, randomized, controlled study of amitriptyline, nortriptyline and placebo in patients with fibromyalgia. An analysis of outcome measures. Clin Exp Rheumatol. 2001 Nov-Dec;19(6):697-702

[43] Choy E, Marshall D, Gabriel ZL, Mitchell SA, Gylee E, Dakin HA. A systematic review and mixed treatment comparison of the efficacy of pharmacological treatments for fibromyalgia. Semin Arthritis Rheum. 2011 Dec;41(3):335-45

[44] Häuser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome. J Pain. 2010 Jun;11(6):505-21

[45] Facts & Comparisons eAnswers, Comparative Tables [database online]. St. Louis, MO: Wolters Kluwer Health, Inc; 2015.

[46] Forte ML, Butler M, Andrade KE, Vincent A, Schousboe JT, Kane RL. Treatments for Fibromyalgia in Adult Subgroups. Comparative Effectiveness Review No. 148. (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-2012-00016-I.) AHRQ Publication No. 15-EHC006-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2015. www.effectivehealthcare.ahrq.gov/reports/final.cfm

[47] Chung JW, Zeng Y, Wong TK. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. Pain Physician. 2013 Nov-Dec;16(6):E685-704.

[48] Cawston H, Davie A, Paget MA, Skljarevski V, Happich M. Efficacy of duloxetine versus alternative oral therapies: an indirect comparison of randomised clinical trials in chronic low back pain. Eur Spine J. 2013 Sep;22(9):1996-2009. [Funded by manufacturer of duloxetine, Eli Lilly and Co.]

[49] White AP, Arnold PM, Norvell DC, Ecker E, Fehlings MG. Pharmacologic management of chronic low back pain: synthesis of the evidence. Spine (Phila Pa 1976). 2011 Oct 1;36(21 Suppl):S131-43

[50] Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD000396

[51] Salerno SM, Browning R, Jackson JL. The effect of antidepressant treatment on chronic back pain: a meta-analysis. Arch Intern Med. 2002 Jan 14;162(1):19-24

[52] Urquhart DM, Hoving JL, Assendelft WW, Roland M, van Tulder MW. Antidepressants for non-specific low back pain. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD001703

[53] Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared to placebo or other treatments for chronic low-back pain. Cochrane Database Syst Rev. 2013 Aug 27;8:CD004959

[54] Martell BA, O'Connor PG, Kerns RD, Becker WC, Morales KH, Kosten TR, Fiellin DA. Systematic review: opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. Ann Intern Med. 2007 Jan 16;146(2):116-27

[55] van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM; Cochrane Back Review Group. Muscle relaxants for nonspecific low back pain: a systematic review within the framework of the cochrane collaboration. Spine (Phila Pa 1976). 2003 Sep 1;28(17):1978-92

[56] Chou R. Subacute and chronic low back pain: Pharmacologic and noninterventional treatment. In: UpToDate, Atlas SJ, Park L (Eds), UpToDate, Waltham, MA. (Accessed on 14 January 2015.)

[57] Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative Effectiveness of Pharmacologic Interventions for Knee Osteoarthritis: A Systematic Review and Network Meta-analysis. Ann Intern Med. 2015;162:46-54

[58] VA/DoD Clinical Practice Guideline for the Non-surgical Management of Hip and Knee Osteoarthritis. Department of Veterans Affairs and Department of Defense. Version 1.0 – 2014. Available at: http://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf . Accessed: 8 Jan 2015.

[59] Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthritis Cartilage. 2008 Feb;16(2):137-62

[60] Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, Towheed T, Welch V, Wells G, Tugwell P; American College of Rheumatology. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken). 2012 Apr;64(4):465-74

[61] Myers J, Wielage RC, Han B, Price K, Gahn J, Paget MA, Happich M. The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis. BMC Musculoskelet Disord. 2014 Mar 11;15:76

[62] Pavelka K. A comparison of the therapeutic efficacy of diclofenac in osteoarthritis: a systematic review of randomised controlled trials. Curr Med Res Opin. 2012 Jan;28(1):163-78. [Supported by Novartis Pharma AG.]

[63] Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P. OARSI recommendations for the management of hip and knee osteoarthritis: part III: Changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthritis Cartilage. 2010 Apr;18(4):476-99

[64] Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I, Sehgal N, Shah R, Benyamin R, Vallejo R, Fellows B, Christo PJ. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. Pain Physician. 2011 Mar-Apr;14(2):91-121

[65] Verkleij SP, Luijsterburg PA, Bohnen AM, Koes BW, Bierma-Zeinstra SM. NSAIDs vs acetaminophen in knee and hip osteoarthritis: a systematic review regarding heterogeneity influencing the outcomes. Osteoarthritis Cartilage. 2011 Aug;19(8):921-9

[66] Derry S, Matthews PR, Wiffen PJ, Moore RA. Salicylate-containing rubefacients for acute and chronic musculoskeletal pain in adults. Cochrane Database Syst Rev. 2014 Nov 26;11:CD007403

[67] Aziz MT, Good BL, Lowe DK. Serotonin-norepinephrine reuptake inhibitors for the management of chemotherapy-induced peripheral neuropathy. Ann Pharmacother. 2014 May;48(5):626-32

[68] Chu SH, Lee YJ, Lee ES, Geng Y, Wang XS, Cleeland CS. Current use of drugs affecting the central nervous system for chemotherapy-induced peripheral neuropathy in cancer patients: a systematic review. Support Care Cancer. 2015 Feb;23(2):513-24

[69] Deli G, Bosnyak E, Pusch G, Komoly S, Feher G. Diabetic neuropathies: diagnosis and management. Neuroendocrinology. 2013;98(4):267-80

[70] Reddymasu SC, McCallum RW. Pharmacotherapy of gastroparesis. Expert Opin Pharmacother. 2009 Feb;10(3):469-84

[71] Parkman HP, Van Natta ML, Abell TL, McCallum RW, Sarosiek I, Nguyen L, Snape WJ, Koch KL, Hasler WL, Farrugia G, Lee L, Unalp-Arida A, Tonascia J, Hamilton F, Pasricha PJ. Effect of nortriptyline on symptoms of idiopathic gastroparesis: the NORIG randomized clinical trial. JAMA. 2013 Dec 25;310(24):2640-9